WASHINGTON STATE BOARD OF HEALTH

Secondary Packet Info Sheet

Agenda Item 8

Drinking Water Materials and Additives

Supporting Materials

Due to the large file size, this agenda item requires a separate packet for posting online.

Included in this packet are all Agenda Item 8 materials:

a. Cover Memo
b. Secondary Packet Info Sheet
c. Petitions Policy
d. Petition
e. Court Ruling (attachment to petition)
f. Supplemental Materials
g. WAC 246-290-220
h. Presentation

WASHINGTON STATE BOARD OF HEALTH

Date: November 13, 2024

To: Washington State Board of Health Members

From: Kate Dean, Board Member

Subject: Petition for Rulemaking WAC 246-290-220, Drinking Water Materials and Additives – Possible Action

Background and Summary:

The Administrative Procedure Act (RCW 34.05.330) allows any person to petition a state agency for the adoption, amendment, or repeal of any rule. Upon receipt of a petition, the agency has sixty days to either (1) deny the petition in writing, stating the reasons and, as appropriate, offer other means for addressing the concerns raised by the petitioner, or (2) accept the petition and initiate rulemaking.

On October 3, 2024, the State Board of Health (Board) received a petition from Washington Action for Safe Water and Bill Osmunson, DDS MPH. The petitioners request the Board consider amending WAC 246-290-220, Drinking Water Materials and Additives, within the Group A Public Water Supplies rules.

The Board has the authority under RCW 43.20.050 to adopt rules for Group A public water systems as defined in RCW 70A.125.010. Chapter 246-290 WAC establishes the standards for these water systems related to their design, construction, sampling, management, maintenance, and operation practices. The purpose of these rules is to define basic regulatory requirements and to protect the health of consumers using public drinking water supplies.

The petitioners request that The Board amend WAC 246-290-220 to include a new subsection related to water fluoridation that states either of the following:

- The Board of Health does not recommend adding fluoridation chemicals to water with the intent to treat humans or animals; or
- In keeping with the Federal Safe Drinking Water Standards, the Board of Health does not recommend chemicals, including fluoride compounds, be added to the water with the intent to treat or prevent disease in humans or animals.

The petitioner included attachments to support the request, located in the Board materials. Shay Bauman, Board Staff, will present the Board Members with information related to the petition and recommendations.

(continued on the next page)

Recommended Board Actions:

The Board may wish to consider and amend, if necessary, the following motions:

The Board declines the petition for rulemaking to amend WAC 246-290-220 for the reasons articulated by Board Members. The Board directs staff to notify the petitioner of the Board's decision.

OR

The Board accepts the petition for rulemaking to explore the proposed amendment to WAC 246-290-220 to consider additional language related to water fluoridation. The Board directs staff to notify the requestor of its decision and to file a CR-101, Preproposal of Inquiry, to further evaluate the request and possible rule change.

Staff

Shay Bauman, Policy Advisor

Washington State Board of Health
Policy & Procedure

Policy Number:	**2005-001**
Subject:	**Responding to Petitions for Rule-Making**
Approved Date:	**November 9, 2005 (revised August 13, 2014)**

Policy Statement

RCW 34.05.330 allows any person to petition a state agency to adopt, repeal, or amend any rule within its authority. Agencies have 60 days to respond. The agency can deny the request—explaining its reasons and, if appropriate, describing alternative steps it is prepared to take—or it must initiative rule-making. If a petition to repeal or amend a rule is denied, a petitioner can appeal the agency's decision to the Governor.

This policy defines who must be notified and consulted when the Board is petitioned, who may respond on behalf of the Board, and whether Board action is required.

- **Board Response**: When the Board receives a written petition for rule-making within its authority that clearly expresses the change or changes requested, the Board will respond within 60 days of receipt of the petition. The response will be made at the direction of the Board. The response will be in the form of a letter from the Chair denying the petition or informing the petitioner the Executive Director has been directed to initiate rule-making.

- **Consideration of the Petition:** The Chair may place a petition for rule-making on the agenda for a Board meeting scheduled to be held within 60 days of receipt of the petition. Alternatively, if the Board does not have a regular meeting scheduled within 60 days of receipt of the petition, or if hearing the petition at the next regular meeting would defer more pressing matters, the Chair shall call a special meeting of the Board to consider the petition for rulemaking.

Procedure

- **Notifications:** Board staff, in consultation with the Executive Director, will respond to the petitioner within three business days acknowledging receipt of the petition and informing the petitioner whether the request is clear. The Executive Director or staff will notify Board members that a petition for rule-making has been received and will be brought to the Board for consideration at the next regularly scheduled board meeting or will be considered at a special meeting. If

no regular meeting is scheduled before the 60-day response deadline, or if the agenda for the regular meeting cannot accommodate the petition, the Executive Director will notify the Chair of the need to schedule a special board meeting for the purposes of considering the petition. Upon Board action on the petition, the Executive Director shall assure Board members receive electronic copies of the final petition response.

- **Appeals:** If a petitioner appeals the Board's decision to deny a petition to the Governor, the Executive Director will inform the Board of the Governor's action on the appeal at the next scheduled Board meeting.

- **Consultation:** The Executive Director and Board staff will gather background information for the Board's use when it considers the petition. In this regard, the Executive Director will consult with the Board member who sponsored the most recent revisions to the rule being challenged or the appropriate policy committee. The Executive Director may also consult with appropriate representatives of the implementing agency or agencies, and may consult with stakeholders as appropriate.

WSBH Appeal #21. October 1, 2024

Washington State Board of Health

PO Box 47990, Olympia, WA 98504-7990 wsboh@doh.wa.gov

Petitioners: Washington Action for Safe Water and Bill Osmunson DDS MPH

Dear Washington State Board of Health

RE: PETITION FOR RULEMAKING: WATER FLUORIDATION; IN KEEPING WITH THE NATIONAL RESEARCH COUNCIL; THE WASHINGTON STATE BOARD OF PHARMACY; THE U.S. FOOD AND DRUG ADMINISTRATION; THE ENVIRONMENTAL PROTECTION AGENCY SCIENTISTS; THE U.S. SURGEON GENERAL, THE U.S. CONGRESS IN THE SAFE DRINKING WATER ACT; THE U.S. CENTERS FOR DISEASE CONTROL; MOST DEVELOPED NATIONS; THE NATIONAL TOXICOLOGY PROGRAM; AND THE UNITED STATES DISTRICT COURT OF THE NORTHERN DISTRICT OF CALIFORNIA,

OUR PETITION FOR RULE CHANGE

Consistent with health and safety issues in Title 246, Title 173, Title 296, WAC 173-340, and WAC 296-62-07521; this petition is made in compliance with RCW 34.05.330 and WAC Chapter 82-05.

This petition is for amendment to WAC 246-290-220

Suggested wording:

(8) The Board of Health does not recommend adding fluoridation chemicals to water with the intent to treat humans or animals.

Alternate wording:

(**8) In keeping with the Federal Safe Drinking Water Standards, the Board of Health does not recommend chemicals, including fluoride compounds, be added to the water with the intent to treat or prevent disease in humans or animals.**

When questioned about the scientific evidence for the alleged benefit and safety of fluoridation, the Washington Department of Health responded: "DOH will rely on known national entities like the CDC and EPA to assess the science. . . ." (Letter from DOH)

1. The CDC Oral Health Division does not assess science on drugs and has no scientific papers, label, or dosage on the safety and efficacy of fluoridation. CDC Oral Health Division relies primarily the fluoridation lobby.
2. The EPA has not determined the safety or alleged efficacy of adding fluoride to public water. The EPA regulates fluoride as a protected contaminant. The EPA did not provide their scientists to the court for their defense in the Toxic Substance Control Act. EPA scientists are competent, they simply disagree with fluoridation and superiors are protecting the practice. The Safe Drinking Water Act prohibits the EPA from adding anything to public water for the treatment of humans.

The Department said they relied on known National entities and we list National, state and international entities here which the Department and Board have ignored.

I. **U.S. District Court is a National Authority and under the Toxic Substance Control Act (TSCA) ruled fluoridation is an unreasonable risk. The ruling in *Food & Water Watch, Inc. v. United States Envtl. Prot. Agency*, 17-cv-02162-EMC (N.D. Cal. Sep. 24, 2024)** Based on 7 years, 4 weeks of two trials, several experts on both sides, and hundreds of thousands of dollars in costs, the court concluded:

"IV. CONCLUSIONS OF LAW

"121. Plaintiffs have proven, by a preponderance of the evidence, that water fluoridation at the level of 0.7 mg/L – the prescribed optimal level of fluoridation in the United States – presents an "unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation under the conditions of use."

122. The Court thus orders the Administrator to initiate rulemaking pursuant to Subsection 6(a) of TSCA. . . ."

The Board would be foolish and negligent not to immediately stop promoting the addition of what RCW defines as a poison and the Board of Pharmacy exempted from poisons when regulated as a legend drug.

The Court ruling Page 5.

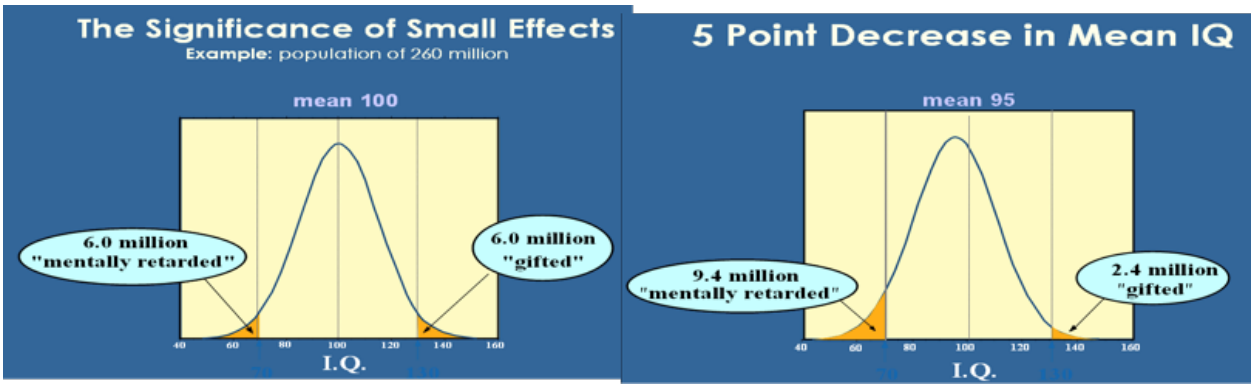
*"The pooled benchmark dose analysis concluded that **a 1-point drop in IQ of a child is to be expected for each 0.28 mg/L of fluoride in a pregnant mother's urine**. This is highly concerning, because maternal urinary fluoride levels for pregnant mothers in the United States range from **0.8 mg/L** at the median and 1.89 mg/L depending upon the degree of exposure. Not only is there an insufficient margin between the hazard level and*

these exposure levels, for many, the exposure levels exceed the hazard level of ***0.28 mg/L.”*** (Court supplied emphasis)

Based on data and analysis presented at trial, the Court at page 75 states, "*fluoride presents a risk of a decrease in IQ [for such offspring] ranging from 2.86 to 6.75 points.*" The lower number is the expected median loss and the upper number is the 95th percentile loss applicable to offspring of 1 in 20 mothers who drink the most fluoridated water.

However, we must not ignore the 5% of mothers who drink the most water, fail to fully rinse their mouths out after brushing with fluoride toothpaste and swallow some toothpaste, fail to eat organic foods, or ingest medications high in fluoride and have the highest urine fluoride concentration. About 250,000 babies are born in Washington State each year, 5% is about 12,500 babies and about 46% in Washington State on fluoridated water. Thus, **about 5,750 babies are estimated to have greater than 6.76 IQ point loss** and the Board must not ignore any babies.

Consider the charts below from the website of Physicians for Social Responsibility. When a population has 5 IQ loss, the mentally handicapped increase by 60% and we have data on those. We do not have data on the more than 60% decline in gifted or what you and I in the middle could have accomplished with 5 more IQ points.



Not all kidneys function to their optimal level and not all mothers have the same intake of other toxins which have a synergistic effect on the development of the brain of their fetus and infant, such as lead and arsenic.

The fluoridation lobby argues like the tobacco lobby, "but we do not have proof." When the Judge asked the expert witness in court, "what would it take for you to change your mind?" The expert responded, "one or two more studies." Many more have been published and the fluoridation lobby still responds, "one or two more studies are needed" and they will always want one or two more and require 100% proof of harm.

The Court Ruling understood the need for a margin of error: P6.

"The EPA's default margin of error requires a factor of 10 between the hazard level and exposure level due to variability in human sensitivities. Put differently, only an exposure that is below 1/10th of the hazard level would be deemed safe under Amended TSCA, given the margin of error required."

P 6. "In all, there is substantial and scientifically credible evidence establishing that fluoride poses a risk to human health; it is associated with a reduction in the IQ of children

and is hazardous at dosages that are far too close to fluoride levels in the drinking water of the United States. And this risk is unreasonable under Amended TSCA. Reduced IQ poses serious harm. Studies have linked IQ decrements of even one or two points to e.g., reduced educational attainment, employment status, productivity, and earned wages. Indeed, the EPA recognizes that reduction of IQ poses a serious community health issue."

Lower IQ is well-know, to result in increased Special Education rates, High School Drop-out rates, lower income, less job stability, less productivity, increased crime, increased homelessness, increased incarceration, increased divorce, decreased self-worth, increased public assistance, increased illicit drug addiction, and decrease gifted and brilliant members of our community. We are all harmed.

II. **National Research Council 2006:** The Board and Department refused to follow the advice of the **National Research Council 2006** authoritative report to the EPA nor the Dose-Response Analysis or Relative Source Contribution of the EPA 2010 or the scientists at the EPA who have said fluoridation is no longer effective and boarders on a criminal act of governments.

1. The National Research Council 2006 (NRC) unanimous decision that EPA's MCLG was not protective of harm, included numerous risks. Other risks raised by the NRC in 2006 and scientifically more fully confirmed during the last 18 years include:
    a. **Tooth damage**
    b. **Rheumatoid and osteoarthritic-like pain**
    c. **Bone cancer**
    d. **Bone fractures**

e. **Thyroid reduction**

f. **Diabetes**

g. **Obesity**

h. **Kidney damage**

i. **Reproductive problems**

j. **Lower IQ --developmental neurotoxicity**

k. **Allergies (overactive immune system)**

l. **Gastrointestinal disorders.**

If too much of a highly toxic substance causes spots on the hard tissue teeth, we would be seriously presumptive to rule out "spots" on the soft tissues or other hard tissues. My professions of dentistry and public health have been negligent in not researching the **safety** of fluoride ingestion. Without FDA approval, the study of safety has been mostly absent and risks ignored.

III. **Washington State Board of Pharmac**y: The Board of Pharmacy was the highest authority on toxic substances and drugs in Washington State, until disbanded. The Department of Health and the Board of Health have disagreed with the **Washington State Board of Pharmac**y which determined fluoride to be a legend drug, i.e. requires the patient's doctor's prescription and patient consent rather than poison. See **RCW 69.38.010.** Unfortunately, the Board of Pharmacy's reward for honesty was to be disbanded and placed under the heel of the Department of Health. The only legal option under RCW is for fluoride to be regulated as a poison because fluoride is highly toxic and poison laws are very strict and exempt when regulated as a legend drug needing FDA CDER approval with the patient's approval under the

supervision of a licensed health care provider. Based on science, laws and ethics, the Board of Pharmacy was indeed correct.

A. U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) is a National Authority: The Board of Health has put itself as a higher authority and expert disagreeing with the **Food and Drug Administration (FDA).** The Department of Health has not relied on the authorized national authority.

a. The FDA warns, “Do Not Swallow” on the toothpaste label, referring to 0.25 mg of fluoride. The same dosage as one 11 oz glass of fluoridated water.

b. In a warning to drug manufacturers, the FDA was clear and correct, that the evidence of fluoride’s effectiveness was incomplete. Only one randomized controlled trial of fluoride ingestion has been published and it reported no statistical evidence of fewer dental caries, i.e. benefit. Yet the Board of Health claims benefit in disagreement with the FDA CDER.

c. The Board’s first denial of our request for the Board or water purveyors to apply for FDA CDER NDA (Food and Drug Administration, Center for Drug Evaluation and Research, New Drug Application) would have taken the thorny, complex job of determining the safety, dosage, label, GDMP (Good Drug Manufacturing Practices), product purity, and the legal, ethical, and science off the Board’s shoulders and placed the task in the lap of the authorized authorities, the FDA CDER.

d. In fact, the Board did call the FDA and the FDA specifically warned the Board that if the Board tried to gain FDA approval, fluoridation would be banned. What about “Do Not Swallow”, “incomplete evidence” and “banned” does the Board not understand and can dismiss as not relevant?

B. **National Toxicology Program (NTP) is most certainly a National Authority:** In 2015, I nominated cancer, thyroid harm and developmental neurotoxicity to the **National Toxicology Program (NTP)** for review. The NTP accepted the developmental neurotoxicity of fluoride for review and told me in a phone call the review usually takes about 2 years, inclusive of animal testing.

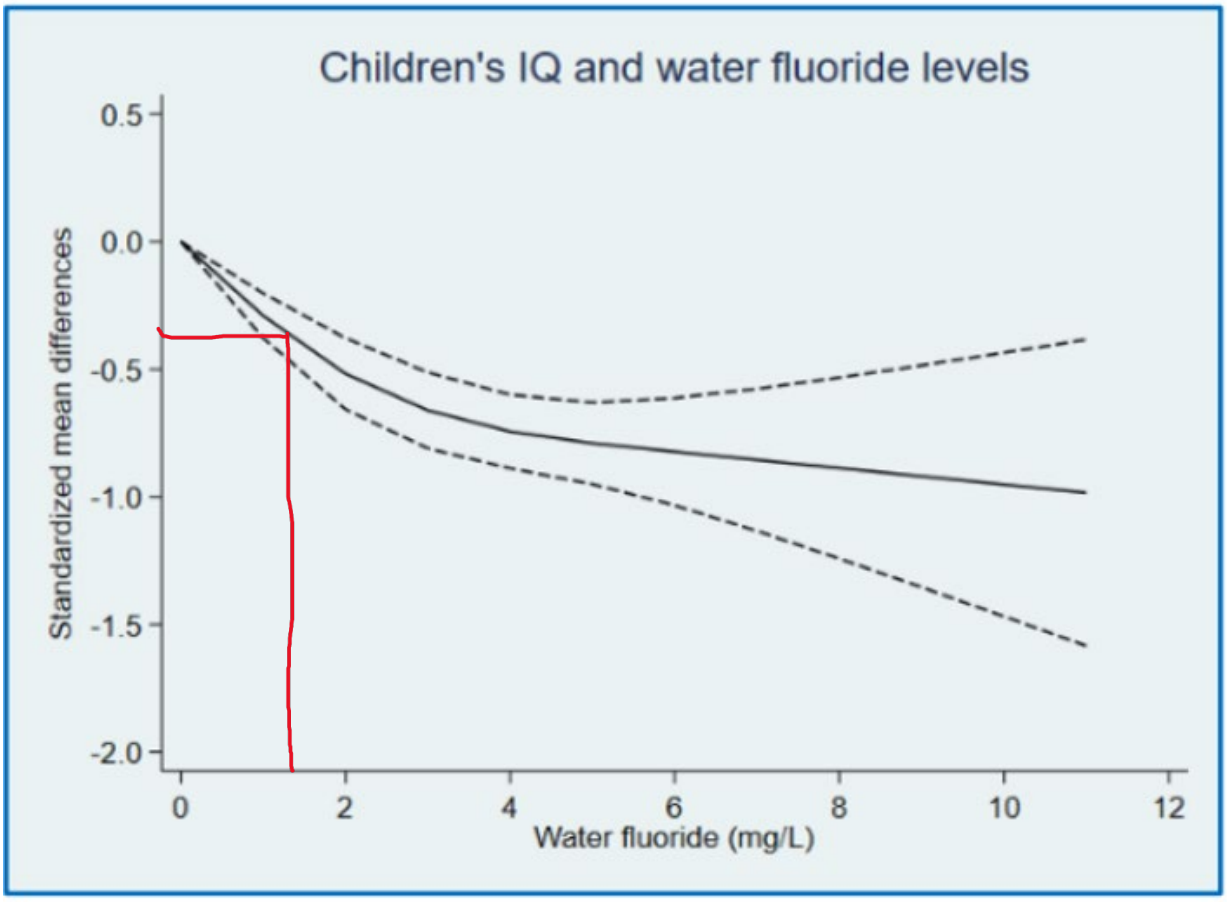
The 700-page draft had repeated peer reviews, (more than one is highly unusual) both internal and external of HHS, including the fluoridation lobby, and was blocked by HHS from release until the Court ordered the draft released. Eight years and eight months after nomination, the first section was published and the meta-analysis which has the strongest conclusions is supposed to be published later this year. The draft reported a presumed developmental neurotoxicant and the published reports moderate confidence. The NTP report did not suggest a "safe" concentration. Below 1.5 mg/L the meta-analysis shows there is no threshold of safety and at 0.7 mg/L fluoride in water has about 3 IQ loss.

A few considerations must be made on the NTP graph eFigure 17. Pooled Dose-Response Association Between Fluoride in water and Standardized Mean Differences in Children's IQ pasted below.

a. About half of fluoride ingested is from water and half from other sources, the NTP listed risk from water and the Board must consider total fluoride exposure. We have added two orange lines at the 1.5 mg/L fluoride concentration in water and the second going over to the standardized mean difference of about 0.4.
b. Water fluoride concentration of 0.7 mg/L is about half (30-70%) the total fluoride exposure. Thus 1.5 mg/L in water is approximately the total fluoride exposure of individuals. The fluoridation lobby and EPA have tried to separate the water from total fluoride exposure. Real-world exposure is total fluoride and the two cannot

and should not be separated. Thus, 1.5 mg/L is used here and the orange lines demonstrate the approximate 0.4 standardized mean difference (SMD).

c. The fluoridation lobby will discount 0.4 SMD as not significant, and they would be correct if SMD were the same as IQ. However, 1 SMD is 15 IQ points and 0.4 is 6 IQ point loss.



Now consider the 5% ingesting 10 times the mean quantity of water who would have babies with 10 to 15 IQ point loss.

C. **The U.S. District Court** September 2024, ruling supported the NTP and determined that fluoridation at 0.7 mg/L in water is an **unreasonable risk** and not only referred to a published Benchmark Dose Analysis but in effect did one.

*"The pooled benchmark dose analysis concluded that **a 1-point drop in IQ of a child is to be expected for each 0.28 mg/L of fluoride in a pregnant mother's urine**. This is highly concerning, because maternal urinary fluoride levels for pregnant mothers in the United States range from **0.8 mg/L** at the median and 1.89 mg/L depending upon the degree of exposure. Not only is there an insufficient margin between the hazard level and these exposure levels, for many, the exposure levels exceed the hazard level of **0.28 mg/L**."* (Court supplied emphasis)

a. It should be understood that the median urine fluoride concentration of 0.8 mg/L and 1.89 mg/L is not exactly the same as the concentration of fluoride in water, 0.7 mg/L accounting for various quantities of water consumed and other sources of fluoride. About half the fluoride is retained in the body (depending on kidney function etc.) and about half is excreted. And about half the total exposure of fluoride is from water and about half (estimated 30-70%) from other sources. Thus, the Court's 0.8 mg/L fluoride in urine is similar to 0.7 mg/L fluoride in water. For ball park estimations, urine and water concentrations are reasonably comparable. And 1.89 mg/L represents a reasonable variation in water consumption for up to the 95th percentile of mothers. On page 75 of the Court's findings the 95th percentile of mothers drinking 2-3 liters of water a day with children having 6.75 points IQ loss is reasonable.
b. As stated earlier, the Board cannot call fluoridation safe for a mother drinking the average of 1 liter per day of fluoridated water. Mothers drinking 2 to 3 liters of water are at the 95th percentile and their children would probably have 6.75 IQ loss. Even worse are the 5% of mothers who drink more than 2 to 3 times times

the mean/media. A few mothers drinking for example 4 liters of water a day would expect closer to a 10 IQ point loss for their child.

D. Based on FOI documents, **the U.S. Surgeon General** quietly stopped endorsing fluoridation.

E. **The U.S. Environmental Protection Agency scientists** through their union: *"In summary, we hold that fluoridation is an unreasonable risk. That is, the toxicity of fluoride is so great and the purported benefits associated with it are so small - if there are any at all – that requiring every man, woman and child in America to ingest it borders on criminal behavior on the part of governments."* Dr. J. William Hirzy, Senior Vice-President, Headquarters Union, US Environmental Protection Agency, March 26, 2001

F. **The Centers for Disease Control:** CDC: "Ingestion of fluoride is not likely to reduce tooth decay." Drinking Water to Prevent Dental Caries. MMWR, 48(41); 933-940, October 22, 1999 Achievements in Public Health, 1900-1999:

The Oral Health Division of the CDC is in the pocket of the American Dental Association and seldom in statements even alters the words enough to avoid plagiarism.

The CDC does not approve drugs, the FDA CDER has drug approval authority. The CDC does provide free drugs for investigational purposes, fluoride is not one.

G. **International authorities opposed to fluoridation. 97% of Europe** is fluoridation free. Most developed countries do not fluoridate public water.

H. Austria REJECTED: "toxic fluorides" NOT added

I. Belgium REJECTED: encourages self-determination – those who want fluoride should get it themselves.

J. Finland STOPPED: "...do not favor or recommend fluoridation of drinking water. There are better ways of providing the fluoride our teeth need." A recent study found ..."no indication of an increasing trend of caries...."

K. Germany STOPPED: A recent study found no evidence of an increasing trend of caries

L. Denmark REJECTED: "...toxic fluorides have never been added to the public water supplies in Denmark.“

M. Norway REJECTED: "...drinking water should not be fluoridated“

N. Sweden BANNED: "not allowed". No safety data available!

O. Netherlands REJECTED: Inevitably, whenever there is a court decision against fluoridation, the dental lobby pushes to have the judgment overturned on a technicality or they try to get the laws changed to legalize it. Their tactics didn't work in the vast majority of Europe.

P. Hungary STOPPED: for technical reasons in the '60s. However, despite technological advances, Hungary remains unfluoridated.

Q. Japan REJECTED: "...may cause health problems...." The 0.8 -1.5 mg regulated level is for calcium-fluoride, not the hazardous waste by-product which is added with artificial fluoridation.

R. Israel SUSPENDED mandatory fluoridation until the issue is reexamined from all aspects.: June 21, 2006 “The labor, welfare and health Knesset committee” As of 2024 still suspended.

S. China BANNED: "not allowed“

T. International Academy of Oral Medicine and Toxicology is opposed to fluoridation. Position paper

U. American Academy of Environmental Medicine “Fluoridation has been called one the ten great public health achievements of the 20th century by the Centers of Disease Control in the US. As research continues to unfold the truth about the use of this supposed ‘healthy mineral’ has become clear. Fluoridation is more

likely one of the ten most dangerous public health practices in this country and in the world. The American Academy of Environmental Medicine's position is that there is absolutely no benefit to public health that Fluoride should be recommended or utilized."

V. **The Nuffield Council, Bioethics on fluoridation:** "public health policy involving the water supply should be considered in relation to:

a. the balance of risks and benefits [brains are more important than teeth]

b the potential for alternatives that rank lower on the intervention to achieve the same outcome. [oral hygiene and diet]

c. the role of consent where there are potential harms"[1] [fluoridation lacks consent and has known harm, more than potential harms.

The US Department of Bioethics has not yet responded and I will inform the Board when they respond.

FLUORIDATION LOBBY: For about the first 25 years of practice I promoted fluoridation and was part of the fluoridation lobby. After reading the science and all streams of evidence, I became opposed to fluoridation. With further study I realized I, like most dentists, had made millions of dollars selling fluoride topical in my office and

[1] Ethics Consultation Report Ethical Considerations in Community Water Fluoridation, by the Public Health Agency of Canada's Public Health Ethics Consultative Group, December 18, 2018 p.2. https://www.caphd.ca/sites/default/files/Ethical%20Considerations%20for%20Community%20Water%20Fluoridation.pdf

treating both cosmetic and functional dental fluorosis with fillings, crowns, root canals, extractions, bridges, implants and more.

a. The fluoridation lobby, those employed to promote fluoridation, those with memberships supporting fluoridation, the fluoride manufacturers, dental product manufacturers using fluoride, those selling fluoride in their offices, are biased because of money. For example, a dentist with 1,000 patients (many have more) charges about $30 for fluoride treatments 2x a year or $60 per person per year X 1,000 patients is $60,000. My office with 4,000 patients generated close to half a million dollars a year with almost no doctor time and very little materials costs. Functional harm can exceed cosmetic harm easily costing thousands of dollars per patient.
b. The fluoridation lobby discounts the Court ruling due to misunderstanding and bias. The fluoridation lobby often fails to understand the difference between concentration and dosage. Concentration of fluoride in water is held reasonably constant but dosage is not controlled because not everyone drinks the same amount of water, some 10 times more than the mean. (NRC 2006)
c. The pushback from the fluoridation lobby/salesmen is reminiscent of the tobacco defense of tobacco, which for decades delayed public health action. Simply delay, delay, delay and raise doubt.
d. The fluoridation lobby attempts to separate out just the fluoride from water from all the other fluoride and when talking is referring to just the fluoride contributed by the fluoridation. In the real world to determine hazard, total fluoride exposure needs to be considered.

e. The fluoridation lobby fails to consider the chemicals added to the water are industrial grade rather than pharmaceutical grade.

f. The fluoridation lobby fails to include individual consent.

g. Dentists are prohibited from diagnosing general health diseases such as developmental neurotoxicity and without evidence have claimed fluoridation is safe. . . meaning for teeth, not the entire body. However, fluoridation harms teeth, dentists think they are doing good and forget the harm.

h. The fluoridation lobby has been so intent on protecting fluoridation they have failed to provide quality research and gain FDA CDER approval.

i. The fluoridation lobby usually only considers up to the 90th percentile who drink twice the average of 1L of water/day, about 330,000 of the 3.3 million people in Washington State.

j. The fluoridation lobby does not include a margin of error or intraspecific variability which should be 10x for each, 100 X the hazard benchmark.

k. The fluoridation lobby accepts observational studies for proof of efficacy; however, they reject observational studies of risk and harm as inadequate quality.

l. The fluoridation lobby has failed to gain FDA CDER approval.

m. The Fluoridation lobby has failed to follow RCW such as provide a forum. Washington Legislature, **RCW 43.20.05** designates authority for health and safety rules onto the Board of Health.

"RCW 43.20.050 Powers and duties of state board of health—Rule making—Delegation of authority—Enforcement of rules.

(1) The state board of health shall provide a forum for the development of public health policy in Washington state . . . ."

(2) In order to protect public health, the state board of health shall:
*(a) Adopt rules for group A public water systems, as defined in RCW **70A.125.010**, necessary to assure safe and reliable public drinking water and to protect the public health."*

n. We are unable to find in Washington State or Federal Laws where the Board or Department of Health is specifically authorized to determine the **efficacy** of a substance added to public water intended to treat humans.

However, WAC 246-290-220 permits the Department to continue use of non-certified chemicals which would encompass fluoride chemicals, provided:

"(b)There exists no substantial evidence that the use of the chemical or material has caused consumers to register complaints about aesthetic issues, or health related concerns, that could be associated with leachable residues from the material;''

o. We again register our complaint of dental fluorosis aesthetic and functional harm and other health concerns is made to the Department of Health.

For the health of the public, we have requested a forum as provided in RCW 43.20.050 where experts can provide the Board with evidence and we can hear concerns, objections, and questions.

p. **"RCW 43.20.050** does not authorize the Board to dilute drugs in the water with the intent to treat humans rather than treat water, nor does it permit the Board to reduce the safety of the water.

q. **RCW 43.20.050** does not appear ambiguous or uncertain. The Board is the authority in Washington State and SHALL assure the water is safe. Fluoridation is NOT safe.

r. **FLURODIE IS HIGHLY TOXIC:** fluoride is a highly toxic substance, a hazard, and must not be taken lightly or casually dismissed.

There is no physiologic process which requires fluoride, no "minimum daily requirement." Fluoride is not a nutrient. No disease is caused by the absence of fluoride ingestion.

Fluoride is one of the most powerful elements known.

***"RCW 69.38.010 "Poison" defined**. As used in this chapter "poison" means:*
(1) Arsenic and its preparations;
(2) Cyanide and its preparations, including hydrocyanic acid;
(3) Strychnine; and (4) Any other substance designated by the state board of pharmacy which, when introduced into the human body in quantities of sixty grains or less, causes violent sickness or death."

60 grains =3,888 mg.

The probable violent sickness or death of fluoride is estimated at 5 mg/Kg body weight. Although it might take 50 mg to cause violent sickness or death in an adult, an estimated 20 mg NaF could cause violent sickness or death in an infant. The probable fetus lethal dosage is unknown, however, preliminary studies indicates a higher rate of miscarriage in fluoridated communities. Without dispute, fluoride is an extremely toxic substance, poison, more lethal than lead or gasoline.

s. FLUORIDATION IS AN UNAPPROVED ILLEGAL DRUG

Drugs are defined as: *"articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease"* [FD&C Act, sec. 201(g)(1)].

The Board of Health responded in 2010, to my question of the intent of fluoride ingestion, responding:

"*This agency, therefore, is not in possession of any records related to the Board's " purpose and intent for supporting the addition of fluoride to public drinking water."*

Seriously, the Board . . . had NOTHING to back up why they recommended adding fluoride to public water. However, FOI evidence with thousands of pages clearly disagreed with the Board's claim of "no records" were available at the time on the intent of fluoridation.

The Board's claim of "no records" was simply a "white lie."

The Board now clearly states,

"if the Board accepted the language proposed in the petition, (for FDA CDER approval) it effectively would ban public water fluoridation in Washington."

Our point exactly. The Board did not think anyone could get FDA CDER approval. The Board preferred to be dishonest and claim they had no record of intent, rather than protect the public health. Intent determines jurisdiction.

t. **In contrast, to the Washington State Board of Health the Washington State Board of Pharmacy determined***:*

"Fluoride is a legend drug regulated under chapter 69.41 RCW. RCW 69.41.010 defines a 'legend drug' as drugs 'which are required by state law or regulation of the state board of pharmacy to be dispensed on prescription only or are restricted to use by practitioners only."

Note: The Board of Pharmacy referenced the "Red Book," not the list of approved drugs in the FDA "Orange book."

The WSBP references the 2002 Drug Topics Red Book which is industry, not published by the FDA CDER but rather the Physician's Desk Reference. As a doctor, I use the PDR, but the FDA rather than industry approves substances intended to prevent disease in humans.

RCW 69.41.010 (13) *"Legend drugs" means any drugs which are required by state law or regulation of the pharmacy quality assurance commission to be dispensed on prescription only or are restricted to use by practitioners only.*

u. For 14 years the Board of Health has not answered the obvious question, "who is the practitioner under who's license the dispensing the fluoride drug is dispensed to everyone without their consent?"

v. The FDA and Board of Pharmacy newsletter, stated:

"***Manufacturers of unapproved drugs are usually fully aware that their drugs are marketed illegally, yet they continue to circumvent the law and put consumers' health at risk."*** Washington State Board of Pharmacy 7/2008 Newsletter

w. RCW 57.08.012 Fluoridation of water is authorized.

"A water district by a majority vote of its board of commissioners may fluoridate the water supply system of the water district. The commissioners may cause the proposition of fluoridation of the

water supply to be submitted to the electors of the water district at any general election or special election to be called for the purpose of voting on the proposition. The proposition must be approved by a majority of the electors voting on the proposition to become effective."

RCW 57.08.012 permits fluoridation but does not exempt the Board from ensuring the water is safe, nor does the law state the intent to fluoridate. Our rule change petition does not conflict with RCW 57.08.012.

Pause for a moment and seriously let **RCW 57.08.012** soak in. Did the legislature expect each voter to spend the hundreds/thousands of hours to carefully review the many streams of legal and scientific evidence in detail and make judgment on the legality, jurisdiction, efficacy, safety, current dosage, desired dosage, ethics with all streams of evidence of ingesting more fluoride for their neighbors? No.

For example, just because RCW permits an individual to get a drivers license, does not mean they can ignore the laws of the road or the highway jurisdiction can ignore safety standards.

In the denial of our 2010 first petition, the Board, in effect agreed their authority includes determining the "safety" of fluoridation by mistakenly relying on the CDC and EPA to ensure the issue of safety. We agree the Board has jurisdiction over the laws and science relating to **RCW 57.08.012** are followed. In the last 4 decades since **RCW 57.08.012** was passed we have more evidence to consider.

x. The Department appears in violation of WAC 246-290-220

"(5) The department may accept continued use of, and proposals involving, certain noncertified chemicals or materials on a case-by-case basis, if all of the following criteria are met:

(b)There exists no substantial evidence that the use of the chemical or material has caused consumers to register complaints about aesthetic issues, or health related concerns, that could be associated with leachable residues from the material;''

The law requires "substantial evidence." I spent over 4 decades treating aesthetic and functional dental fluorosis, a known adverse effect of excess fluoride ingestion.

y. The substance added to public water is NOT pharmaceutical grade which is assumed in the PDR that the Board of Pharmacy relied on, but rather industrial grade hydrofluorosilicic acid, or industrial grade sodium fluoride, both are contaminated products, often containing:

Arsenic – 90 percent of the arsenic contributed by drinking water treatment chemicals is attributable to hydrofluorosilicic acid. Source: Wang C, Smith DB, Huntly GM. Treatment Chemicals contribute to Arsenic Levels. Opflow (AWWA), October 2000. EPA's MCLG is "0" "Ingestion of inorganic arsenic in drinking water has been linked to skin, lung, bladder, kidney, prostate, and liver cancers." Oregon Dept. Human Services. Drinking Water and Environmental Exposure, 2007

Lead – EPA's MCLG is "0" Ionescu Neuro Endocrinol Lett 2006, $15B to remove - awwa
Beryllium – Increase in cancer. Taylor-McCabe, Poteomics 2006
Vanadium – Mixed results
Cadmium – Increase in breast cancer McElroy J Natl Cancer Inst. June 2006
Mercury – Cancer Increase and Neurological Disorders Ionescu Neuro Endocrinol Lett 2006
Radium – Cancer Increase Lloyd Radiat Res. 2005
Radionuclides – Cancer Increase Sevan'kaev Raiats Biol Radioecol 2006
Silicon – Probably safe
Bauxite – Mixed opinions

It is important to note that not all batches have all of these contaminants, and contaminant concentrations are usually unknown. The fluoride chemical purity is assumed by the National Sanitation Foundation (NSF), a private company who refuses to provide assay data to the public, and at times have said they do not test each batch.

z. THE SAFE DRINKING WATER ACT DOES NOT PERMIT FLUORIDATION.

The Board appears in violation of the **Safe Drinking Water Act** as detailed below

Our point: The SDW Act prohibits the addition of anything to tap water to treat humans.

aa. THE FOOD DRUG AND COSMETIC ACT CHARGES THE FDA TO APPROVE DRUGS.

The Board is also in violation of the **FD&C Act** as detailed below and in Attachment #A.

RCW 18.64.011 (14) and **[FD&C Act, sec. 201(g)(1)].** *"Drugs" means:*

(a) Articles recognized in the official United States pharmacopoeia or the official homeopathic pharmacopoeia of the United States;
(b) Substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in human beings or other animals;
(c) Substances (other than food) intended to affect the structure or any function of the body of human beings or other animals; or. . . "

Fluoride is in the US Pharmacopoeia.

The intent of fluoridation is well known to the public, to prevent dental cavities.

The Board's intent to add fluoride to water is to prevent dental cavities.

Neither the PHS (U.S. Public Health Service) CDC (U.S. Centers for Disease Control), nor EPA (U.S Environmental Protection Agency), have authority from Congress to approve any substance with intent to prevent, mitigate or cure disease in humans.

Only the FDA CDER (U.S. Food and Drug Administration Center for Drug Evaluation and Research) has legal authority to approve substances with intent to prevent disease and they will determine efficacy, dosage for efficacy, safety at that dosage and a label of warning and caution. Other agencies have opinions and endorsements, but not legal authority to approve drugs.

The purpose of drug approval is to protect the public from harmful substances such as fluoride.

As presented above, **RCW 57.08.012** authorizes a water district board of commissioners or public to vote on fluoridation, but does not address the toxicity, efficacy or safety of fluoridation or the agency which has jurisdictional oversight to determine the efficacy, dosage, safety and label, nor does the RCW 57.08.012 designate who the prescribing practitioner, the legal intermediary must be.

Legislators in 1988 did not have the science available to approve RCW 57.08.012, and the dental lobby deceived the Legislature.

Nor does RCW 57.08.012 authorize the Board or Department to be the marketing, promotional or advertising arm for the unapproved drug.

Neither a vote by the public, vote by commissioners, vote by the Board of Health, or vote by the Legislature changes science, empirical facts, the lethality, the poisonous hazardous nature of fluoride any more than they can vote the weather to change.

I contacted the FDA and asked if sodium fluoride was an approved drug, FDA responded:

"A search of the Drugs@FDA database . . . of approved drug products and the Electronic Orange Book. . . does not indicate that sodium fluoride, silicofluoride, or hydrofluorosilicic acid has been approved under a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for ingestion for the prevention or mitigation of dental decay. . . . At the present time, the FDA is deferring any regulatory action on sodium fluoride products. . ."[1] Email from the FDA (7-22-09).

Lack of FDA CDER approval for fluoride ingestion should immediately turn off the fluoride pumps until approval is gained. Anything less, including this petition, will leave many harmed.

The FDA in 2000 responded to the Honorable Ken Calvert, House of Representatives, (See letter at Supplement #D attached) to his question #1:

"If health claims are made for fluoride-containing products. . . do such claims mandate that the fluoride-containing product be considered a drug, and thus subject the product to applicable regulatory controls?"

FDA's response:

"Fluoride, when used in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals is a drug that is subject to Food and Drug Administration (FDA) regulation . . . ."

Question #2:

"Are there any New Drug Applications (NDA) on file, that have been approved, or that have been rejected, that involve a fluoride-containing product (including fluoride-containing vitamin products). . . . "

FDA's response:

"NO NDA's have been approved or rejected for fluoride drugs meant for ingestion.. . . "

Question #3:

"Does FDA consider dental fluorosis a sign of over exposure to fluoride?"

FDA Response:

"Dental fluorosis is indicative of greater than optimal ingestion of fluoride. In 1988, the U.S. Surgeon General reported that dental fluorosis, while not a desirable condition, should be considered a cosmetic effect rather than an adverse health effect. Surgeon General M. Joycelyn Elders reaffirmed this position in 1994."

Question #4:

"Does FDA have any action-level or other regulatory restriction or policy statement on fluoride exposure aimed at minimizing chronic toxicity in adults or children?

FDA Response:

"The monograph for OTC anticaries drug products sets acceptable concentrations for fluoride dentifrices, gels and rinses (all for topical use only). This monograph also describes the acceptable dosing regimens and labeling including warnings and directions for use. FDA's principal safety concern regarding fluoride in OTC drugs is the incidence of fluorosis in children. Children under two years of age do not have control of their swallowing reflex and do not have the skills to expectorate toothpaste properly. Young children are most susceptible to mild fluorosis as a result of improper use and swallowing of a fluoride toothpaste. These concerns are addressed in the monograph by mandating maximum concentrations, labeling that specifies directions for use and age restrictions, and package size limits."

"It is difficult to get a person to understand something when their salary, profit, or reputation is dependent on them not understanding it." Upton Sinclair (paraphrased)

The fluoridation lobby[2], profiting from fluoridation, has bias in favor of fluoridation. This rule change does not prohibit fluoridation but rather states the Board's recommendation and

[2] The profitable sales of fluoride and treatment of dental flurorosis, both cosmetic and functional damage which contributes to increased chipped, broken, cracked teeth, and the resulting fillings, crowns, root canals, extractions, bridges, and implants are included, the average dentist makes millions of dollars throughout their professional lives on fluoride. The American Dental Association, dentists, sponsoring manufacturers, those with salaries (public health) to promote fluoridation, the sugar industry, pesticides, pharmaceuticals, military, and chemical companies are a few of the fluoridation lobby.

begins the process of informing the public. Water purveyors may still fluoridate water; however, this rule change should encourage them to re-evaluate their practice.

The Board's words have an impact and water purveyors and the public have trusted the Board of Health and this rule change of caution will help to protect the Board's credibility. For example, the January 6 insurrection was impacted by words from an authority and many of those trusting the authority are in jail. The Board of Health's claim that fluoridation is safe and effective is harming many, especially our most vulnerable. The Board has recently placed responsibility for fluoridation on cities and water districts. However, the Board as authority must not attempt to hide from the impact of your words.

The impact on the Board of Health of this rule change will be to remove your endorsement from your web page.

This petition builds on the science of our first 20 petitions and they should be reviewed to more fully understand the science and laws supporting this petition. Although this petition has been motivated by the current "US District Court Finding" that fluoridation is an unreasonable risk, the Board must keep in mind:

2. IQ loss is only one way to measure developmental neurotoxicity and developmental neurotoxicity is just one health risk from fluoride ingestion.

The Board would be wise to take a "global" view of all risks, total fluoride exposure from all sources and not just water. And further, to consider all subpopulations such as age, synergistic effects, race, gender, ethics, individual health, and authoritative statements from regulatory authorities worldwide. It is not the duty of the patient to prove with absolute certainty that the Board of Health is harming them, that duty lies on the authorities fluoridating, i.e. the Washington State Board of Health.

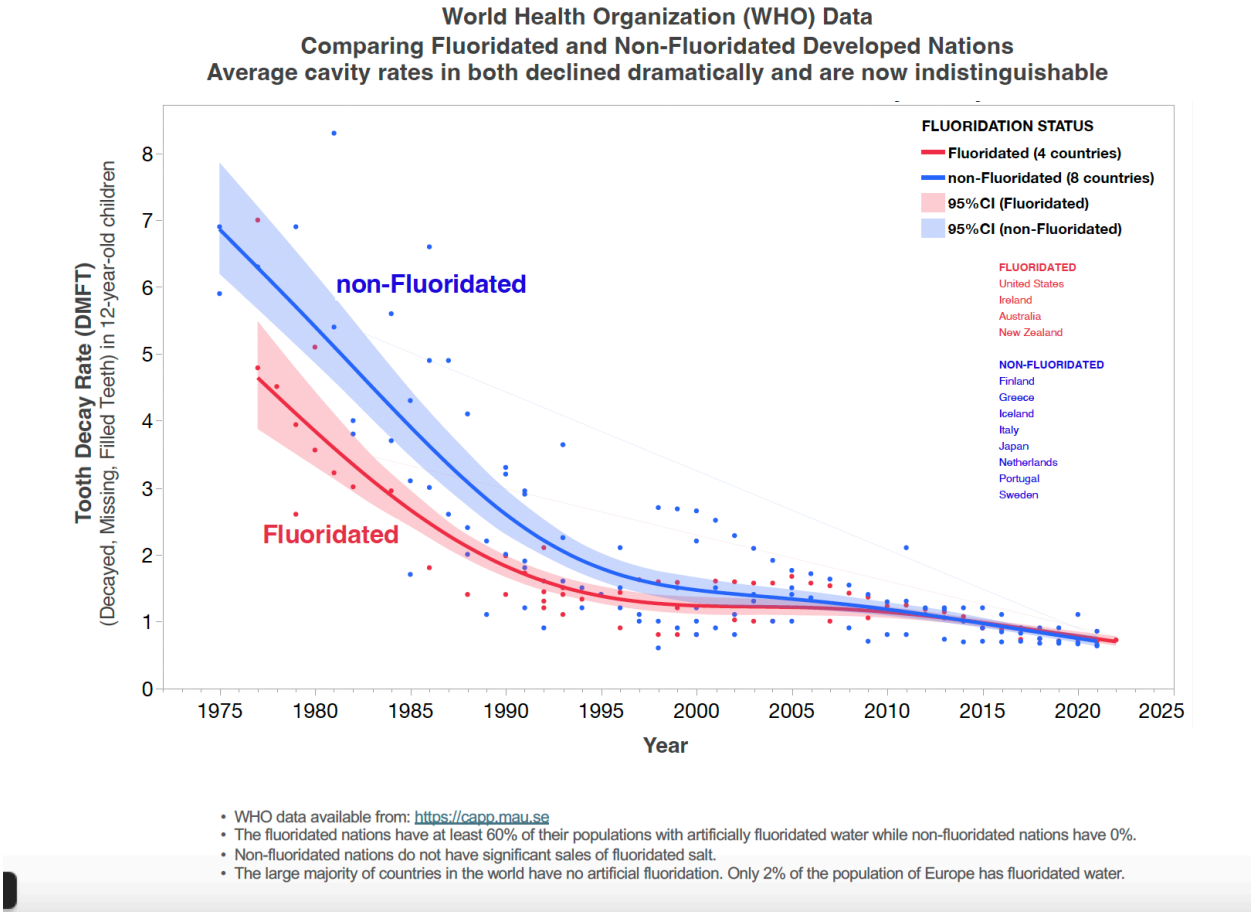
Absolute 100% proof of harm is not necessary to determine unreasonable risk of harm. Science does not operate in 100% proof. For example, we do not fully understand nor have all

the answers on how one body of matter such as the earth has an attraction, i.e. gravity. And we scientists must never anchor a belief, concept or thought in stone. Science is a moving understanding. We should always be learning. The challenge is that health care providers and authorities must make treatment decisions and policy based on the best and yet usually incomplete evidence. And we must be willing to change treatment and policy when the science changes. That is one reason professional continuing education is essential.

My mentor in dental school reminded us that "50% of what we know is wrong. The problem is we don't know which 50%." All of us must be open to learning and correcting our flawed understanding when new science is discovered.

The Board of Health, as the authority in Washington State over fluoridation, would be wise and protective of the public health by following the Court's Finding of Fact and Conclusions of Law Case No. 17-cv-02162-EMC, US District Court, Northern District of California see attached. Although the Court's ruling was the first step against the EPA, as the Toxic Substance Control Act requires, the science and conclusions apply to the Board and all. Fluoride from fluoridation, along with other sources of fluoride, is unreasonably excessive. The EPA will either stop fluoridation or the court will come back with a stronger ruling. The Board should not continue to harm infants and babies for years witing for the EPA delays. Stop promoting fluoridation as most authoritative authorities have done.

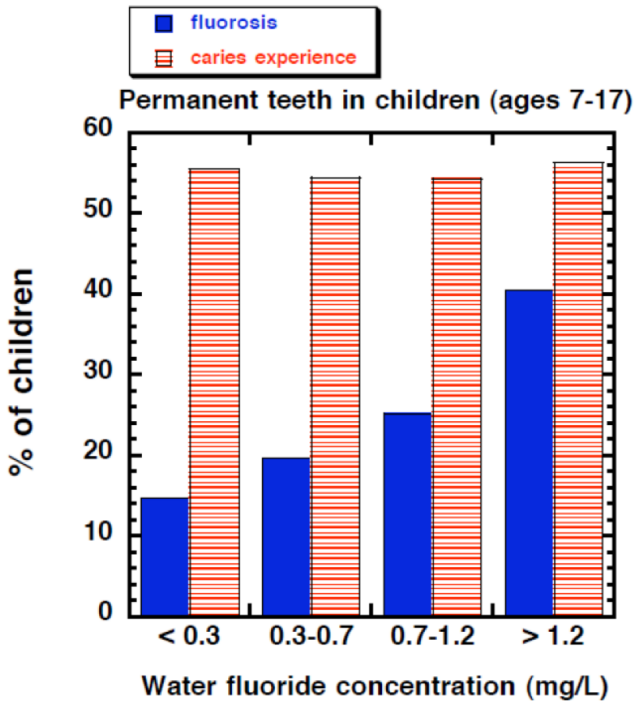
For example, see the graph below comparing cavity rates between fluoridated and non-fluoridated countries. Current evidence does not find public health benefit of fluoridation.



Then how does the fluoridation lobby come up with a 25% reduction in dental caries? As presented in previous petitions, there are several serious limitations to current research and many reasons for reduced caries. Fluoridation has been mistakenly been given credit for a reduction in dental caries.

Consider the following data published in the Journal of the American Dental Association.

Iida, H., and Kumar, J.V. 2009. The association between enamel fluorosis and dental caries in U.S. schoolchildren. JADA 140:855-862.

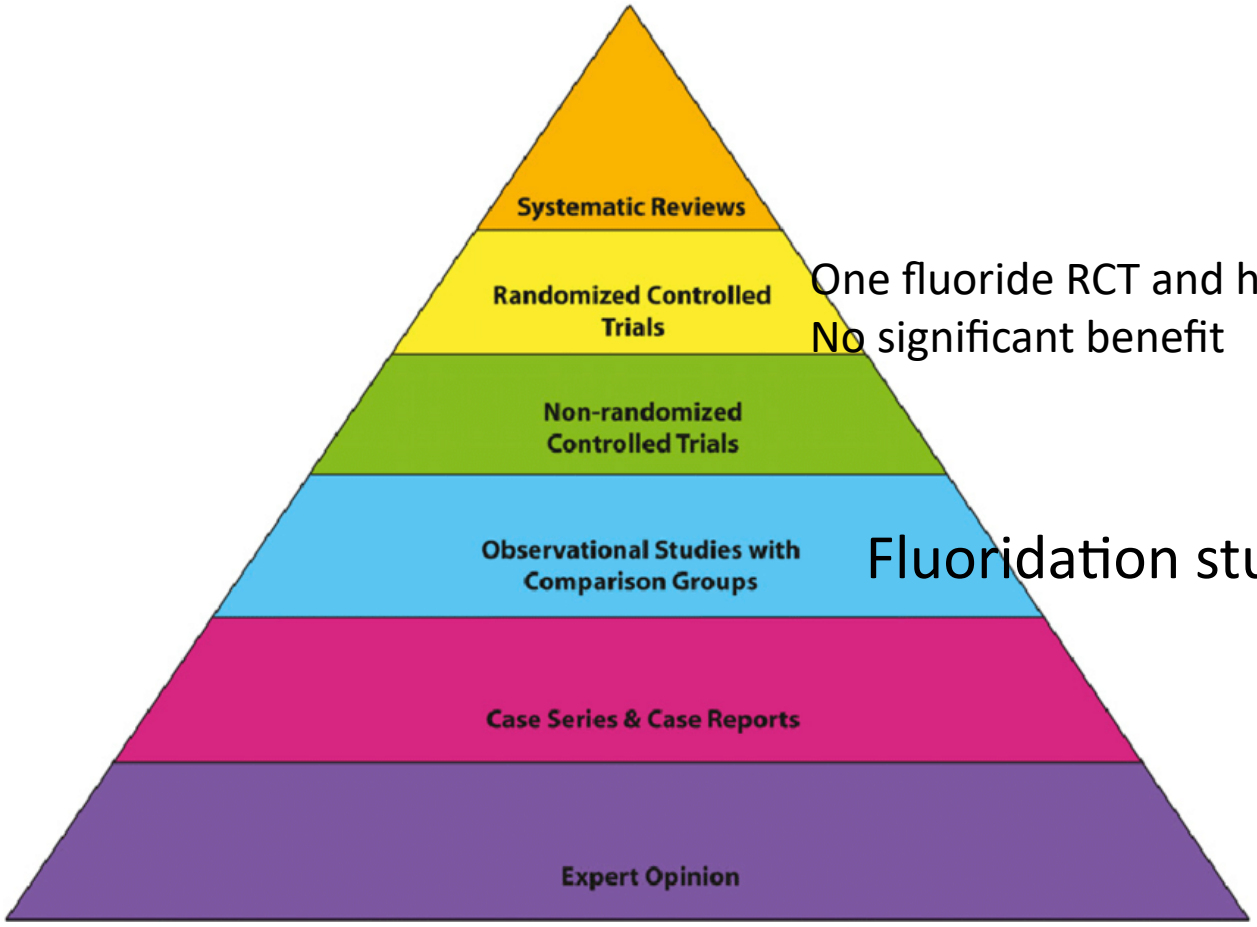


The data was published; however, this graph was produced from the published data.

When fluoride concentration goes up in the water, dental fluorosis goes up but caries has a non-significant change. Claiming a "25%" reduction in dental caries is based on historic flawed observational studies.

A short review of research quality is prudent, see the graph below. Note that the highest quality of research supporting fluoridation's benefit is "observational" which is not adequate for FDA approval. In part, evaluating risks, harm and adverse effects is not likely when only benefits with an observational study are considered. And just because two

events are observed does not mean they are related. Too many factors affect dental caries to have confidence that fluoridation is the cause for some coming into our office with fewer cavities.



By mistakenly giving credit to fluoridation for fewer cavities, public health wastes time and effort which could be spent on promoting better and safer interventions.

SCIENCE:

HOW LETHAL AND CONTAGIOUS ARE DENTAL CARIES?

Dental caries are very common, can become very painful, but are not considered highly lethal nor contagious and is usually considered elective surgery.

Fluoride is not considered an essential nutrient and has no physiologic or minimum daily requirement.

Public Health Authorities have police powers to prevent highly contagious and lethal diseases from harming and spreading throughout the public. As we have seen with the COVID vaccinations, the public has serious reservations when asked to blindly trust my public health profession, even with approved drugs for highly lethal contagious diseases.

Our point: Dental caries are not considered highly contagious or lethal. Even ingestion of pharmaceutical grade fluoride is not FDA CDER approved to mitigate (prevent) caries.

A. How Much Fluoride is Recommended? Dosage and Dose

"The recommended optimal fluoride intake for children to maximize caries prevention and minimize the occurrence of dental fluorosis is often stated as being 0.05-0.07 mg/kg/day." (Levy 1994; Heller et al. 1999, 2000).

Burt (1992) attempted to track down the origin of the estimate of 0.05-0.07 mg/kg/day as an optimum intake of fluoride but was unable to find it." National Research Council 2006 p 68. See a Review by Carton a former EPA scientist.

"Hodge (1950) studied children consuming fluoride in their drinking water. Fluoride levels of 0-14 ppm were investigated. Dental mottling was the parameter of interest. Fluoride levels of 2-10 ppm produced a linear dose- response curve (increasing mottling

with increasing dose). Fluoride levels of 0.1-1.0 ppm produced no observable effect. An assumption of 20 kg bw and 1 L/day water consumption for children was used, since the children studied were 12-14 years old. It is further assumed that a 20-kg child consumes 0.01 mg of fluoride/kg bw/day in the diet (50 FR 20164). Thus, a total intake would be approximately 0.06 mg/kg/day. " http://www.epa.gov/IRISsubst/0053.htm#oralrfd

B. As a side note, the EPA has used 0.06 mg/kg/day as their reference dose for the fluoride contaminant in water until about 2010. The NRC 2006 report on fluoride in water (covered in more detail below) told the EPA their MCL was not protective. Instead of protecting the public, the EPA changed their definition of safe, "RfD" or safe dose to 0.08 mg/kg//day, the opposite recommended by the EPA.

Changing the definition, did not change the science.

C. The fetus, infants, and those drinking more than the 90th percentile were ignored. The only possible risk considered publicly in 1950 was severe dental fluorosis. But they knew much more as evidenced by the release of classified documents from the time. Watch: the Fluoride On Trial: The Censored Science on Fluoride and Your Health | Childrens Health Defense and the NTP 2023 report on fluoride.

D. HHS ASTDR in 2003 suggested infants AI (Adequate intake) be 0.01 mg/day or 0.0014 mg/kg/day, the same as recommended in 1950. (See IOM's Table 2-1) By comparison, mean concentration of mother's milk has been reported at 0.004 mg/L for samples where fluoride was detected.

How much fluoridated water is 0.0014mg/kg/day for a 3 kg (6.6 pound) new born exclusively on formula 3 kg X 0.0014 mg = 0.0042 mg. 0.7 mg/L fluoride in water divided by 0.0042 is 0.006 L of water or about 2.9 teaspoons of food made with fluoridated water per day for the infant.

Our point: An infant needs more than 2.9 teaspoons of food a day.

Note: The Institute of Medicine's AI is "Adequate Intake" and does not reflect a safe dosage and the AI was their best guess/estimate assuming fluoride was effective.

E. Mother's milk provides about 150 to 250 times **less** fluoride than formula made with water at "optimum" fluoride concentrations. In other words, infants bottle fed formula made from fluoridated water have the greatest risk of being overdosed with fluoride.

F. What about the fetus? Although the mother's body protects their milk and infant from significant fluoride, in contrast, fluoride passes through the placenta to the fetus and has been measured in fetal brain. Although the Board claims fluoridation safety has many studies, in reality, not much research is available on the effect of fluoride to every cell, tissue, organ and system of adults, let alone the fetus.

The fetus has another source of fluoride. Human bone retains fluoride and the concentration increases with age. Ranges I've seen are 1,000 ppm (similar to toothpaste at 1,500 ppm) to 8,000 ppm reported in cancer patients.

The bone resorbs (osteoclasts) and builds up (osteoblasts) throughout life. The half life of fluoride in bone is about 20 years. In other words, if a person stopped all fluoride intake for 20 years, the fluoride concentration in the bone would be about half.

The fetus during the final trimester of life needs lots of calcium and in a deficient intake of calcium, the mother's bones resorb to provide the calcium. As the bone is broken, fluoride is released and increases the burden of fluoride on the fetus at the same time the fetal brain is developing.

The fetal brain goes through essential stages of development. If the stages are interrupted, the brain may never recover and fully develop.

For optimal development of the brain, the mother should start out with a low fluoride bone concentration.

Our petition takes this source of fluoride into consideration and we recommend the mother have low fluoride exposure starting at least 20 years prior to pregnancy.

More on this below.

G. **Too many are ingesting too much fluoride,** as evidenced by 2 out of 3 children showing a biomarker of having ingested too much fluoride, dental fluorosis, and the EPA's Dose Response Analysis for Non Cancer Effects and Fluoride Exposure Relative Source Contribution of 2010. EPA Figure 8-1 below is critical to understand and keep in mind.

The proposed mean intake/dosage is shown in mg/day represented by the blue lines for each age group. The black line is the proposed (which was adopted) RfD (maximum safe dose) for each age.

#1. Note: about a third of infants 0.5 to <1 year of age are ingesting too much fluoride. The EPA's estimate indicates about 20,000 infants at this age are ingesting too much fluoride in Washington State.

#2. Note**: Infants, birth to six months of age are omitted, ignored, unprotected.** All under six months on formula made with fluoridated water would exceed the RfD.

RCW does not exempt infants under six months of age from Board protection. New parents are busy and should not be expected to do rigorous research on the toxicology of fluoride.

#3. Note: 10% of the public drinking the most water are not included, about 330,000 directly on fluoridated water and the "halo" effect reaches many more. EPA only includes up to the 90th percentile of the public in their calculations. The EPA/Board is totally ignoring 10% of the 3.3 million drinking the most water. RCW does not exempt the Board from protecting thee people.

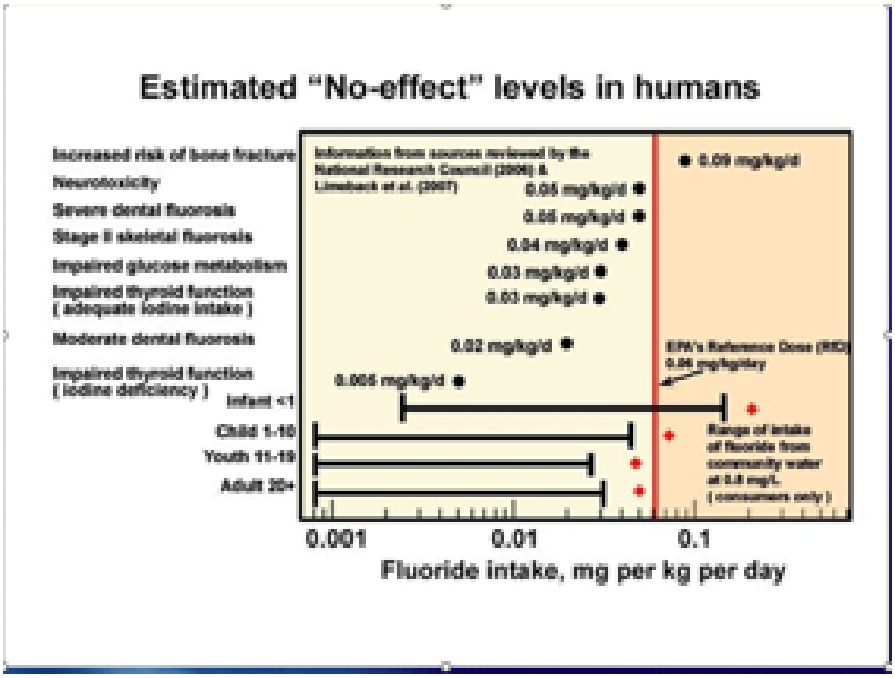
#4. The fetus is ignored. That is all of us. . . at one time. The most vulnerable infants are ignored by the EPA, unprotected. No wonder research demonstrates breast feeding is superior, lack of fluoride maybe one contributing factor.

#5. Note: the “Proposed RfD” is a third higher. EPA was proposing a “safe” dosage from 0.06 mg/kg/day to 0.08 mg/kg/day and the new higher RfD, opposite the NRC 2006 recommendation, was adopted.

#6. And also remember, for Fluoride, the EPA’s margin of error, uncertainty factor, intraspecies variation, is “0”. The EPA is certain all humans fit in the “mean” or “average.”

Our point: NRC (2006) said MCL is not safe. Instead of protecting the public, the EPA protected the contaminant and changed the definition to protect policy rather than the fetus, infants, and children. The EPA did the opposite of the NRC 2006 recommendation.

The NRC 2006 report estimated a “no-effect” level for humans about two decades ago with the following summarized evidence:

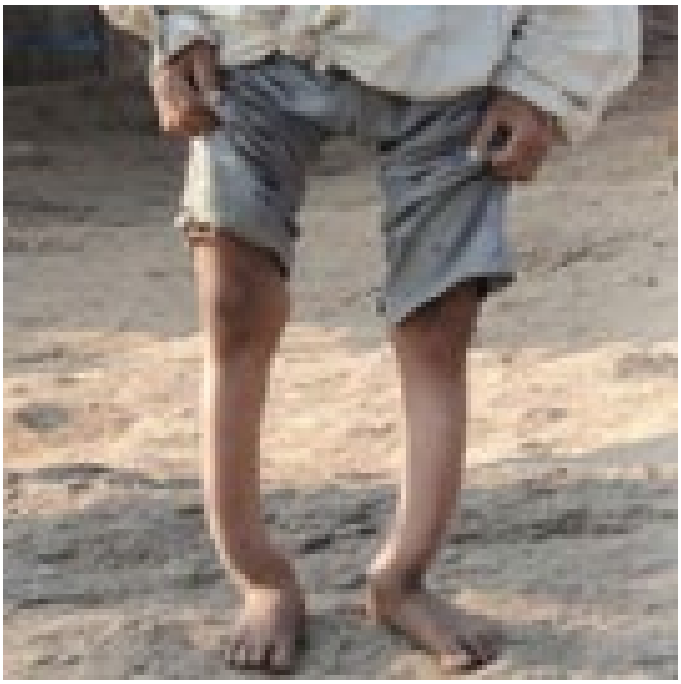


In 2006, we had fair evidence fluoridation was harming many with bone fractures, neurotoxicity, dental and skeletal fluorosis, impaired glucose metabolism, impaired thyroid function, moderate dental fluorosis and impaired thyroid function with iodine deficiency all within the range of fluoride exposure.

We brought these risks to the Board's attention in 2010 and the Board failed to protect the public. No wonder the EPA scientists said, through their union, fluoridation borders on a criminal act of governments.

EPA's THRESHOLD OF HARM

The EPA uses crippling skeletal fluorosis, like these people



or pitting of teeth like this picture as the threshold of harm from fluoride ingestion.

Harm for the EPA does not start till severe structural harm is caused.

The question the EPA fails to answer and the Board must answer*,*

"is there any harm detected before crippling skeletal fluorosis and severe dental fluorosis?"

The answer is a resounding "YES."

The EPA appears to refuse to consider any other risks from excess fluoride exposure even though they have paid researchers to provide the evidence.

Our point: The EPA must not be trusted to determine the efficacy, dosage, safety or label of fluoride ingestion. Congress charged the FDA CDER with that task. EPA does not assume responsibility for determining the efficacy of fluoridation.

RCW instructs the Board to have aesthetic concerns as a threshold and in contrast the EPA has severe harm as a threshold for concern. Again, even if the Board insists the EPA has authority to regulate and approve drugs when mixed with tap water, the Board and public must not trust the EPA to have oversight of fluoridation as a contaminant. While the EPA has 4 ppm MCLG, the rest of the world uses 1.5 ppm.

Both aesthetic and health harm is reported from fluoride

The EPA in 2011 provided "Questions and Answers on Fluoride." None of the questions and answers deal with the effectiveness or effectiveness dosage of fluoride. Silence.

EPA does not weigh the benefit/risk of fluoridation. They simply protect the contaminant so those choosing may.

HOW MUCH FLUORIDE DOES A PERSON INGEST AND HOW MUCH WATER DO THEY DRINK?

Although the concentration of fluoride in water is well controlled, the amount of water ingested is highly variable and thus the dosage is highly variable.

In effect, the Board must NOT use the "statistical mean" or the EPA's RfD or the IOM's AI as a reasonable dosage of fluoride to protect everyone.

The EPA and NRC (2006) reports the median intake of water is about 1 L/day. 90th percentile at about 2 L/day. Some drink over 10 liters/day. The NRC (2006) also reported **2-4 yr. olds ingest 0.125-0.3 mg fluoride per brushing, 2 times as much as from food and water combined and 75% more fluoride ingested for those who do not rinse.** No wonder dental fluorosis, a biomarker of excess fluoride exposure has gone up to 70% of children.,

This petition is to start protecting our most vulnerable.

Although water is most often the largest amount of individual fluoride exposure and toothpaste usually comes in second (or 1st), many other sources of fluoride affect individual exposure.

PROFUME: Ellen Connett has a brief history of a new fluoride product, Profume. Note: if a pesticide or drug has the letter "f" or letters "fu" in the name, it probably contains fluoride. The residue of fluoride on food when "Profume" is applied can be very high, although not all foods are treated. Her report includes:

". . . EPA approved two "tolerances" (permitted levels in or on food): one for Fluoride levels and the other for Sulfuryl Fluoride levels. See the tolerances approved for food by US EPA as of July 15, 2005.
. . . FAN submitted comments and formal Objections and then in 2004 and 2005 EPA approved its use with high fluoride levels on all processed food, beans, grains, flour -and much more, including a fluoride residue of 900 ppm on dried eggs!
Incredibly, after many years of hard work, in January 2011, EPA concluded that it agreed with all but one of our objections and published their proposal to phase-out sulfuryl fluoride.
According to protocol, EPA simultaneously solicited public comments on the phase-out. That was when the Dow Chemical Company, the proprietary owner of Sulfuryl Fluoride, did everything a powerful corporation can do to dissuade EPA from enacting the phase-out. They successfully lobbied Congress to add a few short sentences to the Farm Bill of 2014 that nullified the phase-out. . . ."

There are many sources of fluoride, water and dental products provide the most for many people. However, fluoride in foods such as mechanically deboned meat, tea, wine and medications, may provide significant dosages of fluoride to sub-populations.

GENERAL ANESTHESIA: especially for infants and children:

Characteristics of Anesthetic Agents Used for Induction and Maintenance of General Anesthesia
". . . desflurane (halogenated solely with fluorine halogenation increases potency and is essential to ensure nonflammability), halothane (halogenated with fluorine, chlorine, and bromine), isoflurane (halogenated with fluorine and chlorine), and sevoflurane (halogenated solely with fluorine). Halothane was the first fluorinated inhaled anesthetic that was wildly successful, rapidly displacing all other potent inhaled anesthetics. Efforts to develop other halogenated anesthetics with more of the characteristics of the ideal inhaled anesthetic agent than halothane led to the introduction of isoflurane, desflurane, and sevoflurane." Edgar

Our point: There are many sources of fluoride and each person is exposed to an unknown dosage.

LACK OF AN **UNCERTAINTY FACTOR, MARGIN OF ERROR, OR INTRASPECIES VARIATION**

In contrast, the EPA claims fluoridation is so safe for everyone that a margin of error or uncertainty factor has been set at "0," no margin of error or uncertainty factor for anyone regardless of how much water they drink, toothpaste they swallow, general anesthesia they undergo, post-harvest fumigated foods they eat, kidney function, other toxins they ingest, genetics, etc.

The Board should not be surprised that the EPA scientists ethically spoke up with their concerns:

> *"In summary, **we hold that fluoridation is an unreasonable risk**. That is, the toxicity of fluoride is so great and the purported benefits associated with it are so small - if there are any at all – **that requiring every man, woman and child in America to ingest it borders on criminal behavior on the part of governments."***

- ***Dr. J. William Hirzy, Senior Vice-President, Headquarters Union,***
- ***US Environmental Protection Agency, March 26, 2001***

WAC 246-290-220 requires the Board of Health to have a more protective threshold of aesthetic issues, rather than the EPA's skeletal or dental disability. The Board must protect the public from aesthetic concerns which are long before severe harm occurs such as structural

damage to teeth and crippling of the bones. EPA does not protect the public from harm or aesthetic concerns.

RCW 43.20.50 (1) instructs the board to "protect public health" with "safe and reliable public drinking water" but does not provide excuse for the board to recommend or promote the use of water, or to dispense an illegal drug, a prescription drug (Board of Pharmacy), or an "additive" with known aesthetic harm and without duly authorized designated oversight. Aesthetic harm is harm. If someone scratches your car, it may only be an aesthetic scratch, but it is still harm.

Our point: The statistical mean is not protective of many or most people. An uncertainty factor and margin of error must be added.

BENEFIT OF FLUORIDE INGESTION

Fluoridation is claimed to be one of public health's greatest achievements of the 20th Century. Many English speaking health associations are repeating the claim.

Systemic Fluoride has theoretical benefit while the enamel is developing. NRC 2006 & HHS HTSDR 2003 p 9

". . . fluoride prevents dental caries predominately after eruption of the tooth into the mouth, and its actions primarily are topical for both adults and children…" CDC

Keep in mind, about 60-70% of the population show signs (biomarker) of excess fluoride, dental fluorosis, prior to eruption of the tooth. CDC says benefit is primarily topical after tooth eruption.

Dental saliva has about 0.019 ppm of fluoride and contact time is minimal. Studies report toothpaste below about 1,000 ppm does not show benefit. Swishing with fluoridated water is unlikely to provide significant therapeutic value.

LACK OF KNOWN MECHANISM OF ACTION

The tooth is highly resistant to the migration of fluoride. Fluoride does not flow from the pulp through the tooth to the outside of the enamel where the caries are developing. No rational mechanism for systemic fluoride benefit has been suggested. See more below.

The FDA's determination the evidence for fluoride's efficacy is incomplete has been supported with other studies. [End note]

A closer look at **three (3) false claims** on the Board's **website**

#1. The Board claims: "For water systems serving 20,000 people or more, every $1 invested in fluoridation saves $38 in dental treatment costs." No reference provided.

Cost of **HARM** is not included and the caries reduction is disputed.

The Board's claim does not include the real-world costs of fluoridation, supplies, equipment, wages, and all manufacturing costs and avoids any costs to treat harm.

DENTAL FLUOROSIS:

I have treated dental fluorosis for more than 4 decades. I assumed the good outweighed the bad. I was wrong.

If there were no other risk than dental fluorosis, the Board should at a minimum accept our petition for rule change.

COMPLAINT NOTICE: This petition is notice and registering a complaint of dental fluorosis harm.

WAC 246-290-220 "(5) The department may accept continued use of, and proposals involving, certain noncertified chemicals or materials on a case-by-case basis, if all of the following criteria are met:

(b)There exists no substantial evidence that the use of the chemical or material has caused consumers to register complaints about aesthetic issues, or health related concerns, that could be associated with leachable residues from the material;"

Fluoride's intent of use and the Board of Pharmacy determination places fluoride as a drug and drugs are certified and approved by the FDA CDER. Fluoride chemicals are not certified as effective.

There is no dispute, fluoride causes dental fluorosis and fluoridation increases dental fluorosis. There is no dispute fluoridation increases "**aesthetic issues,"** long before severe skeletal and dental fluorosis for many, if not most, children.

The cost of all "health related concerns" has not been estimated. Just dental damage OR brain damage far exceeds possible caries mitigation.

FLUORIDATION IS NOT COST EFFECTIVE: The cost of treating dental fluorosis harm is almost never included in a cost benefit analysis.

As a treating clinician, having made many hundreds of thousands of dollars treating dental fluorosis both aesthetic and functional, I do not understand how those in ivory towers

have failed to include the cost of harm from just dental fluorosis when considering the cost effectiveness of fluoridation.

Add 3 lower IQ points resulting in lower income, and fluoridation becomes a cruel and unusual punishment for the public. My estimates based on research and clinical experience. PPPY is Per Person Per Year. Dollars adjusted to 2021.

ESTIMATED Cost to fluoridate water $3-$10 PPPY Ko and Thiessen

Averted caries (money saved)	$6.08 PPPY (Ko and Thiessen)
Dental fluorosis Treatment	$3.24-$153 PPPY (Osmunson estimate)
IQ loss (assume 3 IQ loss and $500/yr lower income/year	$2,156 to $2,552 PPPY (Osmunson estimate)

Cost of harm to just the teeth, overwhelms any estimate of cost benefit. A cost estimate resulting in savings requires the dental lobby to only use some costs to fluoridate, minimize harm, exaggerate cost savings, and ignore costs for damage, harm, risks.

Consider the study by Maupome, HMO's over 90,000 cohorts,

"Community water fluoridation was associated with reduced total and restorative costs among members with one or more visits, but the magnitude and direction of the effect varied with locale and age and the effects were generally small. In two locales, the cost of restorations was higher in nonfluoridated areas in young people (<age 18) and older adults (>age 58). In younger adults, the opposite effect was observed. The impact of fluoridation may be attenuated by higher use of preventive procedures, in particular supplemental fluorides, in the nonfluoridated areas."

Maupome squeaked out as much positive as possible and reported the cost savings was negated if only part of the costs of fluoridated materials and equipment repairs were included. No costs for treatment of functional or aesthetic harm, brain damage, thyroid damage or any other risk was included. Looking at his data and children in the non-fluoridated had lower dental costs.

"Harm is the cost, not the treatment."

Ko 2014 "*The U.S. Government states that $1 spent on CWF saves $38 in dental treatment costs. . . . Recent economic evaluations of CWF contain defective estimations of both costs and benefits. Incorrect handling of dental treatment costs and flawed estimates of effectiveness lead to overestimated benefits. The real-world costs to water treatment plants and communities are not reflected. . . .* ***Conclusions :*** *Minimal correction reduced the savings to $3 per person per year (PPPY) for a best-case scenario, but this savings is eliminated by the estimated cost of treating dental fluorosis."*

For example, the Board accepts labor costs between $7 and $9/hour while real world labor is closer to $100/hour. And no risk or harm or cost of treating harm is factored in for the Board'a claim of cost effective.

Below is a patient of mine with early functional dental fluorosis. The teeth look great, nice shiny hard enamel, just a touch of early caries. If the patient had not had fluoride, the enamel might not have been so hard and would have probably broken away sooner and pathology diagnosed sooner, and thus with less depth of caries. We call this the "fluoride bomb." Caries explodes inside before a diagnosis.

The fluoride hardens the teeth and like bones they become more brittle, like this:

Both systemic and topical fluoride excess may increase harm which has not been included in most cost benefit analysis.

I found a couple authors reporting "complete cusp fractures" and more than 300% increase in fractures in the 85% fluoridated community vs the community lacking fluoridation.

Increased fluoride exposure can increase dental caries. If there is a "sweet spot" of fluoride dosage exposure to prevent caries, the spot is not big.

#2. Another Board false claim: "Water fluoridation reduces tooth decay by about 25 percent over a person's lifetime."

A public health intervention should be measured in the public at large and the Board fails to provide the evidence for their claim. The Board's claim of benefit is consistent with the CDC Oral Health Division which is virtually in lock step and part of the fluoridation lobby. The fluoridation lobby is profiting from the disposal of fluoride in public water rather than having to pay thousands of dollars a ton to dispose of the toxic waste.

When fluoridation started a 65% reduction in dental caries was claimed and then shown not to be true. Now a 25% reduction is claimed and shown not to be true. Higher quality research, more careful review of the research does not support benefit.

If such a robust reduction in caries were in fact true (25%), we would see significant decrease in treatment and dental costs in fluoridated communities along with lower insurance payment for dental treatment. But costs are not lower in fluoridated communities and dentist/patient ration is not lower in fluoridated communities.

The Board disagrees with the FDA CDER which has not approved ingestion of fluoride reporting: *". . . there is no substantial evidence of drug effectiveness. . . ."* Drug Therapy 1975

If ingesting fluoride had benefit, the Board and/or industry (dentists) could simply get FDA CDER approval and make a profit from selling the fluoride license/patent. But there is no substantial evidence of drug effectiveness. The FDA CDER have the highest standards, are highly qualified pharmacologists and toxicologists, and have the most respect for drugs of all

federal and state agencies. The Board and dental industry constantly refuse to gain FDA CDER approval, which places the public in harm.

The Cochrane reviews are generally considered some of the best scientific evidence available. They generally rely on randomized controlled trials (RCTs), which are required for drugs. As no RCTs on fluoridation have been published (one on fluoride supplements, not finding statistical benefit), the Cochrane evaluators used lower quality research. The CDC Oral Health funded a Cochrane review of fluoridation and reported some benefit with reservations.

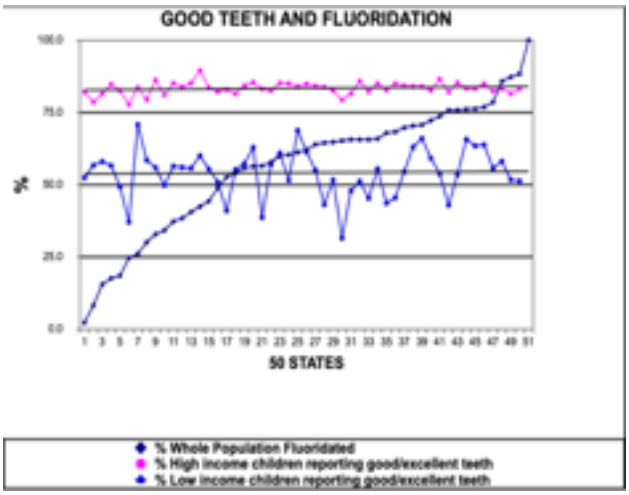
Although the Cochrane review gave cautious support for fluoridation benefit for children (at 1.0 ppm), the review did not cover ethics or risks or costs of harm or even benefit at the reduced concentration of 0.7 ppm. The Cochrane review in part, states:

"*There was insufficient information available to find out whether the introduction of a water fluoridation programme changed existing differences in tooth decay across socioeconomic groups." The Board MUST understand that their intent to protect vulnerable populations from some dental caries is not supported by science and plenty of science reports additional harm to those subpopulations (low socioeconomics, increased lead, etc)*

"*There was insufficient information available to understand the effect of stopping water fluoridation programmes on tooth decay."*

"*No studies met the review's inclusion criteria that investigated the effectiveness of water fluoridation for preventing tooth decay in adults, rather than children."*

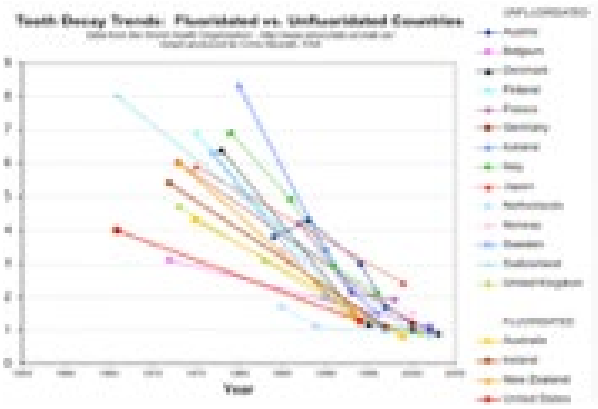
The following correlation graph was generated when I ranked the USA states on the percentage of their whole population fluoridated and reported good to excellent teeth. A 25% reduction, or any reduction, is not evident when similar SES groups are ranked.

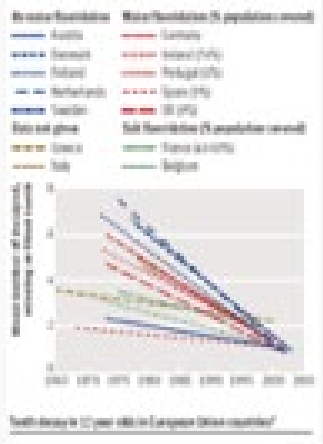


Socioeconomics is highly significant for caries prevalence, but fluoridation has no "common cause" or correlation. For 20 years as a dentist, I promoted fluoridation and thought I could see proof of benefit from fluoridation in my patients. However, after reading the research it was clear I had been comparing socioeconomics rather than fluoridation with better outcomes.

I also ranked Washington State Counties on the percentage of their population fluoridated and dental caries. The Board claims a 25% reduction in caries, but a robust reduction in dental caries is not supported by the population at large in Washington State.

Two published studies ranking WHO data on caries over about 3 decades does not report lower caries in fluoridated countries or those who use fluoride salt, graphs below.





All developed countries have reduced dental caries to low levels, regardless of fluoridation or fluoride salts. Giving fluoride credit for a reduction of caries in non-fluoridated countries is not reasonable.

To the right is a graph of caries over a longer period of time. What caused the decline in dental caries, more than half before the beginning of fluoridation? No one knows. No research on fluoridation has taken into account the huge unknown(s). We cannot give fluoridation credit for caries reduction prior to fluoridation. And any research must be suspect if it does not correct for those unknowns after fluoridation started, and no research corrects for those unknowns because they are unknown.

However, on the CDC website, a 1999 graph (right) is presented which at first glance looks impressive. Indeed, caries declined and fluoridation rates increased, but the graph is misleading by only looking at a few years. And it is not plausible that an increase of perhaps 10% of the public “randomly” fluoridated resulted in a decline from 4 DMFT (adult decayed, missing, filled teeth) to just over 1 for everyone. Simply not plausible. Even if the fluoride were dispensed to only the high-risk children individually, that would not have produced about a 70% decrease in DMFT. Fluoridation is not targeted, and started in some cities, not just for high-risk individuals.

The Journal of the American Dental Association published the following data which was graphed by Thiessen.

The red lines represent caries experience. Any difference in caries experience (red lines), at any concentration, is hard to detect and certainly not 25% as alleged by the Board. All red lines are at a similar height, although perhaps 2% lower at about 0.7 mg/L.

The blue lines represent reported dental fluorosis. As expected, an increase in fluoride concentration in water increases the damage from excess fluoride, dental fluorosis, more than double. Dental fluorosis occurs while the tooth is developing under the skin, mostly before age 6. The developing brain and other organs are developing during the same time, and would not be spared from the excess fluoride. The teeth are not the only tissues harmed, but they are the easiest to diagnose. (The NTP 2023 report and the Fluoride On Trial: The Censored Science on Fluoride and Your Health | Childrens Health Defense must be reviewed.)

Mechanism of Fluoride's Action (continued from above): Topical fluoride at high concentrations (over 1,000 ppm) has been shown to be effective (toothpaste) and is FDA CDER approved and listed in the Orange Book of approved drugs, but not fluoride ingestion.

On the other hand, to be effective, ingested fluoride must go from the pulp chamber through the calcium rich dentin and enamel to the surface of the tooth where the dental caries are forming.

Topical fluoride (like toothpaste) can get to the dental caries, ingested fluoride cannot. The tooth is highly resistant to the migration of fluoride. In the graph below, there is an increase in fluoride concentration near the pulp and at the surface of the tooth from topical fluoride, but in the middle the concentration is low. Saliva has a low concentration of fluoride and cannot have much benefit.

Think of fluoride like suntan lotion. Put it on the outside and “do not swallow.”

“**The results show that the reviewed original studies on economic evaluation of caries prevention do not provide support for the economic value of caries prevention.”**

Former Director of the National Toxicology Program (NTP) and Office of Health Assessment and Translation (OHAT) at (NIEHS) (NIH) Linda Birnbaum, Ph.D., D.A.B.T., A.T.S. is a microbiologist and board-certified toxicologist. (See endnote 1.) Her sworn testimony is critical for evaluation by the Board. VIDEO: Former NTP Director’s Statement on Fluoride Neurotoxicity — Fluoride Action Network (fluoridealert.org)

I am unaware of any fluoridation published studies of current 0.7 ppm fluoride concentration versus 1.0 ppm fluoride concentration in water**.** Even if fluoridation at 1.0 ppm were effective, that does not prove 0.7 ppm fluoride in water is equally effective. . . if at all.

In 1975 my fluoride professor suggested the possible delay in tooth eruption with fluoride ingestion was adequate proof of fluoridation’s benefit. Or could be simply a delay in diagnosis.

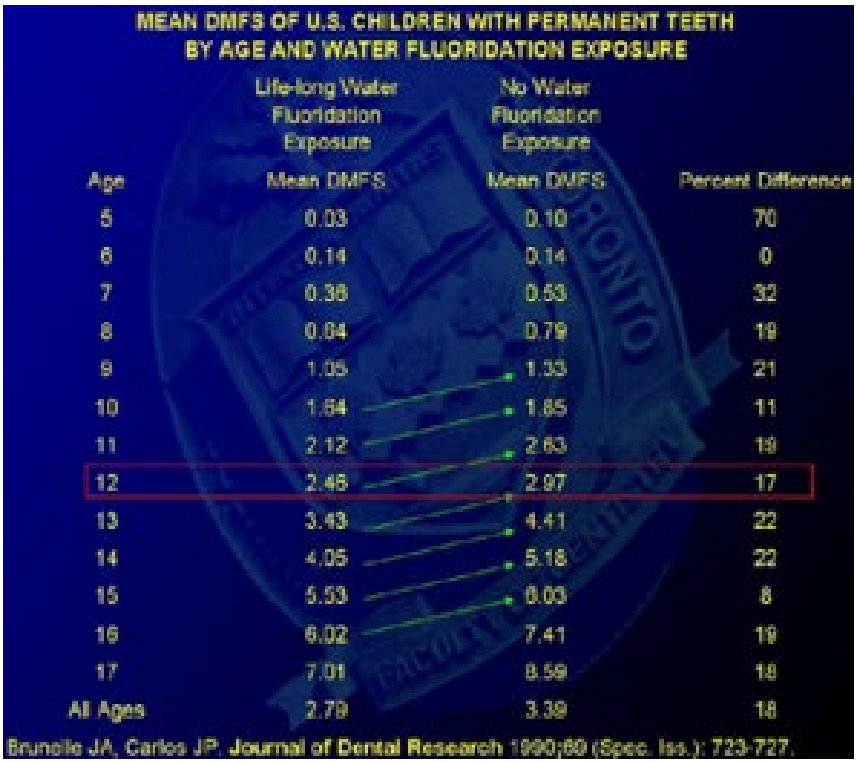
If the tooth is protected under the skin from food and harm for just a few months, researchers evaluating caries by a child’s age, will be comparing different amount of time the teeth have been exposed to the environment. Of course, the concern that a delay in tooth eruption could cause a delay or premature development of other systems and organs must be considered. But we dentists only look at structures of the mouth.

Not all studies agree there is a delay in tooth eruption with fluoridation; however, the evidence should be considered, see data below, the first from 1957, the second from 1990.

Newark, Delaware

	Decayed-Missing-Filled Teeth		Percent Caries-Free Children	
Age	After Fluoridation	Before Fluoridation	After Fluoridation	Before Fluoridation
6	0.2	1.1	88.8	54.8
7	1.1	2.3	44.9	22.7
8	1.7	2.9	31.5	8.6
9	2.8	3.7	11.3	4.8
10	3.4	4.9	6.4	7.5

Reference: Journal American Dental Assoc. Vol. 54, June 1957
Note: 1-year DELAY in DMF per child. At age 10 FEWER caries-free children AFTER fluoridation than BEFORE.



Even when the CDC reported the CDC does not determine the safety of fluoridation and the CDC along with the ADA warned infants should NOT have fluoridated water for formula and drinking, the Washington Department of Health responded in disagreement, reporting: *"Parents and health providers should weigh the balance."* Seriously? Does the Department of health expect parents to review the literature when the Department doesn't have the experts or money to review the evidence? The Board cannot trust the Department.

And the Board doesn't want to weigh the balance, but they expect parents and health providers to do what the Board and Department fails to do. I doubt the legislature expected the public to weigh the complex scientific data. Silence speaks.

#3. The Washington Board of Health also claims: "***Community water fluoridation is safe. After 65 years in service and hundreds of studies it continues show its safety."***

"*Over the past 75 years, health authorities have declared that community water fluoridation-a practice that reaches over 400 million worldwide-is safe. Yet, studies conducted in North America examining the safety of fluoride exposure in pregnancy were nonexistent. . . .*

The tendency to ignore new evidence that does not conform to widespread beliefs impedes the response to early warnings about fluoride as a potential developmental neurotoxin. Evolving evidence should inspire scientists and health authorities to re-evaluate claims about the safety of fluoride, especially for the fetus and infant for whom there is no benefit.*"*

Scientists have avoided the controversies of fluoride exposure. Publishing controversial research is a career killer. As one of my mentors would say, tongue in cheek: *"Never let a rational thought interfere with a lucrative procedure."*

If fluoridation were the only source of fluoride, fluoridation would not be safe.

If teeth were the only tissues of the body, fluoridation would not be safe. Fluoride ingestion may or may not have benefit, but fluoride without dispute harms teeth both

aesthetically and functionally. The dental lobby only considers benefit to teeth and discounts harm as only aesthetic.

Endorsements of benefit, are not science, empirical evidence, facts or evidence of safety.

No rational scientist would claim we have safety studies on the physiologic function of the cells, organs, all systems of the human body throughout all stages of life. If fluoride ingestion were in fact safe, we could make billions of dollars if we got authorized regulatory approval.

In effect, the Board is assuming endorsements by unauthorized agencies, industry, claiming or "declaring" benefit and safety are factual evidence. "The absence of safety evidence is not proof of safety." However, the absence of evidence is also not proof of harm.

CAUTION: When discussing risk, the dental lobby often:

1. Avoids "total fluoride exposure." and assumes no other fluoride intake than fluoridated water.

2.. Ignores subpopulations such as the fetus, infants, children, those allergic to fluoride, those medically compromised, etc.

3. Assumes everyone fits in the statistical median.

4. Assumes everyone drinks the median amount of water.

5. Assumes fluoride ingestion actually prevents dental caries.

6. Discounts any research or experts raising questions on the safety of fluoride exposure and fluoridation.

7. Although safety may involve hundreds or thousands of variables, research attempts to narrow the variables down to 2, if possible. Any research claiming, for example, "No dose-related anomalies in internal organs were observed in fetuses," is an anatomical, not physiologic start for safety research and incomplete.

Not everyone fits in the “statistical mean” (similar to the average person). For example, perhaps the “statistical mean” shoe size is 9.5. Toddlers and children would not be comfortable in those huge shoes, most adults would find the shoe size too small or too large.

The ”statistical mean” is important for generalizations but lacks applicability for all humans at all ages.

THE FETUS:

Consider the fetus. There are no safety studies determining the safety of fluoride exposure for the developing fetus and there is no known benefit to the fetus.

Here are the two most vulnerable cells starting the dividing and growing process of life, the mother is probably not aware. Fluoride passes from the mother through the placenta to those cells.

As the fetus grows, there is no developed blood brain barrier to protect the fetus’s developing brain from toxins. In time, the fetus drinks the amniotic fluid, the developing kidneys excrete some of the fluoride and we assume half stays in the fetus, mostly bones. The fetus drinks the fluoride fluid/urine, concentrating the fluoride mostly in the bones, but also potentially affecting every cell, system, organ of their body, anatomy and physiology.

Excess fluoride is “recycled.”. Yet the Board, without research, blindly assumes the fetus is not affected.

A few NTP quotes:

“Our meta-analysis confirms results of previous meta-analyses and extends them by including newer, more precise studies with individual-level exposure measures. The data support a consistent inverse association between fluoride exposure and children’s IQ.”

When an unnamed government fluoridation proponent claimed:

“The data do not support the assertion of an effect below 1.5 mg/L…all conclusory statements in this document should be explicit that any findings from the included studies only apply to water fluoride concentrations above 1.5 mg/L.”

The NTP responded:

*"**We do not agree with this comment**…our assessment considers fluoride exposures from all sources, not just water…because fluoride is also found in certain foods, dental products, some pharmaceuticals, and other sources… Even in the optimally fluoridated cities…individual exposure levels…suggest widely varying total exposures from water combined with fluoride from other sources."*

"Discussion
The results of this meta-analysis support a statistically significant association between higher fluoride exposure and lower children's IQ. The direction of the association was robust to stratification by risk of bias, sex, age group, timing of exposure, study location, outcome assessment type, and exposure assessment type. There is also evidence of a dose-response relationship. Although the estimated decreases in IQ may seem small, research on other neurotoxicants has shown that subtle shifts in IQ at the population level can have a profound impact on the number of people who fall within the high and low ranges of the population's IQ distribution [50-54] For example, a 5-point decrease in a population's IQ would nearly double the number of people classified as intellectually disabled [55]."

The NTP's meta-analysis raises confidence that fluoride is indeed harming the developing brain at very low dosages. And as with the early reports of lead's harm, further more precise, focused study on lead confirmed rather than disputed the earlier studies.

Urine fluoride concentration of 3 mg/L representing about half a standard deviation would expect to have a child with about 7 IQ less. A mom drinking 3 liters per day at 0.7 mg/L would ingest about 2.1 mg of fluoride just from water, more than the NTP hazard level. Additional fluoride from other sources could easily push the mom over 3 mg fluoride per day.

Figure 2 of the NTP meta-analysis, page 19 presented below:

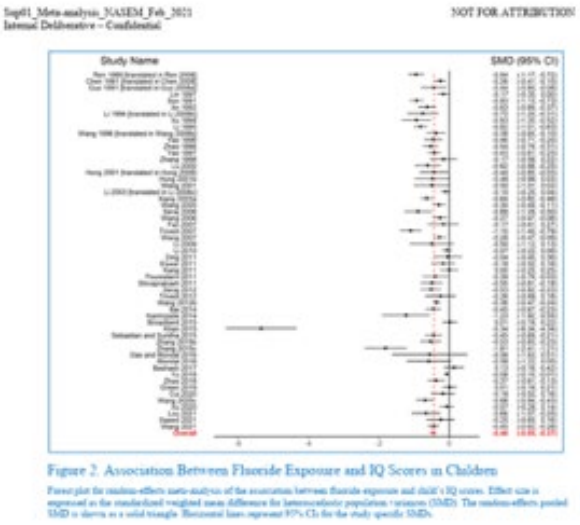


Figure 2. Association Between Fluoride Exposure and IQ Scores in Children

Forest plot for random-effects meta-analysis of the association between fluoride exposure and child's IQ scores. Effect size is expressed as the standardized weighted mean difference for between-exposure population comparisons (SMD). The random-effects pooled SMD is shown as a solid triangle. Horizontal lines represent 95% CIs for the study-specific SMDs.

Research seems to mostly be around -0.46 mean overall standard deviation which represents about 7 IQ point loss. (1 SMD is 15 IQ points)

However, there are several methods to “measure” brain and developmental damage and several types of IQ. **Performance IQ is reported at 8.8 IQ loss, full scale 4.4 IQ loss from the amount of fluoride the Board recommends be added to our water.**

Two studies in Australia, evaluating the same area did not find IQ loss. One did not control for fluoride supplements in the non-fluoridated cohorts. Low exposure levels are more difficult to see.

One study not reporting IQ loss is promoted by the fluoridation lobby and is implausible, an outlier.

Future studies evaluating will likely report with further clarity more serious harm for individuals at various socioeconomic levels, various races, ages, and gender (males), more sensitive to fluoride various types of IQ loss and greater harm.

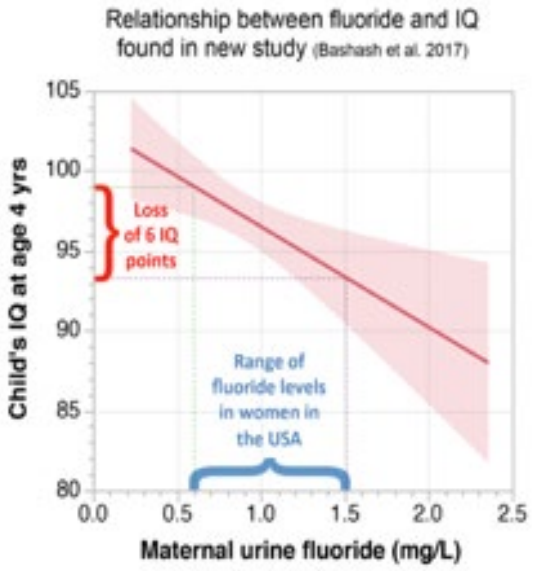
After the 2006 NRC report suggesting possible brain damage from fluoride, I wanted to personally see if I could confirm the NRC 2006 report. I ranked the 50 states and plotted their reported mental retardation (intellectual disability) and percent of the whole population

fluoridated, a correlation study. The trend, more than doubling of “mentally retarded,” about 7-8 IQ loss, (half a standard deviation) raised concerns and is supported with more recent published studies including the NTP meta-analysis.

A doubling of the reported “développemental disability ” would represent close to 7 IQ point loss. The EPA uses just one IQ loss as their threshold, but not for fluoride exposure.

When other confounders are considered for ranking the 50 states, socioeconomics is slightly lower in the more fluoridated states. Socioeconomics and IQ are related, to a degree.

Bashash in 2017, reported about 4 IQ loss at 0.7 ppm fluoride in water.



The Board’s claim and recommendation that fluoridation is safe is factually, empirically unsupported, and is not based on current scientific evidence, law or logic. For almost two decades the Board has been given quality research, but not in as high a scholarly presentation

as the NTP monograph. The Board's claim of efficacy and safety is wrong and harming the public.

Hearing a Board member say, "*but we are not supposed to have to review science"* makes the term "Board of Health" at best a rubber stamp of industry. Either health is based on science or trust. Trust is not empirical and factual evidence. HHS Rachael Lavine's blocking of release of the evidence did not change the science or protect the public health and neither does the Board of Health promote health if they avoid and evade science.

Fluoridation at 0.7 mg/L is not reported safe. **"A Benchmark Dose Analysis for Maternal Pregnancy Urine-fluoride and IQ in children . . . 0.2 mg/L"** Grandjean 2022.

Dr. Granjean is a professor at both Harvard and the University of Southern Denmark and has published hundreds of studies on the toxicity of chemicals. You will hear from equal but not more accomplished research scientists in the field of toxicology.

INFANT MORTALITY

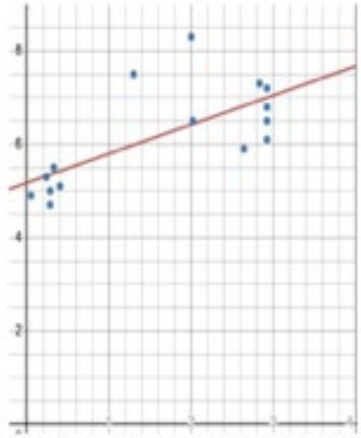
It should be noted that IQ is simply one method of measuring brain damage and developmental toxicity from fluoride. I once again ranked the states on the percentage of their whole population fluoridated and plotted infant mortality per 10,000 live births, about 15% increase in infant death. See graph below.

Infant mortality is complex. The most common causes of infant mortality in the United States are birth defects, preterm birth and low birth weight, sudden infant death syndrome (SIDS), pregnancy complications, accidents and toxins such as lead and the evidence fluoride contributes to infant mortality is growing.

Do not assume these other birth defects are not increased with fluoridation, we simply have not looked.

Data on infant mortality is readily available and the USA has a poor record compared to other countries trying to keep babies alive during their first year of life. Confounding factors need to be considered.

A pilot study using U.S. Government records reported an increase in infant mortality (perhaps 20% increase) and premature births in fluoridated communities with soft water, such as Seattle water. See Figure 3 below.



In other words, add fluoride to soft Seattle water and infants have greater chance of harm and death.

Research reporting an increase in infant mortality in fluoridated communities is growing. The concern for miscarriage and preterm birth must be considered. Although more study is always wanted, the Board must weigh the evidence with judgment.

Even if there were a decrease in dental caries from fluoridation, a potential increase in infant mortality far out-weighs potential alleged benefit to teeth.

I recently compared six highly fluoridated countries paired economically (individual GDP) with six countries without fluoridated water or salt. Comparing these countries results in

almost 30% increase in infant mortality. Six countries is a small sample and fluoride is certainly not the only contributing factor for infant mortality.

The trend is serious and in keeping with the developmental neurotoxicity of fluoride.

Preterm birth is defined as birth prior to 37 weeks of pregnancy. Damage to cerebral white matter is the most commonly recognized pathology of prematurity, say neuroscientists at the Dana Alliance for Brain Initiatives. “Babies born preterm face a range of potential neurological disruptions … The earlier the birth, the greater the risk that these disruptions will produce devastating and potentially life-long cognitive, behavioral, and socialization deficits.”

Hart reported, in 2009,

“Domestic water fluoridation was associated with an increased risk of PTB (9545 (6.34%) PTB among women exposed to domestic water fluoridation versus 25278 (5.52%) PTB among those unexposed, p < 0.0001)). This relationship was most pronounced among women in the lowest SES groups (>10% poverty) and those of non-white racial origin. Domestic water fluoridation was independently associated with an increased risk of PTB in logistic regression, after controlling for age, race/ethnicity, neighborhood poverty level, hypertension, and diabetes.”

The fluoridation lobby demands proof of harm. One public health dentist told me he would promote fluoridation until it was proven people were falling over in the street dead from fluoridation.

These possible deaths of our babies, our future, our most vulnerable who the Board is NOT protecting. Harming their brains and possibly their deaths, certainly harming teeth and bones, without proof of efficacy. The Board members, and all of us who did and still do promote the ingestion of additional fluoride without patient consent are or have been complicit. And I to promoted fluoridation and was complicit in the harm.

The Board makes no sense to medicate everyone with a highly toxic poison, to be regulated as a drug but not, with 2 out of 3 children showing a biomarker of excess fluoride exposure, with doubtful benefit for a non-contagious, almost never lethal disease, without a

doctor's supervision, of a known legend drug, and the Board expects the patient to provide absolute proof of harm and any dosage.

DENTAL FLUOROSIS:

What is the most common disease in children? Frequently the answer is dental caries. Actually, dental fluorosis caused in part by the Board of Health's promotion of fluoridation is the most common disease in children.

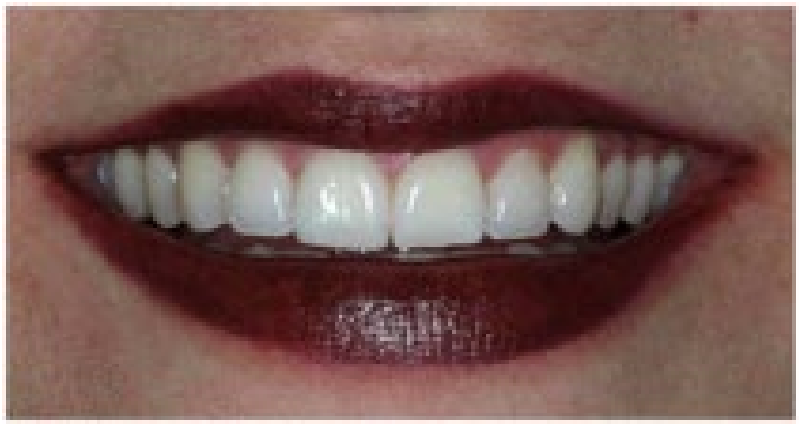
Among children aged **6 to 8 years, over half (52%)** have had a cavity in their primary (baby) teeth. Children from low-income families are twice as likely to have untreated cavities as higher-income children. Among adolescents aged **12 to 19, more than half (57%)** have had a cavity in their permanent teeth. However, NHANES (National Health and Nutrition Examination Survey) 2015-2016 data reported about 70% of children and adolescents have dental fluorosis, a biomarker of excess fluoride ingestion prior to age 8. Although some have suggested that is not plausible, no refuting data has been presented.

A US Environmental Protection Agency (EPA) study+ (1987)., funded by the EPA with fluoride concentrations between 1.0-4.0 mg/L evaluated the cost of treating dental fluorosis, finding:

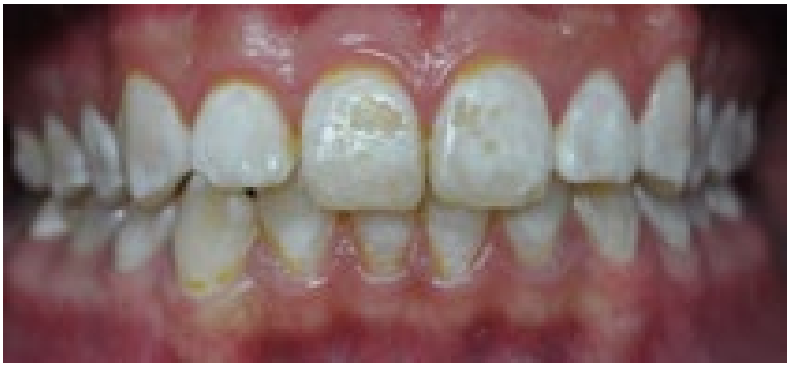
"*A mean cost for all consultants shows that the estimated costs for restoring function exceeds the cosmetic costs in all categories except the minimum later costs. This represents a new finding and raises an issue that has been overlooked or ignored by previous investigators and the profession. i.e . that repair of the cosmetic discoloration was the only cost involved; or that repair of dysfunction was never considered to be a problem."*

Not every case of dental fluorosis will be repaired, but "Damage is the cost, not the repair."

Patient #1 (below) has a normal ideal smile with healthy teeth, no fluorosis detected, and was raised predominantly on mother's milk and no formula was made with CWF.



For comparison, Patient #2, (below) diagnosed with Dean's Fluorosis Index of 4, " discrete or confluent pitting," moderate to severe dental fluorosis and has functional damage with chipped, pitted and warn teeth.



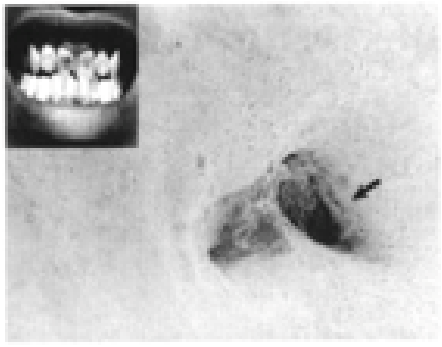
Patient #2 was raised mostly on formula made with fluoridated water. Mom was confident fluoridated toothpaste was not swallowed and no fluoride supplements ingested. In this case, 24 teeth had cosmetic and functional dental fluorosis damage.

A study of adolescents at 12 years of age reported 52% at a fluoride concentration in water of 0.7 mg/L (CWF concentration) had dental fluorosis. Of the subjects, 95% wished to remove the spots. In contrast to the subjects reported concern, only 14.5% had professionally diagnosed mild, moderate or severe dental fluorosis. The contribution of fluoridation to total exposure is authority administered iatrogenic harm. Beauty is in the eye of the beholder rather than the eye of the diagnostician.

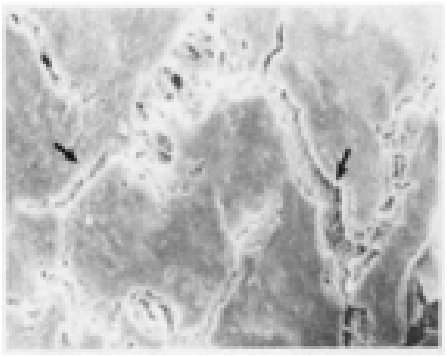
Stopping fluoridation is the simplest, easiest, quickest method to reduce total individual fluoride excess exposure. Sources from pesticides, post-harvest fumigants, medications and swallowing toothpaste are not as easy for the Board to influence.

The cosmetic effects and functional effects of dental fluorosis along with the lack of cost benefit when the cost of harm is included, has been presented here previously.

Dental Fluorosis Viewed by Scanning Electron Microscope



Pits in enamel



Cracks and Fissures in enamel

The Board must not dismiss aesthetic concerns as “lacking harm.” All potential harm must be included in judgment of any benefit/risk from fluoride ingestion.

FLUORIDE AND CANCER

It has been said, “Genes load the cancer gun, environment pulls the trigger.”

One of the problems with cancer research is latency. It can take 20 to 30 years after exposure to the primary etiology.

Dean Burk PhD, head of cytochemistry, National Cancer Institute 1974, Co-discoverer of Biotin compared 10 large unfluoridated cities as controls 6.3 million people with 10 large cities which became fluoridated between 1952-1956, 11 million people

Cancer Deaths/100,000

year	1940	1950	1970
CDRo (+F)	154.2	186.3	222.6
CDRo (- F)	153.5	183.6	188.8

Representing a 31.3/100,000 increase in deaths/yr after 15-20 years of fluoridation

When I was in Dental School, we were shown a critical review of Burk’s work which suggested two significant numbers were transposed and no adverse effect had been shown.

However, we were not told that Burk had responded with evidence that the critics had transposed the numbers and he was indeed correct.

Burk’s study stopped when the unfluoridated cities became fluoridated.

Although NRC (2006) committee reviewing fluoride for the EPA was charged with “non-cancer” effects of fluoride, fluoride increasing cancer is biologically plausible and a connection between fluoride and osteosarcoma and focuses on three facts:

1. Most fluoride is stored in bones, particularly during growth spirts.

Fluoride is a mutagen

1. Fluoride stimulates osteoblasts which "increases the risk for some of the dividing cells to become malignant." (NRC 2006) See a timeline link.

Some history on fluoride and cancer as reported by Ellen Connett in 2014. See endnote

Osteosarcoma: A timeline by Ellen Connett.

The principal finding of NTP's study, performed by Battelle Columbus Laboratories, was a dose-dependent increase in osteosarcoma (bone cancer) among the fluoride-treated male rats.

However, despite the fact that

1) the cancer occurred in the target organ (bone) for fluoride accumulation, 2) the increase in bone cancer was statistically-significant, 3) the doses of fluoride were low for an animal cancer study, and 4) NTP acknowledged it is "biologically plausible" that fluoride could induce bone cancer,

the NTP ruled that the study only provided "equivocal evidence" that fluoride was the cause of the cancer.

According to a 1990 report by Bette Hileman in *Chemical & Engineering News*: "A number of government officials who asked not to be identified also have told C&EN that they have concerns about the conclusions of the 1990 NTP study. They, too, believe that fluoride should have been placed in the "some evidence" category, in part because osteosarcoma is a very rare form of cancer in rodents."

In 2000, Dr. J William Hirzy testified before the U.S. Senate's Subcommittee on Wildlife, Fisheries and Drinking Water on behalf of the EPA's professional union, NTEU Chapter 280, requesting an independent review of NTP's cancer bioassay study.

In 2002, the World Health Organization (Fluorides: Environmental Health Criteria 227) advised scientists to take NTP's finding seriously. According to the WHO: "Such a (dose-

dependent) trend associated with the occurrence of a rare tumour in the tissue in which fluoride is known to accumulate cannot be casually dismissed."

In 2005, the Environmental Working Group "asked the National Toxicology Program (NTP) of the National Institutes of Health (NIH) to list fluoride in tap water in its authoritative Report on Carcinogens, based on its ability to cause a rare form of childhood bone cancer, osteosarcoma, in boys."

In addition to increased bone cancer, the NTP study also found increases in rare liver cancers, oral cavity cancers and thyroid cancers among the fluoride-treated rats. The NTP ruled, however, that the cancers were not related to the fluoride treatment – despite reaching "statistical significance" in some of NTP's analyses.

"We observed that for males diagnosed before the age of 20 years, fluoride level in drinking water during growth was associated with an increased risk of osteosarcoma, demonstrating a peak in the odds ratios from 6 to 8 years of age. All of our models were remarkably robust in showing this effect, which coincides with the mid-childhood growth spurt. For females, no clear association between fluoride in drinking water during growth and osteosarcoma emerged." (Bassin EB, et al. 2006. Age-specific fluoride exposure in drinking water and osteosarcoma (United States). Cancer Causes & Control 17(4):421-8. May.)

Chester Dougles published a small study, 20 controls too small for reliable conclusions, the controls were older (average 41 years and cases averaged 18 years) and fluoride concentration of cases were about 300% higher than average fluoride concentrations for normal bone at 18 years of age. Douglas reported no association between fluoride and osteosarcoma.

Chester Dougles published a small study, 20 controls, too small for reliable conclusions, the controls were over twice the age, representing about 400% higher bone fluoride concentrations for age paired. Douglas not only used controls averaging more than double the age, but compared the osteosarcoma cases with other bone tumors as controls. Clearly, the data was collected to protect fluoride exposure. Just because the concentration of fluoride in bones of osteosarcoma patients and bone tumor patients are similar, does not mean the fluoride concentration in bone is safe. Using bone tumors as controls cooked the evidence.

As Editor of the Colgate report, Douglas received significant funding from Colgate.

FLUORIDE'S IMPACT ON THYROID HORMONES: THYROID, PARATHYROID, PANCREAS, PINEAL, ADRENAL, GONADS, ANTERIOR AND POSTERIOR PITUITARY, AND PLACENTA. See Attachment #E Thyroid

Fluoride is considered an endocrine disruptor. As little as 2 to 5 mg/day can reduce most patient's thyroid activity. (Galletti & Joyet 1958)

For easy estimation, half of fluoride exposure is from fluoridated water. At 0.7 mg/L, **about six glasses of fluoridated** water along with the "average" fluoride from other sources can be expected to reduce thyroid hormones. But wait, many are ingesting more fluoride from other sources and drinking more than six glasses of water.

We in public health tell those with thyroid harm from fluoride that their obesity, diabetes, and malaise is their fault, when in fact we are contributing to their health problems, idiopathic harm.

"We found that higher levels of fluoride in drinking water provide a useful contribution for predicting prevalence of hypothyroidism. We found that practices located in the West Midlands (a wholly fluoridated area) are nearly twice as likely to report high hypothyroidism prevalence in comparison to Greater Manchester (non-fluoridated area)." Peckham S, et al. (2015). *Journal of Community Health & Epidemiology* (see study)

The NRC 2006 review of fluoride's effect on the thyroid gland should be reviewed. See pages 224-236. *"Fluoride in Drinking Water: A Scientific Review of EPA's Standards."*

For a more referenced and scientific discussion of Fluoride's effects on the endocrine system, aggravated by iodine deficiency, effects on goiters, impact on thyroid hormones and excess iodine intake, see here and pubmed.gov.

FLUORID AND LEAD

*Blood **Lead** levels in Fluoridated areas 2X higher for Whites and 6X higher for Blacks*

Prevalence of children with elevated blood lead (PbB>10mug/dL) is about double that in non-fluoridated communities. When FSA was added "lead concentrations spiked to over 900 ppb. Effects of fluoridation and disinfection agent combinations on lead leaching from leaded-brass parts.

FLUORIDE'S IMPACT ON BONES

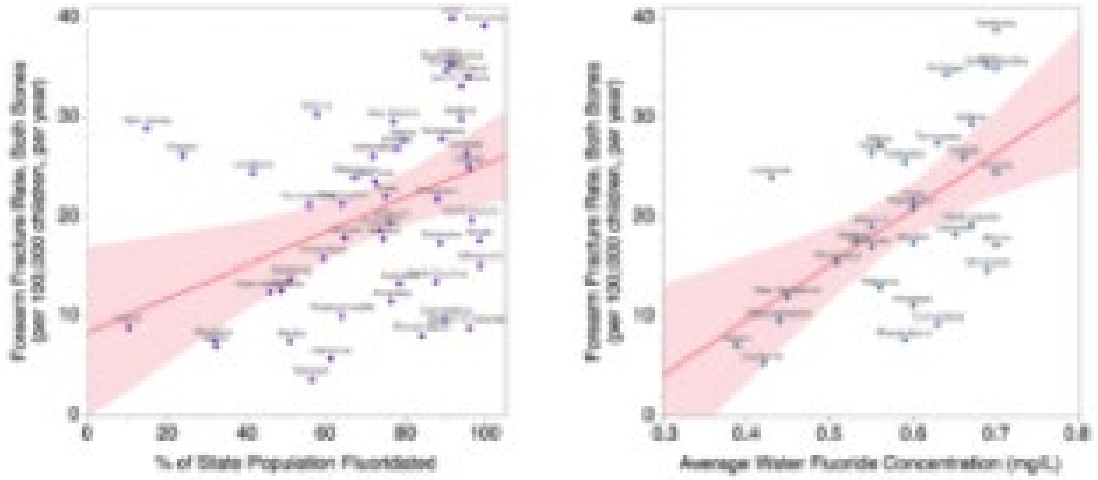
Skeletal fluorosis is an undisputed effect of excess fluoride. The EPA uses severe skeletal fluorosis as a threshold of concern for excess fluoride exposure. But pathology from fluoride starts much sooner than crippling skeletal fluorosis.

Fluoride seemed like a good idea for bones and teeth to make them harder, until studies such as Helte et al raised concerns of bone fracture and osteoarthritis, arthritic like symptoms, stiffness and pain in joints. BAO 2003 (Luo 2012; Su 2012; Bao 2003; Savas 2001; Tartatovskaya 1995; Chen 1988; Xu 1987)

A recent study in the Journal of the American Academy of Orthopaedic Surgeons by Lindsay et al. Results:

"Positive correlations were found between the percentage of state water fluoridation and fracture rates for both bone forearm fracture (BBFFx) and femur fracture. Fluoride levels had positive correlations with fracture rates for all fracture types. Increased fracture rates were found between states in the highest quartiles of percentage of state water fluoridation and fluoride water levels for supracondylar humerus fracture and BBFFx."

The study reported at 0.7 mg/L fluoride in water, rates of child forearm fractures were 2.5 times greater than in states with the lowest average concentration, which was about 0.4 mg/L as illustrated here:



(quality of graph is also hard to read in the Journal, but the data is also printed)

Based on the preponderance of the evidence, fluoridation is not safe and effective.

Sincerely,

Bill Osmunson DDS MPH

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

FOOD & WATER WATCH, INC., et al.,

Plaintiffs,

v.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY, et al.,

Defendants.

Case No. 17-cv-02162-EMC

FINDINGS OF FACT AND CONCLUSIONS OF LAW

I. INTRODUCTION

In 2016, Congress amended the Toxic Substances Control Act ("TSCA"), empowering United States citizens to petition the Environmental Protection Agency ("EPA") to consider whether a chemical presents an unreasonable risk of injury to health. *See* Pub. L. No. 114-182, 114th Congress (Frank R. Lautenberg Chemical Safety for the 21st Century Act) (the "Act"). The Act addresses the modern day reality that "human beings and the environment are being exposed each year to a large number of chemical substances and mixtures," 15 U.S.C. § 2601(a)(1), and that, "among the many chemical substances and mixtures which are constantly being developed and produced, there are some whose manufacture, processing, distribution in commerce, use, or disposal may present an unreasonable risk of injury to health or the environment," *id.* § 2601(a)(2).

To this end, under TSCA, as amended by the Act ("Amended TSCA"), a citizen is entitled to judicial review of the EPA's denial of the citizen's petition, wherein a court considers whether the chemical poses an unreasonable risk *de novo*, *i.e.*, without deference to the EPA's decision. *See id.* § 2620(b)(4)(B). Amended TSCA sets up a system of judicial review that is remarkably different from the usual scope of judicial review of administrative actions under the Administrative Procedure Act, which confers substantial deference to administrative agencies. *See id.* Under Amended TSCA, the Court owes no deference to the EPA in assessing the risk posed by chemical substances. *See id.* If the Court finds anew that the chemical at issue presents

an unreasonable risk, it then orders the EPA to engage in rulemaking regarding the chemical. *See id.* The EPA is afforded in the first instance the authority to respond; regulatory actions can range from requiring a mere warning label to banning the chemical. *See id.* § 2605(a)(1)-(7). The EPA, in short, has options. *See id.*

The issue before this Court is whether the Plaintiffs have established by a preponderance of the evidence that the fluoridation of drinking water at levels typical in the United States poses an unreasonable risk of injury to health of the public within the meaning of Amended TSCA. For the reasons set forth below, the Court so finds. Specifically, the Court finds that fluoridation of water at 0.7 milligrams per liter ("mg/L") – the level presently considered "optimal" in the United States – poses an unreasonable risk of reduced IQ in children. It should be noted that this finding does not conclude with certainty that fluoridated water is injurious to public health; rather, as required by the Amended TSCA, the Court finds there is an unreasonable *risk* of such injury, a risk sufficient to require the EPA to engage with a regulatory response. This order does not dictate precisely what that response must be. Amended TSCA leaves that decision in the first instance to the EPA. One thing the EPA cannot do, however, in the face of this Court's finding, is to ignore that risk.

A. Context

Water fluoridation has a long history in the United States and has been a source of political discord, at times. *See, e.g.*, Dkt. No. 429-3, Trial Ex. 13 at 15.[1] In 1975 the EPA recommended adding fluoride to water, with an optimal level up to 1.2 mg/L for its dental health benefits. *Id.* at 16. Between 1981 and 1984, fluoride's association with adverse effects including osteosclerosis, enamel fluorosis, and psychological and behavioral problems was contested. *Id.* at 17-18. Still, as of 1986, up to 1.2 mg/L water fluoridation was considered optimal, and the maximum level was 4 mg/L. *Id.* at 14-18. After evidence increasingly established fluoride's connection to adverse

[1] Controversy over fluoridation of drinking water has even found its way into Hollywood. *See* DR. STRANGELOVE (Columbia Pictures 1964) (General Ripper characterizing fluoridation as a threat to our "precious bodily fluids" and "the most monstrously conceived and dangerous communist plot we've ever had to face").

effects, including severe enamel fluorosis, risk of bone fracture, and potential skeletal fluorosis, recommended levels were lowered in 2006. *Id.* at 10. Community water fluoridation has since continued at levels believed to be safe for its dental health benefits. At present, fluoride is added to tap water in the United States, with an optimal level of 0.7 mg/L.

However, scientific evidence has increasingly identified a link between fluoride exposure and adverse cognitive effects in children (reduced IQ). Accordingly, Plaintiffs exercised their power under Amended TSCA and petitioned the EPA to consider whether fluoride in drinking water presents an unreasonable risk of injury to human health. Notwithstanding the growing and robust body of evidence indicating an association between fluoride intake and cognitive impairment in children, the EPA denied Plaintiffs' petition. Plaintiffs filed suit in this Court, arguing that the EPA was wrong and that community water fluoridation at 0.7 mg/L (the "condition of use") poses an unreasonable risk of injury to human health.

B. Summary

To succeed in a suit brought under the Amended TSCA, Plaintiffs must prove, by a preponderance of the evidence, that a risk of injury to human health is present and that such risk is unreasonable. For a risk to be present, Plaintiffs must show that some segment of the United States population is exposed to the chemical at issue at levels that either exceed, or are too close to the dosage at which the chemical presents a hazard.[2] The reasonableness of the risk is informed by several factors, including *inter alia*, the size and susceptibility of impacted populations, severity of the harm at issue, and the frequency and duration of exposure.

There is little dispute in this suit as to whether fluoride poses a hazard to human health. Indeed, EPA's *own expert* agrees that fluoride is hazardous at some level of exposure. And ample evidence establishes that a mother's exposure to fluoride during pregnancy is associated with IQ decrements in her offspring. The United States National Toxicology Program ("NTP") – the federal agency regarded as experts in toxicity – undertook a systematic review of all available literature near the time of publication considering whether fluoride poses cognitive harm,

[2] The level at which the chemical presents a hazard is known as the "hazard level." The level at which human populations are exposed to the chemical is known as the "exposure level."

reviewing 72 human epidemiological studies considering this question. The NTP concluded that fluoride is indeed associated with reduced IQ in children, at least at exposure levels at or above 1.5 mg/L (*i.e.*, "higher" exposure levels). And notwithstanding inherent difficulties in observing effects at lower exposure levels, explained in further detail below, scientists have observed a statistically significant association between fluoride and adverse effects in children even at such "lower" exposure levels (less than 1.5 mg/L).

Notwithstanding recognition by EPA's expert that fluoride is hazardous, the EPA points to technicalities at various steps of the risk evaluation to conclude that fluoride does not present an unreasonable risk. Primarily, the EPA argues the hazard level and the precise relationship between dosage and response at lower exposure levels are not entirely clear. These arguments are not persuasive.

Importantly, the chemical at issue need not be found hazardous at the exposure level to establish that a risk is present under Amended TSCA. Instead, the EPA requires a *margin* exist between the hazard level and exposure level to ensure safety; if there is an insufficient margin then the chemical poses a risk. The trial evidence in this case establishes that even if there is some uncertainty as to the precise level at which fluoride becomes hazardous (hazard level), under even the most conservative estimates of this level, there is not enough of a margin between the accepted hazard level and the actual human exposure levels to find that fluoride is safe. Simply put, the risk to health at exposure levels in United States drinking water is sufficiently high to trigger regulatory response by the EPA under Amended TSCA.

To this end, as mentioned previously, the NTP compiled and analyzed all relevant studies it could find and concluded that, at least at dosages of 1.5 mg/L or higher, fluoride is associated with reduced IQ in children. Subsequently, toxicology experts endeavored to put a finer point on the impact of fluoride on children's IQ at "lower" exposure levels, *i.e.*, those below 1.5 mg/L, and conducted a pooled benchmark dose analysis to define the precise hazard level of fluoride. For reasons described below, this pooled benchmark dose analysis benefited from increased statistical power relative to the NTP's assessment due to its methodology (*i.e.*, the benchmark dose analysis used individualized, continuous data, while the NTP assessment did not, due to quantity and variety

of studies the NTP reviewed in that assessment). The pooled benchmark dose analysis concluded that **a 1-point drop in IQ of a child is to be expected for each 0.28 mg/L of fluoride in a pregnant mother's urine**. This is highly concerning, because maternal urinary fluoride levels for pregnant mothers in the United States range from **0.8 mg/L** at the median and **1.89 mg/L** depending upon the degree of exposure. Not only is there an insufficient *margin* between the hazard level and these exposure levels, for many, the exposure levels *exceed* the hazard level of 0.28 mg/L.

The EPA challenges, for a variety of reasons, whether this 0.28 mg/L hazard level (measured in maternal urinary fluoride) is appropriate for this risk evaluation. The EPA argues, among other things, that the hazard and exposure levels should not be expressed in maternal urinary fluoride because that metric reflects total fluoride exposure – not just exposure resulting from drinking fluoridated water from one's community. Fluoride may also be ingested through, *e.g.*, tea, fish, toothpaste, and commercial food and beverage made with fluoridated water. Nonetheless, the risk analysis should consider the *additive* effect of the chemical under the subjected condition of use (here, fluoridated community drinking water), especially where, as here, the fluoridated drinking water is a significant (and likely primary) contributor to aggregate exposure to fluoride. Indeed, the Amended TSCA, expressly contemplates that the *aggregate* exposure to a chemical will be considered when conducting a risk assessment. *See* 15 U.S.C. § 2605(b)(4)(F). In this sense, maternal urinary fluoride is not just an acceptable metric, it is highly useful in assessing the real-world end result of exposure from drinking fluoridated water along with other sources.

Even if urinary fluoride were not the appropriate metric in assessing health risk, or even if the toxicologically determined hazard level of 0.28 mg/L were deemed insufficiently substantiated, evidence in the record still establishes with little doubt that fluoridated drinking water presents a risk of injury to health. Using a highly conservative estimate of the hazard level of 4 mg/L measured in drinking water fluoride (well above the 1.5 mg/L identified as hazardous to children by the NTP) based on the consistent and repeated observation of adverse effects summarized in the NTP's assessment, a risk is present. There is little dispute that there is a

statistically significant association between IQ decrements in children and fluoride concentration levels at 4 mg/L.

The EPA's default margin of error requires a factor of 10 between the hazard level and exposure level due to variability in human sensitivities. Put differently, only an exposure that is below 1/10th of the hazard level would be deemed safe under Amended TSCA, given the margin of error required. Here, an even greater margin (100x) is owed because the methodology (which yields the 4 mg/L hazard level) uses the lowest observed adverse effect level ("LOAEL"); this methodology adds an additional level of uncertainty (and hence the application of a 100x rather than 10x margin). But even if only the default 10x margin is required, the safe level of fluoride exposure would be 0.4 mg/L (4 mg/L (hazard level) divided by 10). The "optimal" water fluoridation level in the United States of 0.7 mg/L is nearly double that safe level of 0.4 mg/L for pregnant women and their offspring.

In all, there is substantial and scientifically credible evidence establishing that fluoride poses a risk to human health; it is associated with a reduction in the IQ of children and is hazardous at dosages that are far too close to fluoride levels in the drinking water of the United States. And this risk is unreasonable under Amended TSCA. Reduced IQ poses serious harm. Studies have linked IQ decrements of even one or two points to *e.g.*, reduced educational attainment, employment status, productivity, and earned wages. Indeed, the EPA recognizes that reduction of IQ poses a serious community health issue. Moreover, highly susceptible populations are impacted, including over two million pregnant women and babies, a number far exceeding population size the EPA has looked to in determining whether regulatory action was warranted in other risk evaluations (*i.e.*, 500 people or less).

Thus, the Court finds Plaintiffs have met their burden in establishing, by a preponderance of the evidence, that community water fluoridation at 0.7 mg/L presents an unreasonable risk of injury to health under Amended TSCA and that the EPA is thus obliged to take regulatory action in response. The Court does not in this order prescribe what that response should be.

II. BACKGROUND

A. Factual and Procedural Background

1. Section 6(a) of the Toxic Substances Control Act ("TCSA") requires Defendant United States EPA[3] to regulate the use of certain chemical substances that it determines pose an unreasonable risk to health or the environment. 15 U.S.C. § 2605(a).

2. The TSCA was initially passed in 1976, codified at 15. U.S.C. § 2601 *et seq.* Congress enacted the original TSCA, motivated by findings that "human beings and the environment are being exposed each year to a large number of chemical substances and mixtures," 15 U.S.C. § 2601(a)(1), and that, "among the many chemical substances and mixtures which are constantly being developed and produced, there are some whose manufacture, processing, distribution in commerce, use, or disposal may present an unreasonable risk of injury to health or the environment," *id.* § 2601(a)(2).

3. On June 22, 2016, the Frank R. Lautenberg Chemical Safety for the 21st Century Act was signed into law. *See* Pub. L. No. 114-182, 114th Congress. The Act amended the TSCA. *See id.*

4. Amended TSCA requires the EPA to regulate the use of certain chemical substances that pose an unreasonable risk of harm to health or the environment. 15 U.S.C. § 2605(a). If a chemical substance poses a risk of unreasonable harm, the EPA must promulgate a rule imposing one or more of a wide range of possible requirements. *See id.* § 2605(a)(2). Specifically, the rule adopted by the EPA must impose one or more of the following: a prohibition, restriction, or limitation of the amount of such substance that may be manufactured, processed, or distributed in commerce, *id.* § 2605(a)(1); a prohibition, restriction, or limitation upon such manufacture, processing, or use in connection with "a particular use" or "a particular use in a concentration in excess of a level specified by the Administrator," *id.* § 2605(a)(2); labeling requirements for such substance, *id.* § 2605(a)(3); record-keeping requirements for manufacturers or processors of the substance, *id.* § 2605(a)(4); commercial-use regulations, *id.* § 2605(a)(5); disposal requirements,

[3] Scott Pruitt, Administrator of the EPA is also named as a Defendant in his official capacity. Dkt. No. 372 (Supplemental Complaint ("FAC")) ¶ 1.

id. § 2605(a)(6); and/or notice requirements, *id.* § 2605(a)(7). The EPA may limit the application of such requirements to "specified geographic areas." *Id.* § 2605(a).

5. After the Act's amendment to TSCA, there are three pathways to obtain a Section 6(a) rule regulating a chemical: (1) an EPA's *sua sponte* designation of a chemical as "high priority," resulting in a finding that it presents an unreasonable risk,[4] 15 U.S.C. § 2605(c)(1); (2) an EPA risk evaluation of a chemical at the request of a manufacturer, *see id.* § 2605(b)(4)(C)(ii), which results in a finding of unreasonable risk; or (3) a successful Section 21 "citizen petition," *see id.* §§ 2620(a), (b)(3).

6. A Section 21 citizen's petition to the EPA to initiate Section 6(a) rulemaking is to be granted if the petitioner demonstrates a chemical substance poses an unreasonable risk of harm. *Id.* § 2620(a). Amended TSCA provides judicial review of a denial of such a petition to the EPA. *Id.* § 2620(b)(4). In contrast to the typical standard of judicial review under the Administrative Procedure Act, in considering a Section 21 citizen's petition, the Court considers the issue *de novo*; no deference is owed under to the EPA's denial of the petition. *See id.* § 2620(b)(4)(B).

7. Plaintiffs in the instant suit are non-profit advocacy organizations and associations and individuals suing on behalf of themselves and their children. FAC ¶ 1.[5]

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[4] To elaborate, Section 6(b) requires the EPA to perform its own evaluations of the risks posed by certain chemical substances. 15 U.S.C. § 2605(b)(4)(A). To this end, the EPA is required by Amended TSCA to designate chemical substances as "high-priority" or "low-priority" based on a risk screening process. *See id.* § 2605(b)(1). "High-priority" chemicals are those that "may present an unreasonable risk to health or the environment because of potential hazard and a potential route of exposure under the conditions of use." *Id.* § 2605(b)(1)(B)(i). A "low-priority" substance, in contrast, is one that the Administrator "concludes, based on information sufficient to establish . . . does not meet the standard" to be designated a high-priority substance. *Id.* § 2605(b)(1)(B)(ii). Once the EPA has designated a chemical substance "high-priority," it must initiate a Section 6(b) "risk evaluation." *Id.* §§ 2605(b)(3)(A), (4)(C)(i). A risk evaluation is not required for a "low-priority" substance. *Id.* § 2605(b)(1)(A). The EPA must pursue these risk evaluations at a minimum pace established by statute: within 6 months, risk evaluations must be underway on at least 10 substances drawn from the 2014 TSCA Work Plan for Chemical Assessments, *id.* § 2605(b)(2)(A); within three and a half years, risk evaluations must be underway on "at least 20 high-priority substances," *id.* § 2605(b)(2)(B); a new high-priority substance must be designated anytime a risk evaluation has been completed (other than those commenced at the request of a manufacturer), *id.* § 2605(b)(3)(C); and, generally, the EPA must continue designating substances and conducting evaluations "at a pace consistent" with its ability to meet the 3-year deadline to complete each risk evaluation, *id.* § 2605(b)(2)(C).

[5] Specifically, Plaintiffs are Food & Water Watch, Fluoride Action Network, and Moms Against Fluoridation ("Organizational Plaintiffs"), and Audrey Adams individually and on behalf of Kyle

8. On November 22, 2016, a group of organizations and individuals including Plaintiffs petitioned the EPA under Section 21 of Amended TSCA to regulate the fluoridation of drinking water supplies under Section 6(a). Dkt. No. 117-1, Ex. 1. Plaintiffs asserted that the ingestion of fluoride poses an unreasonable risk of neurotoxic harm to humans including IQ loss and other neurotoxic effects, particularly for infants, young children, and other subpopulations standing at elevated risk. *Id.*

9. On February 17, 2017, the EPA denied Plaintiffs' petition. Dkt. No. 28-1; 82 Fed. Reg. 11,878 (Feb. 27, 2017).

10. After the EPA denied Plaintiffs' petition, Plaintiffs filed this suit seeking judicial review of the EPA's denial pursuant to 15 U.S.C. § 2620. Dkt. No. 1 (Complaint ("Compl.")) ¶¶ 106-07.

11. Beginning on June 8, 2020, after the parties engaged in fact and expert discovery, the Court held a seven-day bench trial, which included expert testimony regarding the state of the scientific research on fluoride neurotoxicity ("Trial Phase 1"). *See* Dkt. Nos. 219, 238.

12. On August 10, 2020, the Court stayed the case due to concerns about Plaintiffs' standing and developments in scientific literature regarding fluoride. *See* Dkt. No. 262. The Court explained that the stay would allow EPA to consider new scientific studies published after EPA's denial of Plaintiffs' administrative petition and allow the Court to consider the imminent publication of the NTP systematic review "Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects." *Id.* at 3-5.

13. Thereafter, Plaintiffs filed a supplemental administrative petition for reconsideration to the EPA. Dkt. No. 270.

14. EPA again denied the petition. Dkt. No. 278.

15. On October 28, 2022, the Court granted Plaintiffs' motion to lift the stay and take the case out of abeyance, finding that Plaintiffs had standing and that there was new evidence that scientific developments had changed, including the fact that the aforementioned NTP's systematic review

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Adams, Kristen Lavelle individually and on behalf of Neal Lavell, and Brenda Staudenmaier individually and on behalf of Ko Staudenmaier and Hayden Staudenmaier ("Individual Plaintiffs") (collectively "Plaintiffs" or "FWW"). FAC ¶ 1.

had since undergone three additional rounds of peer review resulting in a near-final version of the document. *See* Dkt. No. 319 at 2-5.

16. Beginning on January 31, 2024, the Court held a second, ten-day bench trial ("Trial Phase 2") which included expert testimony regarding the updated state of the scientific research on fluoride neurotoxicity. *See* Dkt. Nos. 407-413, 422-424.

B. Relief Requested

17. Plaintiffs contend that the addition of fluoridation chemicals to drinking water at levels recommended in the United States (0.7 mg/L) presents an unreasonable risk of neurological harm when assessed under the risk evaluation framework that EPA uses under the Amended TSCA. Dkt. No. 378 (Joint Pretrial Conference Statement ("PTC Statement")) at 1-2.

18. Plaintiffs seek a declaration that fluoridation of water at 0.7 mg/L presents an unreasonable risk of injury to health and injunctive relief requiring the EPA to initiate the rulemaking proceeding requested by Plaintiffs in their Petition to the EPA. PTC Statement at 2. Specifically, Plaintiffs seek an order requiring the EPA to "initiate a proceeding for the issuance of a rule," but the order would not "prescribe the content of a rule or the outcome of such a proceeding." *Id.* In short, rulemaking would be left in the first instance to the EPA.

19. Plaintiffs also seek recovery of their costs of suit and reasonable fees for attorneys and expert witnesses, as permitted by 15 U.S.C. § 2620(b)(4)(C), and such further relief that the Court may deem just and proper. PTC Statement at 2.

C. Statutory Standard and Burden

20. Plaintiffs bear the burden of proving, by a preponderance of the evidence, that the chemical substance at issue presents an "unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation under the conditions of use." 15 U.S.C. § 2620(b)(4)(B)(ii). The Court considers the issue *de novo*; no deference is owed under TSCA to the EPA's denial of the petition. *Id.* § 2620(b)(4)(B).

21. If the Court determines that petitioner has met its burden, demonstrating unreasonable risk by a preponderance of the evidence, the Court "shall order the Administrator to initiate the action

requested by the petitioner." *Id.* Specifically, EPA would be directed to engage in rulemaking pursuant to Subsection 6(a) of TSCA wherein the EPA would consider applying one or more methods to neutralize the risk, ranging from requiring a notice be provided to the public of risks (*i.e.*, utilizing a warning label or disseminating a public advisory), *see id.* § 2605(a)(7), to prohibiting manufacturing or distributing the chemical at issue, *see id.* § 2605(a)(1).

D. Standing

22. The Court previously held, in lifting its stay on proceedings and allowing the case to proceed to phase two of trial, that Plaintiffs had standing. Dkt. No. 319 at 2-3. The Court reaffirms this finding. At a minimum, Organizational Plaintiff FWW has standing in a representative capacity. An association has standing to sue on behalf of its members when: "(1) its members would otherwise have standing to sue in their own right; (2) the interests it seeks to protect are germane to the organization's purpose; and (3) neither the claim asserted nor the relief requested requires the participation of individual members in the lawsuit." *Am. Unites for Kids v. Rousseau*, 985 F.3d 1075, 1096 (9th Cir. 2021) (citing *Hunt v. Wash. State Apple Advert. Comm'n*, 432 U.S. 333, 343 (1977)). Each prong is satisfied:

a. In its previous order, the Court found that Jessica Trader, a member of FWW, has standing. Dkt. No. 319 at 2-3. Article III standing requires: (1) an injury-in-fact that is concrete and particularized and actual or imminent, (2) a causal connection between the injury and the conduct complained of, and (3) probable redressability. *Id.* (citing *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 560–61 (1992)). Ms. Trader became pregnant in November 2020 and gave birth in August 2021 (during the pendency of this lawsuit) and testifies that she plans to have several more children; she has taken steps to effectuate this goal including discontinuing her use of birth control medication. Dkt. No. 430-18, Trial Ex. 66 (Declaration of Jessica Trader) ¶¶ 5-8 & Ex. A. Ms. Trader has incurred costs and taken measures to avoid fluoridated water during her first pregnancy and continues to do so to protect her future children. *Id.* ¶¶ 9-16. As the Court previously explained, neurodevelopmental harm from fluoride exposure to Ms. Trader's child and future children is concrete and imminent; there is a credible causal connection between that neurodevelopmental harm and EPA's regulation of fluoride exposure or lack thereof; and the harm

would likely be redressed if EPA were to pass a rule prohibiting the addition of fluoridation chemicals to public drinking water supplies. Dkt. No. 319 at 2-3. Moreover, the EPA has conceded that standing would be satisfied by "someone who is an expectant parent who – who could be consuming fluoridated water, and, and – that could have potential effects on the baby she's carrying in utero. It could be a potential – a parent, someone with very young children." *Id.* (quoting Dkt. No. 133 at 14:9-17). Ms. Trader is such an individual. Thus, the first prong is satisfied; a member has standing.

b. As for the second prong, there is no dispute that FWW's mission is to ensure "clean, safe water for drinking" which it views as a "fundamental right that should be afforded to all people," and to "advocate for more government responsibility in protecting our drinking water resources." Dkt. No. 430-8, Trial Ex. 52 (Second Amended Declaration of Scott Edwards, Co-Director of FWW) ¶¶ 4, 6. Thus, the interests at stake in this suit – regulation of water fluoridation to protect public health – are germane to the organization's purpose. *See, e.g.*, *Am. Unites for Kids*, 985 F.3d at 1097 (explaining that where there is a close connection between the organization's mission and the interests of others it seeks to represent, organizational standing is appropriate); *G.G. by & through A.G. v. Meneses*, 638 F. Supp. 3d 1231, 1241 (W.D. Wash. 2022) (finding nonprofit disability rights organization had associational standing to bring claims on behalf of disabled members as rights of people with developmental disabilities was an interest the organization sought to protect).

c. The third prong is a "judicially fashioned and prudentially imposed" question, as opposed to a constitutional requirement of standing. *Or. Advocacy Ctr. v. Mink*, 332 F.3d 1101, 1109 (9th Cir. 2003). This suit is appropriately brought by a representative plaintiff; analysis under Amended TSCA focuses on scientific evidence substantiating the alleged risk to public health rather than focusing upon anecdotal evidence from plaintiffs. *See* ¶¶ 26-95; *accord Laborers Int'l Union Loc. 261 v. City & Cnty. of San Francisco*, 2022 WL 2528602, at *6 (N.D. Cal. July 6, 2022) (explaining that unlike claims seeking damages which require individualized proof, claims seeking injunctive relief are well-suited for adjudication by organizational plaintiff) (citing *Comm. for Immigrant Rts. of Sonoma Cnty. v. Cnty. of Sonoma*, 644 F. Supp. 2d 1177,

1194 (N.D. Cal. 2009)). The harm redressable herein is precisely the kind of harm that Amended TSCA is designed to address. For these reasons, the Court reaffirms its finding that requirements of standing have been satisfied.

III. FINDINGS OF FACT

23. To discern whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation, under the conditions of use, under TSCA section 6, the EPA engages in a TSCA risk evaluation process. 15 U.S.C. § 2605(b)(4); 82 Fed. Reg. 33,726 (July 20, 2017); Dkt. No. 434-18, Trial Ex. 544.

24. The TSCA risk evaluation is comprised of a risk assessment and risk determination. *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 653:22-655:11 (Barone). The National Research Council (NRC, 1983) has defined risk assessment as including the following components: (1) hazard assessment (including hazard identification and quantitative dose response analysis); (2) exposure assessment; and (3) risk characterization. A risk evaluation under the Amended TSCA includes the three aforementioned steps of a risk assessment, as well as a fourth and final step: (4) a risk determination. *See id.* The "risk assessment" is the scientific technical evaluation, encompassing the first three parts of this process, resulting in an unbiased, transparent, and reproducible description of the risk. *See id.* The "risk determination" is the final step of the risk evaluation process, where EPA summarizes its findings and determines whether a chemical does or does not present unreasonable risk. *See id.*

25. The following is a summary of the risk evaluation steps. *See id.*; *accord* 15 U.S.C. § 2605(b)(4)(F)(i)-(v).

a. At step 1 (hazard assessment) the EPA determines if a chemical is considered hazardous and if so, the EPA endeavors to determine the point at which the chemical becomes hazardous ("point of departure" or "hazard level"). *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 653:22-655:11 (Barone); *accord* 15 U.S.C. § 2605(b)(4)(F)(i)-(iii), (v).

b. At step 2 (exposure assessment) the EPA determines the level at which populations are exposed to the chemical. *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 653:22-655:11 (Barone);

accord 15 U.S.C. § 2605(b)(4)(F)(i)-(iii), (v).

c. At step 3 (risk characterization), the EPA compares the point of departure with the exposure level to determine if a risk is present. *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 575:8-583:13 (Barone). Because of uncertainty in data, the EPA establishes a margin between the point of departure and the community's exposure level. There must be a sufficient margin to find absence of risk. *See id.* The appropriate margin varies based upon how much uncertainty there is in the chosen point of departure. *See id.* The appropriate or required margin is referred to as the benchmark margin of exposure ("benchmark MOE"). *See id.* The actual margin is the actual margin of exposure ("actual MOE"). If there is an insufficient margin, *i.e.*, the actual MOE is less than the benchmark MOE, a risk has been identified. *See id.*

d. At step 4 (risk determination) if a risk is identified, the EPA will then determine if that risk is unreasonable, considering various factors such as the type of harm at issue and number of people exposed. *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 653:22-655:11 (Barone); *accord* 15 U.S.C. § 2605(b)(4)(F)(iii)-(v). Each step of the risk assessment is discussed in turn below.[6]

A. Step 1: Hazard Assessment

26. The Hazard Assessment step is comprised of three subparts: (a) hazard identification; (b) weight-of-the-scientific evidence; and (c) dose-response assessment. *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 654:19-655:11 (Barone). Each are addressed in turn below.

1. Step 1A: Hazard identification

a. *Framework*

27. The first component of the hazard assessment is hazard identification. Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 489:11-17 (Barone), 656:8-661:16 (Barone). At the hazard identification step of the risk evaluation framework, the reviewer determines if an adverse effect is associated with a chemical exposure. *See* Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 489:11-17 (Barone), 656:8-661:16 (Barone).

[6] The evaluation of fluoridation chemicals under TSCA follows the same standards for demonstrating hazard and risk that EPA uses for its evaluations of other industrial chemicals under TSCA; there is no justification for holding fluoridation chemicals to a higher burden. *See* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 742:25-743:8 (Barone).

28. Proof of causation is not required to establish a hazard of neurotoxicity, only association between the chemical exposure and the adverse effect is required for a hazard to be identified. *See id.* at 490:1-5.

29. At this stage of the process EPA reviews, searches, screens, and evaluates all studies related to different hazards to determine whether the data are sufficient or insufficient for identified adverse effects. *Id.* at 492:24-494:9.

b. *Key finding*

30. The hazard identification step of the hazard assessment here is satisfied; exposure to the chemical fluoride is associated with the adverse effect of reduced IQ in children, and particularly in boys.

c. *Underlying findings*

31. The NTP is headquartered within the National Institute of Environmental Health Sciences ("NIEHS"). Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1425:23-1426:8 (Barone). By May of 2022, the NTP completed its systematic review of fluoride, titled *NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review* (hereafter "NTP Monograph"). Dkt. No. 431-1, Trial Ex. 67. *See also* Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1427:5-8 (Barone); Dkt. No. 400, Feb. 4, 2024, Trial Tr. at 535:15-21 (Berridge). In August 2024, the NTP Monograph was formally published. *See* Dkt No. 442 (letter from parties recognizing publishing of document). The parties agree that there are no material differences between the published Monograph and the pre-publication version that was the subject of testimony and argument at trial (*i.e.*, Trial Exhibit 67). *Id.*[7]

[7] The parties originally filed a letter agreeing that the published version of the NTP Monograph was the same in all material respects as the Monograph this Court reviewed at trial. Dkt. No. 442. Subsequently, Plaintiffs filed a letter suggesting that certain aspects of the published NTP Monograph were modified in a way that lends *additional* support for their case. *See* Dkt. No. 443. In particular, Plaintiffs assert:

> Page 101 of the now-published version of the NTP Monograph summarizes the findings of the "in-press" meta-analysis as follows:
>
> The group-level meta-analysis of 59 studies (n = 20,932 children) used SMD as the effect measure and reported statistically significant

32. According to the EPA, a systematic review is "a scientific investigation that focuses on a specific question and uses explicit, pre-specified methods to identify, select, assess, and summarize the findings of similar but separate studies." Dkt. No. 255 (EPA Proposed Findings of Fact, Trial Phase 1) at 15 (citing 82 Fed. Reg. at 33,734). Moreover, "[t]he goal of systemic review methods is to ensure that the review is complete, unbiased, reproducible, and transparent." *Id.* The EPA explains that a systematic review is pertinent and is ideal in conducting a risk assessment under TSCA. *See id.* at 14-19 (arguing that during the first phase of trial, before the NTP Monograph was finalized, that Plaintiffs failed to meet their burden because they did not conduct a systematic review).

33. The NTP Monograph is a systematic review as the EPA has defined that term. The NTP Monograph is a scientific investigation, focusing on a specific question using explicit, pre-

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> inverse associations between fluoride exposure measures and children's IQ. There was also a significant dose response relationship between group-level fluoride exposure and IQ. **In stratified dose-response meta-analyses of the low risk-of-bias studies, the direction of association remained consistent when group-level exposure was restricted to <4mg/L, <2 mg/L, and <1.5 mg/L fluoride in drinking water and <4 mg/L, <2 mg/L, and <1.5 mg/L fluoride in urine.** The regression slopes meta-analysis of 13 studies (n = 4,475 children) with individual-level measures of fluoride found **a significant decrease in IQ of 1.63 points (95% CI: −2.33,−0.93; p-value <0.001) per 1-mg/L increase in urinary fluoride.** In subgroup analyses of both group-level and individual level data, the direction of the association remained inverse when stratified by study quality (high versus low risk of bias), sex, age group, outcome assessment, study location, exposure timing, and exposure metric.

Dkt. No. 443 (citing *NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition: A Systematic Review*, National Toxicology Program (August 2024), https://ntp.niehs.nih.gov/sites/default/files/2024-08/fluoride_final_508.pdf (emphases added)).

The EPA disputes whether the post-trial version of the NTP Monograph is properly considered by this Court. *See* Dkt. No. 444. Because the Court finds in Plaintiffs favor based upon the version of the NTP Monograph that the Court reviewed at trial, and because neither party suggests the aspects of the NTP Monograph that the Court reviewed therein have changed in a way that undermines Plaintiffs' case, the Court need not resolve this dispute. Instead, the Court bases its finding upon the version of the NTP Monograph reviewed at trial (Trial Exhibit 67), though noting that it has since been published formally, and that if it were considered, it would find the published Monograph even more supportive of the decision reached herein.

specified methods. Namely, the objective of the NTP Monograph was "[t]o conduct a systematic review of the human, experimental animal, and mechanistic literature to evaluate the extent and quality of the evidence linking fluoride exposure to neurodevelopmental and cognitive effects in humans." NTP Monograph at xii (Abstract). Regarding the methods: "[a] systematic review protocol was used following the standardized OHAT [referring to the Office of Health Assessment and Translation] systematic review approach for conducting literature-based health assessments. This monograph presents the current state of evidence associating fluoride exposure with neurocognitive or neurodevelopmental health effects and incorporated predefined assessments of study quality and confidence levels. Benefits of fluoride with respect to oral health are not addressed in this monograph." *Id.* Ultimately, the NTP Monograph analyzed all available studies assessing impacts of fluoride, including seventy-two human studies that assessed the association between fluoride exposure and IQ in children and integrated the findings in the studies to draw conclusions about the impact of fluoride to neurodevelopmental and cognitive effects in humans. *Id.* at xii-xiii. Moreover, the NTP Monograph's protocol underwent multiple rounds of peer review. *Id.* at G-1. And the Monograph's substance underwent multiple rounds of peer review, including assessment of technical accuracy, and the sufficiency of evidence supporting the NTP Monograph's conclusion. *Id.* at x. The peer review panel includes professors from Brown University School of Public Health, Columbia University Medical Center, Johns Hopkins Bloomberg School of Public Health, and other epidemiological experts. *See id.* The EPA does not dispute that the NTP Monograph is likely to have captured all relevant studies that were in existence as of the Monograph's literature cutoff date analyzing human data regarding neurodevelopmental impacts of fluoride. Dkt. No. 421 at 12-13. Even before the NTP Monograph was formally published, the EPA agreed that the NTP Monograph "followed the rules that have been developed by NTP for conducting systematic reviews" and utilized a "rigorous approach to assembling the evidence," "clearly defined rules for identifying and evaluating studies," and "a well-defined protocol for drawing inferences" from the studies. *Id.*[8] Indeed,

[8] Plaintiffs submitted evidence indicating that the delay in publication was highly irregular, and perhaps politically motivated. *See* Dkt. No. 385 at 12-13. The Court excluded evidence regarding

EPA's expert, Dr. Barone agreed that the NTP Monograph is a "high quality review." Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1427:2-4 (Barone). Accordingly, the Court finds that the NTP Monograph is probative and afforded significant weight in the risk evaluation analysis.

34. The NTP Monograph concludes that the majority of the 72 epidemiological studies on fluoride and IQ that had been published by April 2021 found an association between fluoride and reduced IQ in children, including 18 of the 19 studies the NTP Monograph deemed "high quality" and "low-risk-of-bias" as well as 46 of the 53 lower-quality studies. NTP Monograph at xii (NTP Monograph Abstract describing 46 of the 53 low-quality studies found an association between higher fluoride exposure and lower IQ in children and 18 of 19 high-quality studies reported an association between higher fluoride exposure and lower IQ in children including 3 prospective cohort studies and 15 cross-sectional studies); *accord* Dkt. No. 428-1, Trial Ex. 69 at 65 (NTP Board of Scientific Counselors Working Group Report agreeing that low-risk-of-bias studies were "consistent," meaning generating results in the same direction, in finding a negative association between fluoride exposure and children's IQ); Dkt. No. 396, Feb. 1, 2024, Trial Tr. at 313:25-314:5 (Grandjean) (summarizing and agreeing with NTP Monograph's finding that higher fluoride exposure (at or above 1.5 mg/L) was found to be associated with lower IQ scores in children in the majority of both low- and high-quality studies the NTP Monograph reviewed); Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1197:2-15 (Savitz) (expressing confidence in NTP's literature search strategy and its ability to identify all relevant studies on fluoride exposure published prior to the closing date of April 21, 2021, and confirming that the "vast majority of studies" that NTP reviewed identified an association between fluoride and reduced IQ), 1114:24-1115:1 (describing NASEM critique of adequate definition of the term "consistent" in NTP Monograph, but not disagreeing with characterization of NTP Monograph finding association between IQ and fluoride). The NTP Monograph explained its key finding regarding the impact of fluoride on children's IQ as follows:

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partisanship relating to publishing of the Monograph, in large part because the EPA did not argue the Monograph be afforded less weight for its draft status. *Id.* at 17. Eventually, the NTP Monograph was published, in August 2024. *See* Dkt. No. 442.

> ***In summary, the high-quality studies (i.e., studies with low potential for bias) consistently demonstrate lower IQ scores with higher fluoride exposure [e.g., represented by populations whose total fluoride exposure approximates or exceeds the WHO Guidelines for Drinking-water Quality of 1.5 mg/L of fluoride (WHO 2017)].*** The consistency in association is observed among studies of varying study designs, exposure measures, and study populations. Although some studies that conducted multiple analyses observed within-study variations in results (e.g., differences between subsets of IQ tests), these variations were unique to individual studies and did not detract from the overall consistency in the findings that higher fluoride is associated with lower IQ scores.

Trial Ex. 67 at 47 (emphasis added).

35. To come to this conclusion: the NTP Monograph identified 19 studies as being high-quality (*i.e.*, low risk-of-bias); all but one identified an association between fluoride and reduced IQ in children: Bashash et al. 2017; Choi et al. 2015; Cui et al. 2018; Ding et al. 2011; Green et al. 2019; Rocha-Amador et al. 2007; Saxena et al. 2012; Seraj et al. 2012; Sudhir et al. 2009; Till et al. 2020; Trivedi et al. 2012; Wang et al. 2012; Wang et al. 2020b; Xiang et al. 2003a; Xiang et al. 2011; Yu et al. 2018; Zhang et al. 2015b. NTP Monograph at 40, 29-39 (Table 6). To summarize these high-quality studies:

a. Bashash (2017): This study evaluated 211 mother-child pairs that were participants in The Early Life Exposures in Mexico to Environmental Toxicants Project ("ELEMENT Cohort")[9] and concluded that higher prenatal fluoride exposure was associated with statistically

[9] Bashash (2017) (like Green (2019) and Till (2020), discussed in subparagraphs (b) and (c)), is a longitudinal cohort study, evaluating fluoride in the urine of pregnant mothers. In such a cohort study design:

> [A] healthy group of people is assembled and followed forward in time and observed for the development of dysfunction. Such studies are invaluable for determining the time course for development of dysfunction (*e.g.*, follow-up studies performed in various cities on the effects of lead on child development). This approach allows the direct estimate of risks attributed to a particular exposure, since toxic incidence rates in the cohort can be determined. Prospective study designs also allow the study of chronic effects of exposure. One major strength of the cohort design is that it allows the calculation of rates to determine the excess risk associated with an exposure. Also, biases are reduced by obtaining information before the disease develops. This approach, however, can be very time-consuming and costly. In cohort studies information bias can be introduced when individuals provide distorted information about their health because they know their exposure status and may have been told of the expected health effects of the exposure under study.

significant lower scores on tests of cognitive function in offspring at ages 4 and 6-12 years; an increase in maternal urine fluoride of 0.5 mg/L predicted a 3.15 lower General Cognitive Index ("GCI") score and 2.50 lower IQ score of the offspring. Dkt. No. 432-2, Trial Ex. 106 at 1. ELEMENT collected urinary samples from women during pregnancy and from their children when the children were 6-12 years old (299 mother-child pairs) recruited from hospitals caring for low to moderate income populations in Mexico City. *Id.* at 1-2. The mean urinary fluoride in mothers and children was 0.90 mg/L (mothers) and 0.82 mg/L (children). *Id.* Child intelligence was measured via GCI for children at age 4 and IQ and from the Wechsler Abbreviate Scale of Intelligence ("WASI") at ages 6-12. *Id.* Fluoride exposure derived from fluoridated salt and naturally occurring fluoride in drinking water in Mexico City, ranging from 0.15 to 1.38 mg/L. *Id.* at 2. A second morning void ("spot") urine sample was targeted for collection during each trimester of pregnancy from mothers and the offspring children at time of measurements of intelligence. *Id.* A total of 1,484 prenatal samples was measured; after controlling for, *e.g.*, quality, duplicates, covariates, and outliers, 877 urine samples adjusted for creatinine were retained, stemming from 512 unique mothers. *Id.* at 3. A total of 287 mother-child pairs had complete data on exposure and outcome for children at 4 years and 211 for children at 6-12 years. Dkt. No. 434-27, Trial Ex. 656 (Savitz Summary of Methods in Key Studies of Fluoride Exposure and Neurodevelopment).

b. Green (2019): Green et al. (2019) studied mother-child pairs in Canada that were

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> More credence should be given to those studies in which both observer and subject bias are carefully controlled (*e.g.*, double-blind studies). A special type of cohort study is the retrospective cohort study, in which the investigator goes back in time to select the study groups and traces them over time, often to the present. The studies usually involve specially exposed groups and have provided much assistance in estimating risks due to occupational exposures. Occupational retrospective cohort studies rely on company records of past and current employees that include information on the dates of employment, age at employment, date of departure, and whether diseased (or dead in the case of mortality studies). Workers can then be classified by duration and degree of exposure.

Dkt. No. 429-7, Trial Ex. 17 at 17-18. Moreover, "[p]ositive or negative results from a properly controlled prospective study *should weigh heavily* in the risk assessment process." *Id.* (emphasis added).

participants in the Maternal-Infant Research on Environmental Chemicals program ("MIREC Cohort") and found a statistically significant, negative association between fluoride exposure and IQ in boys, but not girls. Dkt. No. 432-5, Trial Ex. 109 at 940, 944. The study concluded that 1 mg/L increase in maternal urinary fluoride was associated with a 4.49-point lower IQ score in boys and 1 mg higher daily intake of fluoride among pregnant women was associated with a 3.66 lower IQ score in boys and girls. *Id.* MIREC collected urinary spot samples and estimates of daily fluoride intake from water consumption for pregnant women recruited from cities across Canada (Vancouver, Montreal, Kingston, Toronto, Hamilton, Halifax). *Id.* at 941-942. Urinary samples from the women were collected across each trimester of pregnancy; the mean maternal urinary fluoride of mothers was 0.42 mg/L in fluoridated communities and 0.27 mg/L in non-fluoridated communities. *Id.* at 944. The mean estimated intake of water fluoride concentration was 0.39 mg/day; 0.43 mg for women in communities with fluoridated drinking water and 0.26 for those living in communities without fluoridated drinking water. *Id.* Children were between ages 3 and 4 years at testing. *Id.* at 940. Data on exposure and outcome was complete for 512 mother-child pairs measuring exposure through maternal urinary fluoride and 400 mother-child pairs estimating water fluoride intake. *Id.*

c. Till (2020): Till (2020) studied samples taken from 398 mother-child pairs that participated in the MIREC Cohort project (the cohort studied in Green (2019)), to evaluate IQ of children that were breastfed compared to formula-fed as infants in areas that had fluoridated and non-fluoridated water. Dkt. No. 432-19, Trial Ex. 123 at 1. This study found that an increase in fluoride intake from infant formula corresponded to an 8.8 decrement in performance IQ which was statistically significant, including after controlling for fetal fluoride exposure. *Id.*[10]

d. Cross-sectional studies[11] of children in China found significant inverse association

[10] Till (2020) and Green (2019) exemplify how the same samples from one cohort may be analyzed in multiple studies to either confirm results from a previous study or to extract different information from the same samples from a given cohort.

[11] Cross-sectional studies are afforded less weight than cohort studies. As the EPA guidelines explain:

> In cross-sectional studies or surveys, both the disease and suspected risk factors are ascertained at the same time, and the findings are

between fluoride and children's IQ score: Xiang (2003a) (finding significant inverse correlation between IQ and urinary fluoride; significant association of fluoride on IQ score based on drinking water levels); Ding (2011) (significant association between urinary fluoride and decrease in IQ score); Xiang (2011) (significant association between serum (blood-derived sample) fluoride and reduced IQ score in children); Wang (2012) (significant correlation between total fluoride intake and reduced IQ); Zhang (2015b) (significant correlation between reduced IQ score and children's serum fluoride, and urinary fluoride), Cui (2018) (significant association between IQ score and urinary fluoride); Yu (2018) (significant difference in mean IQ scores in high water fluoride areas compared to normal water fluoride areas); and Wang (2020b) (significant negative association between IQ and water and urinary fluoride and IQ in boys and girls). NTP Monograph at 29-33 (Table 6). One study, Cui (2020) identified a directionally negative, though not statistically significant decrease in mean IQ score with increasing fluoride levels. *Id.* at 32.

e. Rocha-Amador (2007), a cross-sectional study of children in Mexico found significant associations between fluoride and IQ scores. *Id.* at 33.

f. Cross-sectional studies of children in India found significant association between fluoride and intellectual impairment: Sudhir (2009) (found a significant increase in proportion of children with intellectual impairment with increasing drinking water fluoride levels); Saxena (2012) (significant correlations between reduced IQ and water fluoride and urinary fluoride levels); Trivedi (2012) (found significantly lower mean IQ scores in high fluoride villages compares to low-fluoride villages for boys and girls combined and separately). *Id.* at 38.

g. Siraj (2012), a cross-sectional study of children in Iran found a significant negative association between water fluoride and IQ score. *Id.* at 39.

> useful in generating hypotheses. A group of people are interviewed, examined, and tested at a single point in time to ascertain a relationship between a disease and a neurotoxic exposure. This study design does not allow the investigator to determine whether the disease or the exposure came first, rendering it less useful in estimating risk. These studies are intermediate in cost and time required to complete compared with case reports and more complex analytical studies, but should be augmented with additional data.

Dkt. No. 429-7, Trial Ex. 17 at 16.

h. Soto-barreras (2019), a cross-sectional study of children in Mexico 9-10 years of age did *not* find a significant association between fluoride and IQ levels. *Id.* at 34.

36. In addition to the studies that the NTP Monograph deemed "high-quality," and thus most relevant to understanding impact of fluoride, the NTP Monograph explains that 46 of the 53 studies deemed low-quality by the NTP Monograph also found an association between fluoride exposure and reduced IQ in children. NTP Monograph at xii.

37. Several studies published after the NTP Monograph literature cut-off date (April 2021), *see* NTP Monograph at 5-12, 12 n.8, B-2, C-2-C-44, also found negative association between fluoride and IQ, and acutely, for boys – bolstering the NTP Monograph's finding of a negative association between IQ in children and fluoride exposure:

a. Goodman (2022a): studied samples from the ELEMENT cohort and concluded that an increase in maternal urinary fluoride predicated an average 2.12-point decrease in GCI scores of 4-year-olds and a 2.63 decrease in performance IQ of 6- to 10-year-olds. Dkt. No. 432-11, Trial Ex. 115 at 1-2. The study also found a marginal association with maternal urinary fluoride and verbal IQ across time. *Id.* at 2. The study concluded that visual-spatial and perceptual reasoning ability may be more impacted by prenatal fluoride exposure as compared to verbal abilities. *Id.*

b. Cantoral (2021): studied 103 mother-child pairs from the Programming Research in Obesity, Growth, Environment and Social Stressors ("PROGRESS Cohort") program. Dkt. No. 432-6, Trial Ex. 110 at 2. The PROGRESS Cohort collected data regarding dietary fluoride intake from mothers (via food and beverage) during pregnancy and neurodevelopmental testing from their offspring for 948 mother-child pairs from Mexico City. *Id.* at 2. Dietary fluoride intake was measured via food frequency questionnaires from mothers in trimesters two and three of pregnancy and children's cognitive, motor, and language outcomes were measured at 12 and 24 months. *Id.* at 1. Cantoral (2021) studied data from 103 mother-child pairs from the PROGRESS Cohort to understand if dietary fluoride intake during pregnancy is associated with toddlers' neurodevelopment. *Id.* The study found a statistically significant association between maternal fluoride intake and cognitive outcome in 24-month-old boys (0.5 mg/day increase in overall dietary fluoride intake associated with 3.5-point lower cognitive outcome). *Id.* There was no

statistical association for girls or boys at 12 months of age. *Id.* Averaging across the entire age group, a 0.5 mg/day increase was associated with a 3.46-point lower cognitive outcome in boys, which was statistically significant. *Id.* The study concludes: "[t]hese findings suggest that the development of nonverbal abilities in males may be more vulnerable to prenatal fluoride exposure than language or motor abilities, even at levels within the recommended intake range." *Id.*

c. Godebo (2023): this study assessed the association between chronic exposure to naturally occurring fluoride and drinking water and cognitive function in school-aged children, measured by two distinct assessments: a drawing test with familiar objects and the Cambridge Neuropsychological Test Automated Battery, Paired Associate Leaning ("CANTAB PAL")[12] test. Dkt. No. 432-14, Trial Ex. 118 at 15-16. The population studied was recruited from eight communities exposed to chronic fluoride ranging from 0.41 to 15.5 mg/L fluoride in water sources. *Id.* at 15. The study reported adverse associations of fluoride exposure in drinking water with children's drawing and CANTAB task performance, with the most significant negative impacts observed for more challenging drawing tasks (*i.e.*, drawing a donkey rather than a house or a person). *Id.* at 16. The study concluded that this may be indicative of a greater challenge "accessing working memory for this task." *Id.*

d. Adkins (2022): this study evaluated data collected from the Cincinnati Childhood Allergy and Air Pollution Study ("CCAAPS"). Dkt. No. 432-8, Trial Ex. 112 at 1. CCAAPS collected urine samples from children at 12 years of age and collected Behavior Assessment System for Children-2 which evaluates internalizing symptoms such as anxiety depression and somatization. *Id.* at 2. The study found that higher children's urinary fluoride concentrations were significantly associated with increased somatization, but not depression or anxiety. *Id.* The study found that male participants exhibited higher internalizing and somatization behaviors relative to female participants. *Id.* at 6. The study concluded that "[d]espite males and females having comparable urinary fluoride concentrations, males may be at greater risk for adverse effects of

[12] The tests present patterns and shapes on a screen and ask children to touch and recount the patterns to assess spatial memory and learning. Dkt. No. 432-14, Trial Ex. 118 at 10-11. Spatial memory and learning are linked to the medial temporal lobe *e.g.*, hippocampus, which the study reports is the brain region thought to be most affected by fluoride toxicity. *Id.* at 5.

fluoride exposure as the association between fluoride concentrations and internalizing symptoms was more robust among males." *Id.* at 9.

e. Risk Sciences International ("RSI"), under contract with Health Canada, also conducted an extensive systematic review of the fluoride neurotoxicity literature: Taher (2024). Dkt. No. 433-4, Trial Ex. 129; Dkt. No. 433-6, Trial Ex. 131 (Taher (2024) Supplementary Materials). Taher (2024) came to a similar conclusion as the NTP Monograph, finding a "moderate to strong magnitude (strength) of association between fluoride and neurocognitive effects with consistent evidence across studies for the impact on childhood IQ." Dkt. No. 433-4, Trial Ex. 129 at 21; Dkt. No. 433-6, Trial Ex. 131 at 1516 ("The overall evidence identified to date strongly suggests that fluoride can affect cognitive outcomes in children (specifically, reduction in IQ scores), at levels close to those currently seen in North American drinking water.").[13]

38. Other post-NTP Monograph studies did not find fluoride was associated with adverse cognitive outcomes in children:

a. Ibarluzea (2021): the study evaluated data from 316 to 248 mother-child pairs from the Infancia y Medio Ambiente cohort project ("INMA Cohort"). Dkt. No. 432-10, Trial Ex. 114 at 1. The INMA Cohort draws on data from mothers and children in Gipuzkoa, Spain (Basque Country) living in fluoridated and non-fluoridated water communities that supplied water with the mean fluoride level of 0.81 mg/L. *Id.* at 1, 3. The INMA study collected maternal urinary fluoride levels in the first and third trimesters of pregnancy, and children's cognitive domains and

[13] Unlike the NTP Monograph, Taher (2024) considered evidence relating to multiple endpoints (*i.e.*, a particular adverse effect, *see* Dkt. No. 434-15, Trial Ex. 535 at 43) aside from reduced IQ to decide which endpoints need be accounted for by regulators; endpoints considered included kidney dysfunction, sex hormone disruptions, and dental fluorosis, *see* Dkt. No. 433-4, Trial Ex. 129 at 21-23. Taher (2024) concluded that dental fluorosis and reduced IQ are critical endpoints; evidence supported the association between fluoride and those two adverse effects. *See id.* at 27. Taher (2024) did find that dental fluorosis should be the primary endpoint used by regulators because data regarding the association between dental fluorosis and fluoride was more certain than evidence regarding the association between IQ reduction and fluoride. *Id.* However, Taher (2024) explained that *both* dental fluorosis, and separately, IQ reduction in children should be considered by regulatory bodies, including the United States EPA, when assessing regulation of fluoride. *Id.* To this end, the review recommended that fluoride at 1.56 mg/L be deemed hazardous, explaining that this level should be utilized by regulators in its calculations to protect the public against *both* dental fluorosis *and* IQ reduction. *See id.* Thus, the findings of Taher (2024) are consistent with the NTP Monograph's finding that fluoride is associated with reduced IQ, particularly at exposure levels above 1.5 mg/L.

intelligence indexes, evaluated used the Bayley Scales (age 1) and McCarthy Scales (age 4). *Id.* at 1. The study concluded that per unit of maternal fluoride across the pregnancy was associated with a sizeable *increase* in IQ scores (15-point increase) and an increase in verbal, performance, numeric, and memory domains in boys. *Id.* For girls, there was no significant association between maternal fluoride and cognitive score. *Id.*

b. Dewey (2023): This study compared data collected from maternal-child pairs in Calgary, Canada pre- and post-May 19, 2011, when the city stopped fluoridating its drinking water (with a recommended level of 0.7 mg/L) to discern if fluoridated drinking water was associated with children's intelligence and executive function at 3-5 years of age. Dkt. No. 432-13, Trial Ex. 117 at 1. The study compared data from maternal-child pairs that were either fully exposed to fluoridated drinking water throughout pregnancy, exposed for part of the pregnancy, and those not exposed to fluoridated drinking water. *Id.* The study found no adverse associations between maternal exposure to fluoridated drinking water for intelligence. *Id.* at 7. The study observed that maternal exposure to fluoridated drinking water was associated with poorer executive function in preschool aged children and, particularly, girls. *Id.*

c. Do (2022): This study collected additional data from participants in Australia's National Child Oral Health Study 2012-14, which gathered data from children aged 5-10 years, and collected additional data from them again 7-8 years later but before the children turned 18 years of age. Dkt. No. 432-9, Trial Ex. 113 at 1. The study estimated lifetime exposure to fluoridated water based upon residential history and postcode-level fluoride levels in public tap water and measured children's emotional and behavioral development and executive functioning using questionnaires. *Id.* The study concluded that exposure to fluoridated water during the first 5 years of life (post-birth) was not associated with altered measures of child emotional and behavioral development and executive functioning by 18 years of age. *Id.*

39. For several reasons, the studies that did not find a negative association between fluoride and IQ, or that observed the association in some groups (boys) but not others (girls) do not undermine the significant evidence finding such an association, reflected in the NTP Monograph and studies published after the Monograph. The Court affords less weight to these studies finding

lack of an association due to various characteristics of those studies:

a. The reliability of Ibarluzea (2021) is questionable in several respects:

i. This study found that per one unit increase in the mg/L maternal urinary fluoride, there was an association with a 15-point increase in the IQ of boys associated with maternal urinary fluoride. Dkt. No. 432-10, Trial Ex. 114 at 1. Dr. Savitz, EPA's expert, agrees that this finding is an outlier and unexpected, insofar as no other study has reported a *positive* association between fluoride exposure upon IQ, and does not meaningfully support that fluoride is beneficial. *See* Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1067:2-1069:11 (Savitz) ("Again, based on what I know, I would doubt that that is an accurate reflection of the causal impact of fluoride on IQ."). Experts also testified that they were not aware of *any* other chemical known to increase the IQ of humans by 15 points. Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 372:14-16 (Grandjean); Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 111:4-6 (Hu). This association appears scientifically implausible and raises questions about the overall reliability of this study.

ii. Further, the 15-point increase in IQ disappeared to reflect a null finding when the maternal urinary fluoride was not adjusted for creatinine. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 109:5-11 (Hu). Adjusting maternal urinary fluoride for creatinine is standard practice, and results from creatinine-adjusted urinary fluoride are considered the informative and reliable results of a study. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 108:7-10 (Hu); Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1089:5-17 (Savitz), 1090:24-1091:2 (Savitz). However, adjusting for creatinine is expected to sharpen results, because the adjustment countervails for urinary dilution which might introduce noise into a study; the adjustment is *not*, however, expected to have any significant impact on the direction of results of the study. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 108:11-22 (Hu); Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 372:25-373:22 (Grandjean), 376:15-378:24 (Grandjean). The results in the Ibarluzea (2021) study, which transitioned from a significant positive association to a null finding when urinary fluoride was adjusted for creatinine, was considered surprising and not a plausible result. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 109:13-110:7 (Hu); Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 372:25-373:22 (Grandjean), 376:15-378:24 (Grandjean). Plaintiffs' experts credibly testified that this discrepancy suggests there was

an error when matching fluoride and creatinine data. Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 372:25-373:22 (Grandjean). EPA's experts at trial could not explain or account for this aspect of the study. Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1091:3-1093:8 (Savitz).

iii. Another concern with the Ibarluzea (2021) study is that it did not adjust for seafood as a covariate in the analysis of fluoride and IQ. Dkt. No. 397, Feb. 2, 2024, Trial Tr. at 453:12-17 (Grandjean). Seafood is both high in fluoride content and omega 3 fatty acids. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 110:20-23 (Hu). This is problematic because omega 3 fatty acids have beneficial effects on cognition, and thus seafood may be a confounding factor, skewing results of a study if the population has a high seafood ingestion rate. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 110:20-111:3 (Hu). The study did adjust for cord blood mercury levels, which could operate as an adjustment for fish consumption because fish often contain mercury. Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1073:20-1074:14 (Savitz). However, the bigger the fish, the more likely the accumulation of mercury; conversely, the smaller the fish, the less likely the accumulation of mercury. *Id.* at 1076:20-1078:9. Yet, in coastal Spain where the study was conducted, sardines and anchovies are popular, which are small fish that are lower on the food chain and accordingly low in mercury. *See* Dkt. No. 417, Feb. 2, 2024 at 458:23-459:17 (Grandjean); Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1269:24-1270:12 (Savitz). Thus, it is not clear that the adjustment for cord blood mercury levels is a sufficient proxy for seafood consumption. To this end, Dr. Savitz agreed that it is a reasonable hypothesis that fish consumption accounted for the beneficial results associated with IQ observed in the Ibarluzea (2021) study. Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1069:23-1070:18 (Savitz).

iv. Taher (2024) likewise concluded that Ibarluzea (2021) does not overcome evidence linking fluoride to reduced IQ in children. Namely, Taher (2024) concluded that "[t]he available evidence demonstrated a moderate to strong magnitude (strength) of association between fluoride and neurocognitive effects with consistent evidence across studies for the impact on childhood IQ at fluoride exposures relevant to current North American drinking water levels." Dkt. No. 433-4, Trial Ex. 129 at 21. This is because, "[f]ocusing on high quality cohort studies, most of the evidence suggests a reduction in childhood IQ scores associated with fluoride levels,

though results from one 2023 study in Spain (Ibarluzea et al. 2022) documented an improvement in specific cognitive domain scores in boys." *Id.*

b. Dewey (2023) is not strong evidence regarding the association between fluoride and reduced IQ because of the design of this study. The study attempted to take advantage of what was thought to be a naturally occurring cohort with an exposure contrast (*i.e.*, one cohort exposed to fluoride and one not exposed to fluoride) to see if there was a meaningful difference in cognitive outcomes amongst the two groups. Dkt. No. 397, Jan. 31, 2024, Trial Tr. at 368:22-369:7 (Grandjean). Specifically, the study looked at individuals from a Canadian community that, for a long time, fluoridated its water and stopped fluoridating the water; the study compared the cognition of children in fluoridated and non-fluoridated groups to discern the impact of fluoride. Dkt. No. 397, Jan. 31, 2024, Trial Tr. at 368:22-369:7 (Grandjean). However, the study did not collect data on the urinary fluoride levels of the mother or assess how long pregnant mothers lived in the area prior to their pregnancy. Dkt. No. 397, Jan. 31, 2024, Trial Tr. at 368:22-369:18 (Grandjean). This is relevant because women who live in a fluoridated area throughout their lives will have fluoride which accumulates in her bones from consumption of fluoridated water, along with other sources; for several years after cessation of fluoride exposure she is likely to release accumulated fluoride from her bones into blood due to skeletal breakdown. Dkt. No. 397, Jan. 31, 2024, Trial Tr. at 370:6-371:12 (Grandjean); Dkt. No. 402, Feb. 8, 2024, Trial Tr. at 932:16-20 (Thiessen). This skeletal breakdown is particularly present during pregnancy, as the maternal skeleton dissolves itself to provide calcium to the growing fetal skeleton. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 121:10-20 (Hu). Accordingly, the group that was considered non-fluoridated in the study, thus creating an exposure contrast between the two groups allowing for a potential association to be observed, may have in fact exposed the child to fluoride during pregnancy if she lived in a fluoridated area prior to the study (a phenomenon that is not reported or considered by the study). This could lessen the exposure contrast and calls the results of the study into question. *See* Dkt. No. 397, Jan. 31, 2024, Trial Tr. at 368:22-369:18 (Grandjean). EPA's expert witnesses did not account for this concern regarding the study design. Thus, the Dewey study is accorded diminished weight.

c. Do (2022) assessed primarily behavioral outcomes rather than impact on IQ in children and, as Dr. Savitz testified, "doesn't stand out as definitive or more persuasive," relative to other studies directly on point to association of fluoride on the IQ of children. Dkt. No. 414, Feb. 9, 2024 Trial Tr. at 1106:22-1107:10 (Savitz). Plaintiffs' experts also expressed concerns with the study. The study utilized the "SDQ" test to measure impact of fluoride on children in Australia, which is a test that, for certain cultural or linguistic reasons, has been determined to be unreliable for Australians by another study conducted by the co-author of Do (2022). Dkt. No. 397, Jan. 31, 2024, Trial Tr. at 364:8-14, 365:15-366:4 (Grandjean). EPA's expert witness did not rebut evidence that there were significant problems with the validity of the SDQ test in Australia. Dkt. No. 415, Feb. 12, 2024, Trial Tr. at 1240:1-6 (Savitz). Further, the value of this study is weakened because it did not analyze individualized data, but instead measured exposure based on residence of the child and community-wide data on fluoride in that area. *See* Dkt. No. 396, Feb. 1, 2024, Trial Tr. at 240:17-19 (Lanphear) (explaining that individualized data is generally a strength of a study); Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 366:5-367:4, 367:15-368:4 (Grandjean). Lack of individualized data can lead to exposure imprecision, creating "noise" in the data, which may bias results toward the null, *i.e.*, noise makes it less likely to show an association between the chemical and a result. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 106:18-107:16 (Hu); Dkt. No. 396, Feb. 1, 2024, Trial Tr. at 281:14-17 (Lanphear), 281:24-282:3 (Lanphear), 317:16-24 (Grandjean); Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1176:4-17 (Savitz) (agreeing with a statement made in his textbook that in general exposure misclassification tends to produce results with a bias towards the null). Thus, this study is not particularly probative evidence as to association between fluoride and IQ of children.

40. EPA experts agreed, in line with the NTP Monograph's conclusion, that fluoride is associated with adverse IQ in children at "higher" levels of exposure. Namely, Dr. Barone testified that he agreed that there is "something going on" at higher-dose levels, though unclear about where the threshold is. Dkt. No. 415, Feb. 12, 2024, Trial Tr. at 1372:9-1373:9 (Barone). Dr. Barone agreed that, at 4 mg/L of fluoride exposure and above, there is more data to support a finding of an adverse effect associated with fluoride. *Id.* at 1373:1-9 (Barone). Dr. Barone further

testified: "I agree with the NTP's conclusions that at some level above 1.5 mg/L that there is moderate evidence to support an association between fluoride and developmental IQ decrements." Dkt. No. 416, Feb. 12, 2024, Trial Tr. at 1428:4-11 (Barone).[14] The primary concern presented by EPA's experts relates to lack of clarity as to whether *lower* exposure levels of fluoride (below 1.5 mg/L) results in an adverse outcome and the precise relationship between dose and response. *See* Dkt. No. 415, Feb. 12, 2024, Trial Tr. at 1357:9-1360:10 (Barone). For example, Dr. Savitz (EPA's expert witness) did not opine that the NTP Monograph's main conclusion that fluoride is presumed to be a cognitive neurodevelopmental hazard to humans was incorrect, though expressing concerns as to a previous draft of the Monograph regarding whether its conclusion was well explained and qualified. Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1113:16-1115:23 (Savitz) ("Whether [a committee reviewing a draft of the NTP Monograph] agreed with [the NTP Monograph's conclusion] was not the issue. It was – the story that gets to the punchline at the end we did not find persuasive."). Indeed, Dr. Savitz explained that he does not have a basis to challenge the NTP's conclusion that, with moderate confidence, there is an association or appears to be an association between neurological decrements in fluoride concentrations above 1.5 mg/L. *Id.* at 1140:10-19 (Savitz) ("I don't have any reason to challenge [this conclusion], but I haven't corroborated it by going through the dozens of studies one-by-one to make my own assessment."). Dr. Savitz likewise made clear he did not undertake a complete review of the NTP Monograph, but testified his primary concern was the Monograph's "inferences regarding lower levels of fluoride exposure." *Id*. at 1129:11-1131:3 (Savitz).

41. The robust body of scientific literature systematically assessed by the NTP Monograph (described above, ¶ 35) and literature published after the NTP Monograph cutoff date (described above, ¶ 37), even considering some countervailing scientific literature (described above, ¶¶ 38-39) establishes by a preponderance of the evidence that fluoride is associated with reduced IQ in

[14] Dr. Barone testified that the NTP Monograph was helpful but not complete and thus insufficient to satisfy the hazard identification prong of TSCA hazard assessment. Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1428:22-1429:3 (Barone). That testimony is not credible because it directly contradicts Dr. Barone's prior testimony during his deposition that the literature the NTP reviewed through April 2021 was sufficient to satisfy the human evidence standard for identifying a hazard under the EPA's TSCA guidelines. *Id.* at 11-21.

children – at least at "higher" concentration levels, *i.e.*, above 1.5 mg/L (measured in either water fluoride levels or urinary fluoride levels). At the hazard identification step, the EPA does not require showing that an adverse effect is present at the level akin to the exposure in the community (*i.e.*, 0.7 mg/L) or require the establishment of a dose-response relationship of the chemical at "lower" levels. Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 493:16-495:12 (Barone). The evidence regarding the "higher" exposure levels is sufficient to satisfy the hazard identification step of the analysis.

42. Regardless, scientific literature in the record also indicates there is an association between fluoride and reduced IQ in children even at "lower" levels of exposure (*i.e.*, below 1.5 mg/L).

43. Two of the three high-quality studies that evaluated the effects of "lower" levels of fluoride exposure (below 1.5 mg/L) did observe an association between fluoride and reduced IQ in children or boys. Namely: (1) Bashash (2017), studied mother-child pairs from the ELEMENT Cohort (Mexican population) and observed a statistically significant decrement of 3.15 GCI score and 2.5 IQ score of offspring per an increase of 0.5 mg/L of maternal urinary fluoride where the mean maternal urinary fluoride in mothers was **0.9 mg/L**, Dkt. No. 432-2, Trial Ex. 106 at 1; and (2) Green (2019) studied mother-child pairs in the MIREC Cohort (Canadian population) and found a statistically significant decrement of 3.66 IQ score in boys only (3.66 IQ score decrement per a 1 mg/L per day increase in maternal urinary fluoride) where the mean maternal urinary fluoride of mothers was **0.42 mg/L**, Dkt. No. 432-5, Trial Ex. 109 at 1-3, 5.

44. Another program collected samples from 837 mother-child pairs from the Odense municipality in Denmark: the Odense Child Cohort ("OCC Cohort"). Dkt. No. 432-15, Trial Ex. 119 at 1. The OCC Cohort measured maternal urinary fluoride during pregnancy and the IQ of school-aged offspring of those mothers. *Id.* The maternal urinary fluoride concentrations averaged at **0.58 mg/L** per day. *Id.* at 2. The study, when accounting for covariables did **not** observe a statistically significant association between maternal urinary fluoride and child Full-Scale IQ score, with no clear interaction between sex and fluoride exposure. *Id.*

45. The result of the OCC Cohort does not negate the findings regarding the MIREC and ELEMENT cohorts. It is inherently more difficult to observe an adverse effect of a chemical at

lower exposure levels because of reduced exposure contrast[15] at those levels. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 113:2-25 (Hu), 114:8-14 (Hu); Dkt. No 396, Feb. 1, 2024, Trial Tr. at 213:5-25 (Lanphear); Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 525:9-526:13 (Berridge). EPA's expert, Dr. Savitz, agreed. Dkt. No. 402, Feb. 8, 2024, Trial Tr. at 1009:7-23 (Savitz) ("[Y]ou could think of the worst cases, if we all had the exact same value, everybody in the population had the same exposure, you could not do an informative study of the association of exposure with a disease. And if it's very narrow, of course, you're only able to study – if you're only able to study, let's say, the contrast of, you know, .4 and .5 milligrams per liter fluoride, you're going to have a tough time, even if there were an effect, it's going to be difficult to find because you have a very limited contrast. As you spread that out more, of course, you are – you have a larger contrast and you're able to address a more informative range of exposure."). It is particularly difficult to observe effects of fluoride at lower exposure levels because of challenges in finding a control group with zero or very little fluoride exposure. Dkt. No 396, Feb. 1, 2024, Trial Tr. at 212:7-213:25 (Lanphear). This is because fluoride exposure is prevalent. Some common sources aside from fluoridated water include naturally occurring fluoride in food and beverage, fluoride in food and beverage made with fluoridated water, and other products, like toothpaste. *Id*. at 212:10-19 (Lanphear). Thus, it is difficult to find a control group without any fluoride exposure; the "noise" created by background fluoride exposure tends to obscure the contrast between those who consume fluoridated water and those who do not. *Id*. at 212:19-23 (Lanphear) ("And so if we wanted to ask a question . . . is there a difference in children who are unexposed to fluoride? Well, we really can't find children who are unexposed to fluoride versus kids who have levels in a nonfluoridated community or a fluoridated community."). It is thus more challenging to observe

[15] Exposure contrast refers to the difference between exposure of a chemical in one group (a control group) and another group (the group exposed to the chemical). Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 113:6-22 (Hu). For example, an observer would compare a group with less or no fluoride exposure to a group with more exposure to determine if there is a meaningful difference in the group with more exposure. *See* Dkt. No 396, Feb. 1, 2024, Trial Tr. at 212:10-23 (Lanphear). When trying to observe effects of a chemical at lower levels, there is less "exposure contrast" between the control group and exposed group. *See id.* at 212:10-213:25. Dr. Hu provided an illustration: "It's sort of like looking at, you know, a picture and trying to determine whether this shade is different from that shade. If you increase the contrast, it's easier to see." Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 114:12-14 (Hu).

effects at lower concentration levels of fluoridated water. *Id*. at 212:24-213:25 (Lanphear). Accordingly, the Court finds convincing and credible the expert testimony that studies analyzing the OCC Cohort are not inconsistent with studies analyzing the ELEMENT and MIREC Cohorts; the lower exposure levels account for some difficulty in repeating observed effects. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 116:24-117:4 (Hu).[16] In short, the association between intake of water at lower fluoridated levels and IQ is likely harder to detect. Inconsistent results between studies are not unexpected. The two high-quality studies which detected such an association at lower concentration levels of fluoride remain significant and are not undermined by the OCC Cohort study.

46. In conclusion, Plaintiffs have established by a preponderance of the evidence that exposure to fluoride is associated with the adverse effect of reduced IQ in children, and particularly, young boys. Hence, the hazard identification step of the analysis is satisfied.

2. Step 1B: Weight of the scientific evidence

a. *Framework*

47. Once a hazard has been identified, the EPA assesses the weight of the scientific evidence, wherein the risk assessor considers the weight of that evidence, determining which adverse effects (endpoints) are to be assessed, and which studies are appropriate for use in quantifying the relationship between the dose of the chemical and adverse effect(s) (response) at issue (the "dose-response" assessment). Dkt. No. 400, Feb. 4, 2024, Trial Tr. at 661:18-666:14 (Barone). To this end, not all studies are appropriately utilized in the dose-response assessment. *See* Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 494:17-495:12 (Barone). Rather, the EPA identifies the studies from the hazard identification step that are generally of high or medium quality, and thus are deemed permissible to use in the dose-response assessment. *Id.* at 494:17-495:12; Dkt. No. 421 at 5 (undisputed fact).

[16] Expert witnesses also testified credibly that there are some possible explanations for the differing study results; for example, it is possible that Denmark has higher iodine consumption, accounting for the discrepancy, as iodine deficiency is theorized to be an aggravating factor for impacts of fluoride on neurodevelopment. *See* Dkt. No. 396, Feb. 1, 2024, Trial Tr. at 248:10-250:3 (Lanphear).

48. The parties disagree as to precisely how the weight-of-the-scientific evidence analysis intersects with the subsequent step of the analysis: the dose-response assessment wherein a point of departure[17] is identified (Step 1C, discussed in Section III.A.3.). *See* Dkt. No. 421 at 22-23. Plaintiffs assert that the weight-of-the-scientific evidence analysis is a distinct, qualitative characterization of the evidence regarding a "chemical's potential to produce neurotoxicity," separate from the quantitative dose-response assessment wherein a point of departure is calculated (Step 1C, discussed in Section III.A.3). *Id.* The EPA asserts that there is not a clear distinction between the qualitative and quantitative dose-response assessment. *See id.* Dr. Barone, EPA's expert does recognize that risk evaluation includes a "quantitative track wherein the agency is doing a quantitative measurement, deriving a point of departure, and a qualitative track where [the assessor is] assessing whether that evidence is appropriate for that purpose." *See* Dkt. No. 400, Feb. 4, 2024, Trial Tr. at 666:9-14 (Barone). Moreover, Dr. Barone stated that: "in this weight of the scientific evidence evaluation . . . [we ask] how much data do we actually have for that particular endpoint or that particular outcome, and are there a series of outcomes that are related to neurotoxicity that we should consider as an example or reproductive toxicity. So we may have multiple endpoints to consider and multiple studies within that, that can be ***carried forward*** to dose response." *Id.* at 662:2-19 (emphasis added). This testimony intimates that the weight-of-scientific-evidence analysis occurs prior to, and separately from, the quantitative dose-response assessment wherein a point of departure is calculated. *See id.* However, to avoid any doubt, the Court assesses the weight-of-the-scientific evidence both as a standalone, qualitative issue, characterizing the weight of the evidence assessing the association between the chemical and endpoint (in this section of the analysis (Section III.A.2., as Step 1B)) and also assesses the weight-of-the-scientific-evidence, as part of the quantitative dose-response assessment wherein a point of departure is identified (Section III.A.3, as Step 1C, discussed below).

b. *Key finding*

49. The weight of the scientific evidence regarding fluoride's association with reduced IQ is

[17] As explained in depth in Section III.A.3., the point of departure represents the level at which the chemical at issue becomes hazardous.

sufficient to proceed to the dose-response assessment; the evidence in the record is appropriate for use in calculating a point of departure.

c. *Underlying findings*

50. The term "weight of the scientific evidence" is supported by EPA's systematic analysis of the related information to support the Agency's findings. *Id.* at 651:22–652:5; *accord* 40 CFR 702.33. The assessor uses the "best available science," in the analysis, which means that TSCA risk evaluations need to be unbiased and objective, and the methodologies employed must be transparent and reproducible and generally peer reviewed. Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 652:6-16 (Barone); *accord* 40 C.F.R. 702.33.

51. In the weight-of-the-scientific-evidence analysis, generally, high- or medium-quality studies are adequate to move to the dose-response determination. Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 494:17-495:12 (Barone); Dkt. No. 421 at 5 (undisputed fact). Still, the EPA sometimes carries over low-quality studies into the dose-response analysis as well. Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 494:21-495:1 (Barone). In this weight-of-the-scientific-evidence analysis, some or all factors referred to as the "Bradford Hill" factors may be considered. Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 626:8-24 (Barone). The nine Bradford Hill factors are: (1) strength of the association, (2) consistency of the association; (3) specificity of the association; (4) temporality of the association; (5) biological gradient (*i.e.*, dose response) of the association; (6) plausibility of the association; (7) coherence of the association, (8) experimental support for the association, and (9) analogies for the association. *See* Dkt. No. 198-3, Grandjean Trial Decl. ¶¶ 111-125. However, there is no mandate that each of the Bradford Hill factors be considered in the weight-of-the-evidence assessment in a non-cancer TSCA risk evaluation such as this one. *See* Dkt. No. 437-1, Trial Ex. 96 (hereinafter "PCE Risk Evaluation") at 326 (considering only consistency of association factor); Dkt. No. 437-7, Trial Ex. 102 (hereinafter "Methylene Risk Evaluation") at 285-95 (considering some, but not all, of the Bradford Hill factors).

52. As discussed previously, not every epidemiological study on fluoride has found associations with reduced IQ in children. *See* ¶¶ 35, 38. However, the evidence at issue is overall **consistent** as to the finding that fluoride is associated with reduced IQ in children, and there is a

vast amount of **experimental support** for the association:

a. The NTP Monograph studied a robust amount of literature regarding fluoride's impact on children's IQ: 72 epidemiological studies – 19 of which were deemed "high quality" and "low-risk-of-bias," and 53 lower-quality studies – a large majority of which identified an association between fluoride and reduced IQ. NTP Monograph at xii (describing that 46 of the 53 low-quality studies found an association between higher fluoride exposure and lower IQ in children and 18 of 19 high-quality studies reported an association between higher fluoride exposure and lower IQ in children including 3 prospective cohort studies and 15 cross-sectional studies). Indeed, when narrowing evidence to view only 19 studies that are high quality and low risk-of-bias, all but one identified an association between fluoride and reduced IQ: Bashash et al. 2017; Choi et al. 2015; Cui et al. 2018; Ding et al. 2011; Green et al. 2019; Rocha-Amador et al. 2007; Saxena et al. 2012; Seraj et al. 2012; Sudhir et al. 2009; Till et al. 2020; Trivedi et al. 2012; Wang et al. 2012; Wang et al. 2020b; Xiang et al. 2003a; Xiang et al. 2011; Yu et al. 2018; Zhang et al. 2015b). NTP Monograph at 29-40 (Table 6).

b. The findings of the NTP Monograph are properly afforded substantial weight. The NTP is headquartered within NIEHS, which is "is one of the premier environmental health sciences research institutions in the world." Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1425:23-1426:2 (Barone). The EPA does not dispute this fact. Dkt. No. 421 at 10. Even before the NTP Monograph was formally published, the EPA agreed the NTP Monograph is a high-quality review, followed rules that have been developed by NTP for conducting systematic review, had a "rigorous approach to assembling the evidence," "clearly defined rules for identifying and evaluating studies," and "a well-defined protocol for drawing inferences" from the studies. Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1427:9-21 (Barone), 1427:2-8 (Barone).

c. Though there were some critical peer review comments on earlier drafts of the NTP Monograph, the core conclusion of the NTP Monograph regarding the high-quality studies was not called into question by reviewers. *See, e.g.*, Dkt. No. 438-1, Trial Ex. 69 at 65 (NTP Board of Scientific Counselors Working Group Report agreeing that low-risk-of-bias studies were "consistent," meaning generating results in the same direction, in finding a negative association

between fluoride exposure and children's IQ); Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1114:24-1115:1 (Savitz) (describing NASEM critique of adequate definition of the term "consistent" in NTP Monograph, but not disagreeing with characterization of NTP Monograph finding association between IQ and fluoride). Indeed, EPA's experts at trial expressed confidence in the NTP Monograph's methodologies. Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1197:2-15 (Savitz) (expressing confidence in NTP's literature search strategy and its ability to identify all relevant studies on fluoride exposure published prior to the closing date of April 21, 2021, and agreeing that the "vast majority of studies" that NTP reviewed identified an association between fluoride and reduced IQ). *See also* Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1140:10-19 (Savitz) ("I don't have any reason to challenge [this conclusion], but I haven't corroborated it by going through the dozens of studies one-by-one to make my own assessment."). Further, Dr. Savitz, the expert called by the EPA herein, acknowledged he is not an expert in conducting risk assessment, and particularly not under Amended TSCA. Dkt. No. 415, Feb. 9, 2024, Trial Tr. at 1264:2-6 (Savitz). Formal publication of the NTP Monograph affirms its quality. *See also* ¶ 33.

d. As explained previously, studies published after the NTP Monograph's literature cut-off date likewise observed a negative association between fluoride and children's cognition: Goodman (2022(a)), Cantoral (2021), Godebo (2023), and Adkins (2022)). *See* ¶ 37.

e. Further, notwithstanding difficulties in observing effects of a chemical at lower levels, *see* ¶ 45, adverse outcomes have even been observed at those levels with statistical significance: Green (2019) and Bashash (2017), ¶¶ 42-43.

f. As explained previously, some studies have not observed an association between fluoride and reduced IQ: Soto-barreras (2019), ¶ 35(h); Ibarluzea (2021), ¶ 38(a); Dewey 2023, ¶ 38(b); Do (2022), ¶ 38(c); and the OCC Cohort, ¶ 44. However, complete consistency amongst studies is not expected. Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1172:23-1173:6 (Savitz). To this end, various co-factors or susceptibilities can influence the impact or manifestation of neurotoxicants, and as such, it is to be expected that there will be some variability in results across studies of different populations. *See id.* What may appear to be a discrepant result may, in fact, reflect unmeasured differences in cofactors that influence the course of a chemical's

neurotoxicity. *See* Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 102:22-104:24 (Hu); Dkt. No. 417, Feb. 1, 2024, Trial Tr. at 242:21-243:9 (Lanphear), 328:14-23 (Grandjean). And, as also explained previously, particular characteristics of these studies finding null outcomes render them less probative here. *See* ¶ 39. Namely, Ibarluzea (2021) found an unrealistic 15-point IQ benefit, included unexplained and implausible results regarding creatinine adjustments, and failed to control for seafood, ¶ 39(a); Dewey (2023) did not account for previous residence of mothers or continued excretion of fluoride from skeletal breakdown during pregnancy in the control group, ¶ 39(b); Do (2022) utilized an unreliable IQ test and did not analyze individualized data, ¶ 39(c); and the OCC Cohort measured lower exposure levels which makes it more difficult to observe adverse effects, ¶ 45.

53. Though not definitive, there is additional evidence that supports the **plausibility** of the association by assessing potential *mechanisms* for fluoride to impact IQ. Specifically, studies have endeavored to consider explanations for the observed association between fluoride and IQ and hypothesize that thyroid disruption may be the mechanism by which fluoride impacts cognitive function:

a. Goodman (2022b) studied samples from the MIREC Cohort to assess the three-way interplay between prenatal fluoride exposure, maternal iodine status, and child IQ. Dkt. No. 432-12, Trial Ex. 116 at 1, 8. The study found that the negative association between fluoride exposure and IQ observed in Green (2019) was exacerbated by low maternal iodine in pregnancy among boys. *Id.* The study hypothesized that change in thyroid function may be a mechanism by which fluoride impacts cognition; iodine impacts thyroid function. *Id.* at 1-2.

b. Hall (2023): studied samples from the MIREC Cohort and concluded that fluoride in drinking water was associated with increased risk of hypothyroidism in pregnant women, and that thyroid disruption may contribute to developmental neurotoxicity of fluoride. Dkt. No. 432-16, Trial Ex. 120 at 1-2.

54. A lack of a dose-response relationship in the data may suggest that the effect is not related to the putative neurotoxic effect or that the study was not appropriately controlled. Dkt. No. 429-7, Trial Ex. 17 (Guidelines for Neurotoxicity Risk Assessment, Fed. Reg. 63(93):26926-26954

(hereinafter "EPA Guidelines"))[18] at 50. As discussed in the next section regarding the dose-response assessment, there is some lack of clarity as to the precise dose-response relationship at lower exposure levels of fluoride. However, evidence indicates that there is no **threshold** by which fluoride and adverse IQ cease to be associated. *See* ¶¶ 42-43.

55. In conclusion, this evidence is sufficient to proceed to the dose-response assessment of the analysis. *Cf.* Methylene Risk Evaluation at 262 (conducting dose-response analysis for Methylene under Amended TSCA based upon one animal study).

3. Step 1C: Dose-response assessment

a. *Framework*

56. The point at which the chemical ceases to be safe is known as the "point of departure" (*i.e.*, "POD") or "hazard level." *See* Dkt. No. 429-20, Trial Ex. 38 at 1; Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 495:9-14 (Barone); Dkt. No. 421 at 5. To this end, the dose-response assessment describes the relationship between dosage of the chemical and a response, and endeavors to identify the dosage at which a chemical is safe, and conversely, becomes hazardous; this is the point of departure. *See* EPA Guidelines at 57. *See also* Dkt. No. 429-20, Trial Ex. 38 at 1 (describing that the objective of the dose-response assessment is to "document the relationship between dose and toxic effect").

57. There are different points of departure that can be used in a risk assessment. EPA Guidelines at 57-58. The first approach is the NOAEL/LOAEL approach. *See* Dkt. No. 429-19, Trial Ex. 38 at 3-4. A No-Observed-Adverse-Effect Level ("NOAEL") is the "highest exposure level at which no statistically or biologically significant increases are seen in the frequency or severity of adverse effect between the exposed population and its appropriate control population." *Id.* at 4. In cases in which a NOAEL cannot be identified, the term lowest-observed-adverse-effect level ("LOAEL") is used, which is the lowest dose tested at which an adverse effect is detected.

[18] These Guidelines were published in April 1998 and are the currently applied guidelines for EPA Neurotoxicity Risk Assessment according to the EPA's website. *See Guidelines for Neurotoxicity Risk Assessment*, UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (last visited September 12, 2024), https://www.epa.gov/risk/guidelines-neurotoxicity-risk-assessment.

Id. at 4. Alternatively, when possible, the benchmark dose ("BMD") approach can be used to arrive at a point of departure. *Id.*

58. The BMD approach is preferred over the NOAEL/LOAEL approach, and use of a NOAEL is preferred over the LOAEL. *Id. See also* Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 495:23-496:25 (Barone); EPA Guidelines at 2-3, 57-58; Dkt. No. 421 at 5 (undisputed fact). The NOAEL/LOAEL approach derives the point of departure from a dosage and corresponding response in subjects that was actually observed. *See* EPA Guidelines at 57-59. *See also* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 672:1-11 (Barone) ("So generally a NOAEL or LOAEL, as we described earlier, comes directly from what is the observed concentration for an effect or no effect. So it's directly coming from the study of where that threshold for non-cancer – generally gets a threshold – where does that concentration occur. And that's describing, generally speaking, a single dose. It's within the dose continuum of how many doses were employed in the study, what concentration did they measure an effect."). *See also* EPA Guidelines at 57-59. The NOAEL/LOAEL is thus limited to only dosages observed in the study. *See* EPA Guidelines at 57-59. Other limitations of the NOAEL/LOAEL approach include that this approach is highly dependent upon sample size of a study (*e.g.*, where a sample size is limited, it might present a higher point of departure than the true point of departure), and it does not account for the shape of the dose-response curve from the experiment at issue. *Id*. Because of these limitations, the BMD approach is preferred if the data set is appropriate for such modeling. *See* Dkt. No. 429-20, Trial Ex. 38 at 4; Dkt. No. 400, Feb. 5, 2024, Trial Tr. at at 479:14-580:9 (Barone).

59. In utilizing the BMD approach, a benchmark dose, *i.e.*, BMD or benchmark concentration ("BMC") is identified. *See* Dkt. No. 429-20, Trial Ex. 38 at 4. The BMD/BMC is the dose of a substance that produces a "predetermined change in the response rate of an adverse effect." *Id*. The benchmark dose level ("BMDL") or benchmark concentration level ("BMCL") is the lower end of the statistical confidence limit on the dose that produces the selected response. *Id.* In other words, there is a statistical confidence interval on either side of the BMD/BMC; the BMDL/BMCL is the point at the lower side of that confidence interval. *See id.* Like the NOAEL/LOAEL, the BMCL/BMDL can be used as the point of departure. *Id.*

b. *Key findings*

60. 0.28 mg/L, or alternatively, 0.768 and/or 1.536 mg/L measured in maternal urinary fluoride is associated with a 1-point decrease in IQ of girls and boys and is a legitimate point of departure (BMCL) to use in this risk evaluation.

61. Alternatively, 4 mg/L measured in either urinary fluoride or water fluoride, is a legitimate, conservative point of departure (LOAEL) to use in the risk evaluation.

62. Regarding the weight of the scientific evidence, the quality and weight of the evidence in the record substantiates points of departure derived from either BMD modeling of the data or from a LOAEL/NOAEL approach.

c. *Underlying findings*

(a) POD: 0.28 mg/L BMCL (Grandjean (2023)) or in the alternative, 0.768 mg/L and/or 1.536 mg/L BMCL (Grandjean (2022))

63. Dr. Philippe Grandjean ("Grandjean") was the lead author of two pooled BMCL analyses, one published in 2022 and another in 2023. Dkt. No. 432-20, Trial Ex. 124. (hereinafter "Grandjean (2022)"); Dkt. No. 432-15, Trial Ex. 119 (hereinafter "Grandjean (2023)").

64. Dr. Grandjean and his co-authors are well-regarded for their benchmark dose analyses. To this end, EPA cited a pooled benchmark dose analysis authored by Grandjean as an example of how to perform such an analysis in its Benchmark Dose Technical Guidance Manual, and EPA has relied upon the authors' benchmark dose analysis work in its assessment of other chemicals. Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 287:16-288:18 (Grandjean), 479:25-5 (Grandjean); Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 748:19-750:6 (Barone).

65. Grandjean (2022) analyzed data from two cohorts, the ELEMENT Cohort and the MIREC Cohort to conduct its BMCL analysis. Grandjean (2022) at 1-2. Grandjean (2023) analyzed three cohorts: ELEMENT, MIREC, and the OCC cohorts. Grandjean (2023) at 1.

66. The pooled BMCL analyses of the birth cohorts sought to determine the level of fluoride in maternal urine ("MUF") that is associated with a 1-point drop in the IQ of the mothers' offspring. Dkt. No. 417, Feb. 1, 2024, Trial Tr. at 339:13-23 (Grandjean). As described by RSI, "[t]he choice of a BMR of 1 IQ point (corresponding to a 1% reduction from a mean IQ of 100)

has been adopted as an appropriate benchmark on this endpoint by several regulatory bodies, including the US EPA and EFSA." Dkt. No. 433-4, Trial Ex. 129 at 27. Pooled analyses are also particularly useful because a pooled analysis benefits from heightened statistical power and precision that comes from large samples sizes. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 111:9-112:16 (Hu).

67. Grandjean (2023) concluded that "[t]he joint analysis of all three cohorts showed a statistically significant association between urine-fluoride and IQ, with a BMC of 0.45 mg/L (BMCL, 0.28 mg/L)." Grandjean (2023) at 1-2. Specifically, Grandjean (2023) found that the BMCL associated with a 1-point decrease in IQ scores of boys and girls was 0.28 mg/L maternal urinary fluoride; this BMCL was adjusted for creatinine and derived from use of a linear dose-response model. Grandjean (2023) at 1-2, 9. This BMCL is a legitimate point of departure to use in the risk evaluation for fluoride.

68. When determining whether the point of departure can be derived using the BMD or BMC approach, as opposed to identifying a LOAEL or NOAEL, it is necessary to consider whether the data set is appropriate for use in the BMD/BMC modeling. *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 658:9-659:10 (Barone) (explaining that in identifying studies and key endpoints to "carry forward to the dose-response analysis," the assessor considers whether "are [the studies] amenable to BMDS, benchmark dose modeling? Are they amenable to a LOAEL/NOAEL approach? Should we use some other type of approach?"). To this end, the EPA's technical guidance provides that the following should be considered as to whether the data set is appropriate for BMD modeling: (1) whether there is a statistically or biologically significant dose-related trend in the selected endpoint; (2) whether a response is not only seen at a high dose; and (3) where there are adequate model fits. *See* Benchmark Dose Technical Guidance, U.S. ENVIRONMENTAL PROTECTION AGENCY (June 2012) available at https://www.epa.gov/sites/default/files/2015-01/documents/benchmark_dose_guidance.pdf (hereinafter "EPA's Benchmark Dose Technical Guidance") at 12-18.[19]

[19] This document was not submitted as an exhibit, but the EPA's witnesses rely on the document for their testimony. *See, e.g.*, Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 745:9-25 (Barone) ("Q:

69. For the reasons discussed below, the data that Dr. Grandjean analyzed is appropriate for use in BMD modeling, and for similar reasons, his point of departure is supported by the weight of the scientific evidence. *See* ¶ 51 (discussing weight-of-scientific-evidence factors). It is demonstrated by a preponderance of the evidence.

70. As explained previously, there is a well-supported and documented, statistically significant dose-related trend in the selected endpoint (reduced IQ). *See* ¶¶ 52-53 (discussing the robust body of evidence establishing the relationship between fluoride and reduced IQ, including studies observing this relationship at "lower" exposure levels).

71. Dr. Grandjean rests his BMCL analysis upon studies observing the ELEMENT, MIREC, and OCC cohorts. Grandjean (2023) at 1-2. These high-quality studies are appropriate for use in BMD modeling, particularly because they include data regarding dose-response at "lower" exposure levels, *i.e.*, 0.9 mg/L (mean maternal urinary fluoride in ELEMENT cohort), 0.42 mg/L (mean maternal urinary fluoride in MIREC cohort), and 0.58 mg/L (average maternal urinary fluoride in the OCC cohort). *See* ¶¶ 42-44. Thus, rather than observing only a response at high dosages, the data set utilized by Dr. Grandjean observes dose-response at low exposure levels. The data set are thus appropriate for BMD modeling. To this end, RSI found that the MIREC and ELEMENT cohorts represent a "high quality of evidence partly based on Canadian population, conducted within a context relevant to Canadian drinking water fluoride exposure levels.[20] Both studies included prospective data collection, with prenatal exposure assessment (maternal urine collection over successive trimesters) and follow-up during the early life of the infants and children." Dkt. No. 433-4, Trial Ex. 129 at 23. And the ELEMENT and MIREC cohort studies

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Now, moving beyond semantics, I wanted to ask you about your testimony about benchmark dose, okay? You made comments in your testimony about Dr. Grand[j]ean's BMCL analysis, correct? A. Yes, I did. Q. You based your comments on EPA's BMD guidance technical manual, correct? A. Yes, I did."). The Court thus considers this technical guidance document.

[20] The United States and Canada take a similar approach to water fluoridation; this finding is applicable to United States drinking water fluoride exposure levels. *See* Tr. Ex. 129, Dkt. No. 433-4 at 16 (describing optimal water fluoride levels in Canada of 0.7 mg/L). *See also* Dkt. No. 396, Feb. 1 , 2024 Trial Tr. at 245:1-22 (Lanphear) (describing optimal 0.7 mg/L water fluoride standard in Canada).

are strong for their extensive control for covariates and individualized measurements of fluoride exposure during the prenatal period. Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 95:2-96:5 (Hu).

72. The model fits of the data utilized by Grandjean's BMCL are also adequately supported. On this point, the EPA takes issue with the fact that Dr. Grandjean's BMCL of 0.28 mg/L was derived by applying a linear model of the dose-response curve.[21] Grandjean (2023) at 1-2, 9. To discern the best model fit for a set of data, a model is used to find a fit to the data, and based upon that fit, an "AIC" score is generated; the lower the AIC score, the better the model fit. Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 421:20-21 (Grandjean). To EPA's point, Grandjean (2023) did not include a published table illustrating the AIC scores for all model fits, but did so only for the linear model and piece-wise model, though not the squared model. *See* Grandjean (2023) at 9 (Table S3). The government thus argued at trial that Dr. Grandjean improperly assumed, without testing the assumption, that the linear model was appropriate for the data set evaluated. However, the use of the linear model in Grandjean (2023) to generate the BMCL is sufficiently justified:

i. Dr. Grandjean testified, and the Court finds this testimony credible, that he did not assume that the linear model was the best fit, but rather that he and his co-authors compared various models and determined that the linear model was the preferred model for the data. Dkt. No. 396, Feb. 1, 2024, Trial Tr. at 333:6-19 (Grandjean). Dr. Grandjean did state that "[i]n my communications with the EPA, I was told that the default curve function was the linear one." *Id.* at 333:8-9. However, Dr. Grandjean clarified that this default was only a starting point

[21] When a curve is linear, generally the dose and effect increase or decrease in a somewhat uniform fashion, *i.e.*, when the dose increases, the effect increases; when the dose decreases, the effect decreases. *See* EPA's Benchmark Dose Technical Guidance at 25-26, 77-78 (describing linear, quadratic, and other models), 71 (defining "Linear Dose-Response Model" as "[a] mathematical relationship in which a change in response is proportional to a fixed amount of change in dose, e.g., Response = a + b × Dose. This is in distinction from a more general linear mathematical model, which is a linear combination of parameters"). The shape of the dose-response curve is relevant, particularly because it is used to extrapolate to lower levels of exposure not observed in the study, and thus to calculate the BMCL. *See id.* at 5 ("The dose response assessment under the guidelines is a two-step process: (1) response data are modeled in the range of empirical observation — modeling in the observed range is done with biologically based or curve-fitting models; and then (2) extrapolation below the range of observation is accomplished by modeling, if there are sufficient data, or by a default procedure (linear, nonlinear, or both)."). The model will thus determine the BMCL identified. *See id.* at 5, 25-26, 77-78.

and that "what we've done in our work is to compare that to some variations and the statistical methods so that you can actually compare the fit if, let's say, curvilinear or a broken line fits better. And in our case the linear was actually – was the best fit." *Id.* at 333:10-14. And further, Dr. Grandjean testified that he also used "nonlinear methods to assess whether the dose-response relationship is linear," *id.* at 333:15-19. *See also id.* at 339:24-340:7 ("We started out with EPA's default recommendation, namely that linear association. But we then also looked at a curvilinear, for example, log 2 transformation of exposure. We also looked at broken lines of – and overall the linear association was not inferior to anything. It was sometimes clearly superior."); Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 440:23-419:1 (Grandjean) ("[W]e certainly did look at other models."). Dr. Grandjean and his co-authors did not simply assume that the linear model was the best fit for the data. It was chosen through an analytical process.

ii. Moreover, Grandjean (2022) includes a table that reports the AIC scores for squared models as they fit to data from the MIREC and ELEMENT cohorts and reveals comparable fit scores and supports Dr. Grandjean's testimony as to the validity of the linear model fit:

Table 2.

Benchmark Concentration Results (mg/L Urinary Fluoride, Creatinine-Adjusted) for a BMR of 1 IQ Point Obtained from the MIREC Study and the Two Cognitive Assessments from the ELEMENT Study as Well as the Joint Results. Two Concentration-Response Models are used, a Linear and One with the Squared Exposure Variable. For both Models, Sex-Specific and joint benchmark Results are Provided. The fit of the Regression models was Compared by the AIC (Where Lower Values Indicate a Better Fit)

Study		MIREC (n = 407)		ELEMENT IQ (n = 211)		ELEMENT GCI (n = 287)		MIREC and ELEMENT IQ (n = 618)			MIREC and ELEMENT GCI (n = 694)		
Model	Sex	BMC	BMCL	BMC	BMCL	BMC	BMCL	BMC	BMCL	AIC	BMC	BMCL	AIC
Linear	Both	0.497	0.228	0.200	0.122	0.159	0.099	0.326	0.201	4770.1	0.312	0.192	5491.3
Linear	Boys	0.201	0.125	0.275	0.130	0.148	0.084	0.222	0.144	4766.7	0.184	0.125	5488.4
Linear	Girls	∞	0.609	0.160	0.091	0.169	0.087	1.098	0.275	4766.7	2.972	0.315	5488.4
Squared	Both	1.545	0.896	0.614	0.496	0.611	0.467	1.008	0.768	4768.8	1.133	0.807	5493.9
Squared	Boys	0.840	0.622	0.684	0.496	0.581	0.435	0.787	0.619	4769.4	0.761	0.601	5493.7
Squared	Girls	∞	1.262	0.576	0.449	0.642	0.434	1.637	0.866	4769.4	∞	1.040	5493.7

Abbreviations: AIC, Akaike Information Criterion; BMC, benchmark concentration; BMCL, benchmark concentration level; BMR, benchmark response; GCI, Global Cognitive Index; IQ, Intelligence Quotient.

Grandjean (2022) at 17 (Table 2) (red annotation added). The AIC scores for the linear and squared models were comparable, with the best fit for boys and girls individually, measuring IQ, using a linear model (AIC 4766.7 linear compared to 4769.4 squared), and squared combined (AIC 4768.8 squared compared to 4770.1 linear). *See id.* For GCI (the General Cognitive Index

score), the linear model was a better fit than the squared model for all categories. *See id.* Even if not definitive, the comparable AIC fits for linear and squared models reflected in Grandjean (2022) support that the linear model is a justifiable model to apply to the MIREC and ELEMENT cohort data.

iii. Dr. Grandjean's analysis is also consistent with the NTP's analysis.

The NTP Meta-analysis did not publish AIC scores for models restricted to low-risk-of bias studies. *See* Dkt. No. 431-2, Trial Ex. 68 at 40-41 (eTable 4) (hereinafter "NTP Meta-analysis"). However, it did publish AIC scores for model fit of data in all studies, as reflected in the below table:

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Urinary Fluoride – All Studies					
No. Studies/No. Observations		18/32	13/26	7/11	5/8
Number of Children		8,502	6,885	4,654	3,992
Linear Model[b]	Beta (95% CI)	−0.16 (−0.24, −0.08)	−0.17 (−0.30, −0.05)	−0.06 (−0.14, 0.01)	−0.09 (−0.16, −0.01)
	p-value	p < 0.001	p = 0.005	p = 0.094	p = 0.026
	AIC	AIC = 73.8	AIC = 68.0	AIC = 1.2	AIC= 2.8
Quadratic Model[c]	Beta (95% CI); p-value	−0.10 (−0.31, 0.11); p = 0.360	0.07 (−0.23, 0.38); p = 0.645	−0.22 (−0.65, 0.20); p = 0.303	0.65 (−1.46, 2.76); p = 0.548
	Beta (95% CI); p-value	−0.01 (−0.05, 0.02); p = 0.496	−0.07 (−0.16, 0.01); p = 0.071	0.08 (−0.13, 0.30); p = 0.456	−0.66 (−2.11, 0.80); p = 0.379
	AIC	AIC = 84.3	AIC = 75.8	AIC = 9.2	AIC = 8.3
	p-value*	p* = 0.14	p* = 0.08	p* = 0.42	p* = 0.10
Restricted Cubic Splines Model[d]	Beta (95% CI); p-value	−0.12 (−0.28, 0.04); p = 0.150	−0.03 (−0.22, 0.16); p = 0.741	−0.14 (−0.32, 0.04); p = 0.130	−0.52 (−1.65, 0.62); p = 0.371
	Beta (95% CI); p-value	−0.10 (−0.43, 0.23); p = 0.545	−0.24 (−0.47, −0.002); p = 0.048	0.13 (−0.17, 0.43); p = 0.395	0.63 (−1.32, 2.59); p = 0.524
	AIC	AIC = 79.6	AIC = 73.3	AIC = 8.5	AIC = 6.7
	p-value*	p* = 0.13	p* = 0.07	p* = 0.37	p* = 0.07

Id. Using urinary fluoride as the exposure metric, the linear model reflected the lowest AIC score unilaterally. *See id.* And although the linear model did not generate a statistically significant inverse association at all exposure levels, the linear model generated a statistically significant inverse association at <1.5 mg/L (in line with Grandjean (2023)'s finding relating to lower-exposure levels as noted above), and the findings remained directionally negative at all levels which also supports Grandjean (2023)'s use of the linear model. *See* Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 115:16-25 (Hu) ("In fact, epidemiology is moving away from a simple reliance on just P values and saying 'this is significant, this is not significant.' It's really important to also look at the so-called directionality of the relationships."). Additionally, as explained in more detail below, some of the loss of association observed in the NTP Meta-analysis may be explained by the

use of the means effect method in the Meta-analysis, which results in loss of statistical power and sensitivity in the data. *See* ¶ 74(b). Ultimately, the authors of the NTP Meta-analysis concluded that "[b]ased on the AIC and likelihood ratio tests, the best model fit was achieved when quadratic or restricted cubic spline exposure levels were added to the linear models for drinking water (eFigure 17); ***the linear model was the best fit for urinary fluoride*** (eFigure 18)." NTP Meta-analysis at 10 (emphasis added). This further bolsters the legitimacy of Grandjean (2023)'s use of a linear model to generate the BMCL, expressed in maternal urinary fluoride.

73. Assuming, in the alternative, that the squared model is a more appropriate fit for this data set, as EPA suggested at trial, a BMCL of 0.768 mg/L and/or 1.536 mg/L is appropriately used to conduct the risk assessment. Though Grandjean (2023) did not identify a BMCL using the squared model, Dr. Grandjean's 2022 BMCL analysis did identify a BMCL of 0.768 mg/L utilizing a squared model. Grandjean (2022) at 17 (Table 2); Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 423:12-21 (Grandjean). It is true that this BMCL is derived from the ELEMENT and MIREC cohort data only and excludes data from the OCC Cohort. This is relevant because inclusion of the OCC Cohort data is likely to increase the BMCL; when the OCC cohort data was added to the BMCL analysis in Grandjean (2023), the BMCL increased by 0.08 mg/L, or forty percent[22] (from 0.20 mg/L (MIREC and ELEMENT alone) to 0.28 mg/L (MIREC, ELEMENT and OCC cohort data)). *See* Grandjean (2023) at 3 ("The joint BMC was found to be 0.45 mg/l (BMCL, 0.28 mg/l), *i.e.* slightly higher than previously found (BMC, 0.33 mg/l; BMCL, 0.20 mg/L) for the two North American cohorts alone."). But a preponderance of the evidence indicates the inclusion of the OCC Cohort data would not make a material difference. To be highly conservative, the BMCL of 0.768 mg/L can be *doubled*, to account for any discrepancy caused by the omission of the OCC data: 1.536 mg/L (0.768 mg/L times two). This could be used conservatively as an alternative point of departure implied from the data if the squared model is used. As discussed below, even using this higher point of departure, the ultimate finding of an unreasonable risk would not change.

[22] ((.08 / .20) * 100).

74. One additional concern with Dr. Grandjean's BMCL calculation is that it, at first glance, appears to be in tension with the NTP Monograph's conclusion that "[m]ore studies are needed to fully understand the potential for lower fluoride exposure [i.e., below 1.5 mg/L] to affect children's IQ." NTP Monograph at xiii.[23] However, this ultimately does not undermine the validity of the BMCL identified in Grandjean (2023) for the following reasons:

a. Though the authors of the NTP Monograph recognized some lack of clarity in the precise relationship between fluoride and reduced IQ at lower exposure levels, NTP Monograph at xiii, given the strength of the association between fluoride and reduced IQ, the authors of the NTP Monograph refused to limit the applicability of its findings in the systematic review to higher exposure levels and made clear that its confidence assessment also considered fluoride exposures "that are similar to, or lower than, those associated with optimally fluoridated water supplies in the United States," *i.e.*, 0.7 mg/L. Dkt. No. 438-1, Trial Ex. 69 at 24-25 (comments and responses from NTP Monograph authors and evaluators of the NTP Monograph).

b. The NTP also conducted a Meta-analysis, integrating all of the studies assessed in the NTP Monograph to analyze the dose-response relationship between fluoride and reduced IQ. The findings of the NTP Meta-analysis first appear to be in tension with Dr. Grandjean's findings but are, in fact, consistent with those findings because of the methodologies used. Namely, the NTP Meta-analysis concluded that "the consistency of the data supports an inverse association between fluoride exposure and children's IQ." NTP Meta-analysis at 3. However, the Meta-analysis reported somewhat mixed results regarding the dose-response relationship, particularly at

[23] Regarding "lower" fluoride exposure levels – both Grandjean (2023) and the NTP Monograph analyzed data from the ELEMENT and MIREC cohorts though Grandjean (2023) also analyzed data from the OCC Cohort, another lower-exposure level study.

lower levels of fluoride exposure:

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Linear model	Beta (95% CI) p-value AIC	−0.15 (−0.23, −0.07) p < 0.001 AIC = 74.5	−0.16 (−0.28, −0.04) p = 0.011 AIC = 68.6	−0.05 (−0.14, 0.04) p = 0.259 AIC = 1.3	−0.08 (−0.16, −0.01) p = 0.036 AIC = 3.0
Urinary Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations Number of Children		9/15 5,713	9/15 5,713	5/8 4,141	4/7 3,952
Linear model	Beta (95% CI) p-value AIC	−0.10 (−0.21, 0.01) p = 0.082 AIC = 5.9	−0.10 (−0.21, −0.01) p = 0.082 AIC = 5.9	−0.05 (−0.17, 0.08) p = 0.472 AIC = 2.8	−0.08 (−0.16, −0.01) p = 0.028 AIC = 2.5

Id. at 41 (eTable 4) (red annotation added). In reviewing all studies and measuring exposure of fluoride per urinary fluoride the NTP Meta-analysis found a statistically significant inverse association between children's urinary fluoride exposure and IQ at <4 mg/L urinary fluoride. *Id.* When restricted to <2 mg/L and <1.5 mg/L urinary fluoride, there was still an inverse association. *Id.* This finding is consistent with Grandjean (2023). However, when analyses were restricted to low risk-of-bias publications, the associations at <2 mg/L and <1.5 mg/L became smaller in magnitude and were only statistically significant at <1.5 mg/L, but not at <2 mg/L. *Id.* That finding of an adverse association at <1.5 mg/L is consistent with the conclusion in Dr. Grandjean's pooled benchmark dose analysis (though appearing somewhat anomalous compared to the finding at <2 mg/L). Dr. Grandjean's pooled benchmark analysis uses a method with more statistical precision than the NTP Meta-analysis, and thus could account for the more specific findings as to the relationship between fluoride and IQ at lower exposure levels. Specifically, the NTP Meta-analysis used a "means effect analysis," which is useful for its ability to compare different types of studies with varied methodologies and metrics (72 total and 19 low-risk-of-bias studies) – but it loses sophistication and precision in the underlying data of each study when it converts the findings into standard, comparable metrics. Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 469:3-471:6 (Grandjean). Specifically, so that different studies using different exposures or result metrics could be compared, the data was grouped into buckets (*e.g.*, high exposure, low exposure) and analyzed. *Id.* at 471:6-15. Accordingly, each of the underlying studies lose some of its statistical power when data is simplified to allow for cross-study, like-to-like comparison. *See id.* at 471:6-473:24. On the other hand, the pooled benchmark analysis maintains individualized, continuous

data and does not simplify that data for meta-analysis comparison; the benchmark analysis maintains increased sophistication and statistical sensitivity. *Id.* at 473:18-24. Thus, the findings of the NTP Meta-analysis are not inconsistent with Dr. Grandjean's pooled benchmark analysis.

75. Ultimately, TSCA does not require complete certainty as to the threshold level at which a chemical produces the hazard; indeed, such certainty is very difficult to obtain from epidemiologic studies of human populations. Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1440:18-23 (Barone); Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1173:7-13 (Savitz). Either BMCL of 0.28 mg/L (linear model per the MIREC, ELEMENT, and OCC cohort data) or 0.768 mg/L (squared model per the MIREC and ELEMENT cohort data) identified by Dr. Grandjean and his co-authors are legitimate points of departure to utilize in a risk analysis. So is the implied BMCL of 1.536 mg/L (were the OCC study taken into account). The Court finds, though not with absolute certainty, Dr. Grandjean's BMCLs are supported by a preponderance of the evidence.[24]

(b) POD: 4 mg/L urinary or water fluoride (LOAEL)

76. As described previously, use of the BMD approach is preferred in identifying a point of departure because of limitations of a NOAEL or LOAEL, but where data is not amenable to benchmark dose modeling, a NOAEL or LOAEL may be utilized instead. *See* ¶¶ 57-59. The Court thus examines this alternative approached to establishing a point of departure.

77. Again, notwithstanding the limitations of the NOAEL/LOAEL approach, this approach is properly used, and has been used by the EPA, with the application of uncertainty factors, to determine the point of departure where datasets are, for various reasons, not amenable to BMD modeling. *See* Dkt. No. 429-20, Trial Ex. 38 at 4. For example, the EPA conducted a risk evaluation of Perchloroethylene ("PCE"), pursuant to Amended TSCA, and utilized NOAEL/LOAELs as PODs because it was unable to use BMD modeling. *See* PCE Risk Evaluation at 351 ("For this risk evaluation, non-cancer PODs were all based on NOAELs and LOAELs because the data for the selected endpoints was unable to be BMD modeled. This results

[24] The government also takes issue with the use of maternal urinary fluoride ("MUF") as the metric of the exposure or hazard level utilized in the risk assessment analysis. The validity of maternal urinary fluoride as a metric is taken up subsequently in Section III.B (Exposure Assessment).

in reduced precision in POD estimates because the POD is dependent on the dose selection of the study as opposed to the response rate/level for the effect of interest."); Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 772:3-11 (Thiessen).

78. To the extent that the BMD approach is not appropriate based upon the present data set, in the alternative, 4.0 mg/L (using exposure measurement of water fluoride intake) is a legitimate and highly conservative LOAEL to utilize as a point of departure to conduct a risk assessment of fluoride per the findings of the NTP Meta-analysis. Utilizing 4.0 mg/L as the LOAEL is especially conservative in view of the NTP Monograph's conclusion with moderate confidence that exposure to fluoride concentration in drinking water at or above 1.5 mg/L is associated with lower IQ in children. One could reasonably take 1.5 mg/L as a LOAEL. Nonetheless, the Court uses the more conservative 4.0 mg/L based on a close analysis of the NTP Meta-analysis which establishes with consistency an association with reduced IQ at that level. Specifically, the NTP Meta-analysis observed a statistically significant inverse association between fluoride and reduced IQ at 4 mg/L measured in water fluoride, based on low-risk-of-bias/high quality studies (*i.e.*, 6 epidemiological studies deemed high quality), which is reflected in the below table from the Meta-

analysis summarizing the NTP's dose-response analysis:[25]

eTable 4. Dose-Response Meta-analysis Using Mean Effects—Model Selection[a]

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Water Fluoride – All Studies					
No. Studies/No. Observations		29/39	21/27	7/9	7/7
Number of Children		11,656	8,723	2,971	2,832
Linear Model[b]	Beta (95% CI) p-value AIC	−0.15 (−0.20, −0.11) p < 0.001 AIC = 53.8	−0.22 (−0.27, −0.17) p < 0.001 AIC = 16.1	−0.15 (−0.41, 0.12) p = 0.274 AIC = 11.8	0.05 (−0.36, 0.45) p = 0.816 AIC = 8.2
Quadratic Model[c]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.27 (−0.34, −0.21); p < 0.001 0.02 (0.01, 0.03); p < 0.001 AIC = 48.8 p* < 0.001	−0.12 (−0.35, 0.11); p = 0.318 −0.04 (−0.10, 0.03); p = 0.280 AIC = 21.2 p* = 0.012	0.79 (−0.01, 1.58); p = 0.052 −0.56 (−0.97, −0.16); p = 0.006 AIC = 12.5 p* = 0.007	0.30 (−0.53, 1.14); p = 0.477 −0.23 (−1.01, 0.55); p = 0.561 AIC = 11.3 p* = 0.04
Restricted Cubic Splines Model[d]	Beta (95% CI); p-value Beta (95% CI); p-value AIC p-value*	−0.29 (−0.39, −0.20); p < 0.001 0.48 (0.18, 0.78); p = 0.002 AIC = 42.3 p* < 0.001	−0.14 (−0.34, 0.06), p = 0.162 −0.23 (−0.66, 0.20), p = 0.295 AIC = 16.9 p* = 0.009	1.15 (0.07, 2.22) p = 0.037 −1.20 (−2.03, −0.36) p = 0.005 AIC = 10.5 p* = 0.010	0.49 (−0.50, 1.47) p = 0.334 −0.69 (−2.40, 1.02) p = 0.428 AIC = 10.2 p* = 0.05
Water Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations		6/11	6/9	3/4	3/3
Number of Children		4,355	4,251	921	879
Linear model	Beta (95% CI) p-value AIC	−0.19 (−0.34, −0.05) p = 0.009 AIC = 10.3	−0.22 (−0.36, −0.07) p = 0.003 AIC = 3.9	−0.34 (−0.72, 0.03) p = 0.070 AIC = 4.5	−0.32 (−0.91, 0.26) p = 0.276 AIC = 4.1

Dkt. No. 431-2, Trial Ex. 68 at 39 (eTable4) (red annotation added). That value was derived from a linear model which, for this group of studies, had the lowest AIC score. *See id.* (identifying AIC of 16.1 (linear for all studies), 21.1 (quadratic for all studies), 16.9 (restricted cubic splines for all studies)).

[25] Note that where values in the parenthesis, which represent the confidence interval, are below zero, the finding is statistically significant. *See* Dkt. No. 417, Feb. 2, 2024, Trial Tr. at 394:2-14 (Grandjean).

79. Further, the NTP Meta-analysis observed an association between fluoride and reduced IQ at <4 mg/L measured in urinary fluoride, based on low-risk-of-bias/high-quality studies (9 epidemiological studies deemed high quality):

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Urinary Fluoride – All Studies					
No. Studies/No. Observations		18/32	13/26	7/11	5/8
Number of Children		8,502	6,885	4,654	3,992
Linear Model[b]	Beta (95% CI)	−0.16 (−0.24, −0.08)	−0.17 (−0.30, −0.05)	−0.06 (−0.14, 0.01)	−0.09 (−0.16, −0.01)
	p-value	p < 0.001	p = 0.005	p = 0.094	p = 0.026
	AIC	AIC = 73.8	AIC = 68.0	AIC = 1.2	AIC= 2.8
Quadratic Model[c]	Beta (95% CI); p-value	−0.10 (−0.31, 0.11); p = 0.360	0.07 (−0.23, 0.38); p = 0.645	−0.22 (−0.65, 0.20); p = 0.303	0.65 (−1.46, 2.76); p = 0.548
	Beta (95% CI); p-value	−0.01 (−0.05, 0.02); p = 0.496	−0.07 (−0.16, 0.01); p = 0.071	0.08 (−0.13, 0.30); p = 0.456	−0.66 (−2.11, 0.80); p = 0.379
	AIC	AIC = 84.3	AIC = 75.8	AIC = 9.2	AIC = 8.3
	p-value*	p* = 0.14	p* = 0.08	p* = 0.42	p* = 0.10
Restricted Cubic Splines Model[d]	Beta (95% CI); p-value	−0.12 (−0.28, 0.04); p = 0.150	−0.03 (−0.22, 0.16); p = 0.741	−0.14 (−0.32, 0.04); p = 0.130	−0.52 (−1.65, 0.62); p = 0.371
	Beta (95% CI); p-value	−0.10 (−0.43, 0.23); p = 0.545	−0.24 (−0.47, −0.002); p = 0.048	0.13 (−0.17, 0.43); p = 0.395	0.63 (−1.32, 2.59); p = 0.524
	AIC	AIC = 79.6	AIC = 73.3	AIC = 8.5	AIC = 6.7
	p-value*	p* = 0.13	p* = 0.07	p* = 0.37	p* = 0.07
Urinary Fluoride – Sensitivity analysis including Ibarluzea et al. (2021)[87] Bayley MDI scores					
No. Studies/No. Observations		19/33	14/27	8/12	6/9
Number of Children		8,815	7,445	4,967	4,305
Linear model	Beta (95% CI)	−0.15 (−0.23, −0.07)	−0.15 (−0.28, −0.03)	−0.04 (−0.14, 0.05)	−0.08 (−0.15, −0.003)
	p-value	p < 0.001	p = 0.015	p = 0.371	p = 0.043
	AIC	AIC = 75.0	AIC = 69.0	AIC = 1.7	AIC = 3.6
Urinary Fluoride – Sensitivity analysis including Ibarluzea et al. (2021)[87] McCarthy GCI scores					
No. Studies/No. Observations		19/33	14/27	8/12	6/9
Number of Children		8,749	7,445	4,901	4,239

Exposure Analysis	Parameters	Fluoride Exposure			
		All data	<4 mg/L	<2 mg/L	<1.5 mg/L
Linear model	Beta (95% CI)	−0.15 (−0.23, −0.07)	−0.16 (−0.28, −0.04)	−0.05 (−0.14, 0.04)	−0.08 (−0.16, −0.01)
	p-value	p < 0.001	p = 0.011	p = 0.259	p = 0.036
	AIC	AIC = 74.5	AIC = 68.6	AIC = 1.3	AIC = 3.0
Urinary Fluoride – Low Risk-of-bias Studies					
No. Studies/No. Observations		9/15	9/15	5/8	4/7
Number of Children		5,713	5,713	4,141	3,952
Linear model	Beta (95% CI)	−0.10 (−0.21, 0.01)	−0.10 (−0.21, −0.01)	−0.05 (−0.17, 0.08)	−0.08 (−0.16, −0.01)
	p-value	p = 0.082	p = 0.082	p = 0.472	p = 0.028
	AIC	AIC = 5.9	AIC = 5.9	AIC = 2.8	AIC = 2.5

Dkt. No. 431-2, Trial Ex. 68 at 39 (eTable 4) (red annotation added). That value was also derived from a linear model which, for this group of studies, likewise had the lowest AIC score. *See id.* (identifying 68 (linear for all studies), 75.8 (quadratic for all studies), 73.3 (restricted cubic splines for all studies)).

80. Even if there may be some uncertainty about the dose-response relationship below that exposure level (4 mg/L), significant data supports that there is an adverse effect *at or above the specified level*. *See* Dkt. No. 415, Feb. 12, 2024, Trial Tr. at 1373:1-9 (Barone) (testimony from

Dr. Barone agreeing that at 4 mg/L of fluoride exposure and above there is relatively more data to support a finding of an adverse effect associated with fluoride.), 1428:4-11 (Barone) ("I agree with the NTP's conclusions that at some level above 1.5 that there is moderate evidence to support an association between fluoride and developmental IQ decrements."). Again, TSCA does not require absolute certainty as to the threshold level at which a chemical produces the hazard, and indeed as noted above such certainty is very difficult to obtain from epidemiologic studies of human populations. Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1440:18-23 (Barone); Dkt. No. 414, Feb. 9, 2024, Trial Tr. at 1173:7-13 (Savitz). In view of the record evidence, 4 mg/L as the lowest-observed-effect-level would be a conservative point of departure to utilize in the analysis; it is certainly well-supported by scientific evidence as described in the conclusion of the NTP Monograph: "the high-quality studies (*i.e.*, studies with low potential for bias) consistently demonstrate lower IQ scores with higher fluoride exposure [*e.g.*, represented by populations whose total fluoride exposure approximates or exceeds the WHO Guidelines for Drinking-water Quality of 1.5 mg/L of fluoride (WHO 2017)]." NTP Monograph at 47.

81. The EPA has identified a LOAEL based upon far less evidence than that in the record before this Court. In the EPA's risk evaluation of Methylene, conducted pursuant to Amended TSCA, it used a LOAEL for developmental neurotoxicity, derived from the analysis of ***one study conducted upon mouse pups*** (Fredriksson et al., 1992). *See* Methylene Risk Evaluation at 262. Here, there are between six and nine[26] high-quality, epidemiological studies of human populations underlying the point of departure. Dkt. No. 431-2, Trial Ex. 68 at 39, 41 (eTable 4).

82. To restate, in conclusion, either the LOAEL of 4.0 mg/L, measured either in urinary fluoride or water fluoride, or the BMCL of 0.28 mg/L, 0.768 mg/L, or even 1.536 mg/L measured in maternal urinary fluoride, is a well-supported point of departure to utilize in the risk evaluation. Each of these measures of the point of departure is supported by a preponderance of high-quality evidence.

[26] Six studies measuring fluoride exposure by way of water fluoride and nine studies measuring urinary fluoride. Dkt. No. 431-2, Trial Ex. 68 at 39, 41 (eTable 4).

B. Step 2: Exposure Assessment

a. *Framework*

83. At this step, the EPA conducts an exposure assessment to identify the exposure level under the conditions of use for the chemical at issue. Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 567:18-568:2 (Barone); 15 U.S.C. § 2605(b)(4)(F)(iv) ("In conducting a risk evaluation under this subsection, the Administrator shall . . . take into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the conditions of use of the chemical substance."). Namely, the EPA identifies sources of exposure to the chemical (*e.g.*, food or water), estimates what the intake level of exposure is, and endeavors to understand and characterize the population that is exposed. Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 694:4-695:11 (Barone).

84. To understand the level of exposure, the EPA estimates a range of exposure levels for a condition of use from the central tendency exposure (*e.g.*, 50th percentile) to high-end exposure (*e.g.*, 95th percentile). Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 649:1-650:10 (Barone), 697:15-698:6 (Barone); *see also* EPA Guidelines at 64 (describing consideration of upper percentile exposure and highest-exposed individuals in risk assessment).

85. As discussed in depth in the next section (Section III.C), the exposure level is important because it is used to calculate whether the chemical presents a risk to humans. Specifically, in the next step of the analysis (risk characterization), the exposure level is compared to the point of departure to determine if a risk is present. *See* Dkt. No. 401, Feb. 6, 2024, Trial Tr. (Barone) at 705:7-706:21. At that step, the EPA determines the appropriate margin that needs to exist from the point of departure (*i.e.*, point at which the chemical becomes hazardous). *See id.* This is the benchmark Margin of Exposure ("MOE"). *See id.* The benchmark MOE is calculated by multiplying the point of departure by Uncertainty Factors ("UFs") to account for assumptions or uncertainty in the data. *See id.* The benchmark MOE is then compared to the actual MOE, *i.e.*, the existing margin between the exposure level and the point of departure, to determine if that margin is sufficient. *See id.*

b. *Key findings*

86. For reasons discussed below, **maternal urinary fluoride** is an appropriate metric to use in conducting the risk evaluation of fluoride under the condition of use, *i.e.,* community water fluoridation at 0.7 mg/L.

87. Pregnant mothers in fluoridated communities in the United States have a median exposure level to fluoride of **0.8 mg/L**, measured in **maternal urinary fluoride**; at the 95th percentile,[27] pregnant mothers have an exposure level to fluoride of **1.89 mg/L**, measured in **maternal urinary fluoride**. Approximately half of these maternal urinary fluoride levels is attributed to community water fluoridation.

88. Alternatively, the exposure levels of **0.7 mg/L,** or **0.56 mg/L** measured in **water fluoride**, is an appropriate exposure level to use in this risk evaluation.

c. *Underlying findings*

89. Two studies are highly probative in assessing exposure levels in this risk evaluation: Till (2018), and Malin (2023). To summarize these studies:

a. Till (2018) studied samples collected from the MIREC Cohort (1,566 pregnant women in Canada) to assess the relationship between maternal urinary fluoride in pregnant women and water fluoride concentrations and concluded that "[c]ommunity water fluoridation is a major source of fluoride exposure" for the pregnant women studied. Dkt. No. 432-4, Trial Ex. 108 at 1. Specifically, the study observed that the mean urinary fluoride values were almost two times higher for pregnant women living in fluoridated regions compared to non-fluoridated regions, and "significantly lower" for women living in non-fluoridated regions. *Id.* at 6. The median concentration of fluoride in drinking water in Canada was 0.56 mg/L in fluoridated areas. *Id.* at 8 (Table 2). Given that the United States fluoridates its water levels at an optimal 0.7 mg/L (higher than the median in Till (2018)), the urinary fluoride levels in this sample are lower, if anything, relative to the condition of use at issue (fluoridation at 0.7 mg/L). The findings of Till (2018),

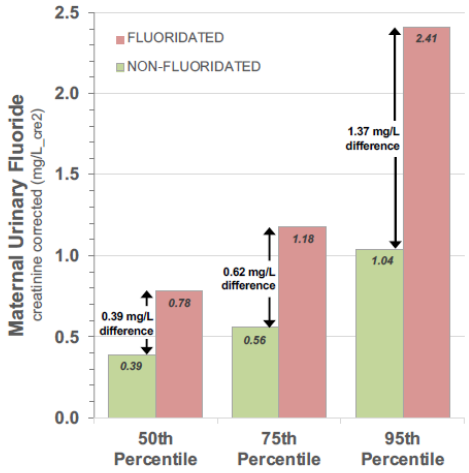
[27] The 95th percentile reflects individuals that have exposure levels greater than 95 percent of the population. *See* Dkt. No. 108 at 6. The median, on the other hand, reflects individuals at the mid-point of exposure. *See id.*

comparing the maternal urinary fluoride levels of pregnant women in fluoridated compared to non-fluoridated reasons are exemplified in the below tables, summarizing the key results of this study:

Table S4. Fluoride concentrations in the urine of pregnant women from the MIREC cohort living in fluoridated versus non-fluoridated communities.

	Trimester	N	Arith Mean	Arith SD	Geo Mean	Geo SD	Min	5%	25%	50%	75%	95%	Max
NON-FLUORIDATED													
MUF_Unadjusted	1	541	0.24	0.29	0.15	2.65	0.01	0.03	0.08	0.15	0.30	0.69	3.56
	2	509	0.32	0.33	0.23	2.22	0.03	0.06	0.13	0.22	0.38	0.90	3.54
	3	476	0.47	0.39	0.36	2.05	0.04	0.11	0.22	0.36	0.60	1.23	3.77
MUF_{SG}	1	541	0.31	0.39	0.20	2.56	0.01	0.04	0.12	0.20	0.35	0.84	4.67
	2	507	0.39	0.32	0.31	1.89	0.04	0.12	0.21	0.29	0.46	0.96	2.44
	3	475	0.48	0.32	0.40	1.78	0.08	0.17	0.28	0.38	0.56	1.09	2.71
MUF_{CRE_1}	1	533	0.50	0.50	0.35	2.40	0.01	0.08	0.22	0.37	0.60	1.41	4.5
	2	502	0.58	0.44	0.48	1.85	0.06	0.19	0.31	0.46	0.69	1.47	3.31
	3[a]	386	0.67	0.47	0.56	1.75	0.12	0.24	0.40	0.54	0.79	1.45	4.61
MUF_{CRE_2}	1	534	0.41	0.45	0.29	2.42	0.01	0.06	0.18	0.30	0.49	1.15	4.81
	2	502	0.43	0.32	0.35	1.85	0.04	0.14	0.23	0.34	0.51	1.08	2.43
	3[a]	386	0.48	0.33	0.40	1.75	0.08	0.17	0.29	0.39	0.56	1.04	3.29
FLUORIDATED													
MUF_Unadjusted	1	762	0.57	0.49	0.40	2.57	0.02	0.06	0.23	0.43	0.79	1.48	3.98
	2	728	0.71	0.53	0.56	2.03	0.04	0.17	0.35	0.56	0.89	1.68	3.77
	3	712	0.82	0.60	0.63	2.04	0.11	0.19	0.39	0.64	1.06	1.99	4.36
MUF_{SG}	1	762	0.52	0.46	0.37	2.44	0.01	0.07	0.25	0.4	0.64	1.30	3.84
	2	728	0.71	0.47	0.59	1.84	0.03	0.23	0.40	0.58	0.87	1.63	3.78
	3	711	0.88	0.55	0.74	1.81	0.08	0.27	0.51	0.77	1.08	1.89	3.97
MUF_{CRE_1}	1	757	0.83	0.68	0.60	2.44	0.01	0.12	0.39	0.65	1.09	2.19	4.89
	2	723	1.13	0.77	0.93	1.91	0.05	0.32	0.61	0.91	1.42	2.63	4.89
	3[a]	546	1.30	0.82	1.10	1.86	0.12	0.41	0.72	1.08	1.63	3.10	4.63
MUF_{CRE_2}	1	759	0.68	0.58	0.49	2.46	0.01	0.09	0.31	0.53	0.88	1.80	4.61
	2	727	0.85	0.60	0.69	1.92	0.04	0.24	0.45	0.67	1.05	2.00	4.66
	3[a]	553	0.97	0.68	0.80	1.90	0.09	0.29	0.52	0.78	1.18	2.41	4.78

Id. at 25 (Table S4) (red annotations added). This data is reflected in the below bar graph, illustrating that Till (2018) found that fluoride levels were approximately two times higher in fluoridated vs. non-fluoridated areas:[28]



[28] Though not in evidence, the Court includes this demonstrative bar graph (presented to the Court

b. Malin (2023) studied the maternal urinary fluoride levels of pregnant women in Los Angeles, California (*i.e.*, samples collected from the Maternal and Developmental Risks from Environmental and Social Stressors cohort ("MADRES Cohort")) to discern if those levels of American women were comparable to levels observed amongst pregnant women in Mexico and fluoridated communities in Canada. Dkt. No. 432-18, Trial Ex. 122 at 9. Malin (2023) concluded that the maternal urinary levels observed in Los Angeles were comparable to those found in pregnant women in Mexico and Canada. *Id.* at 1, 9. These findings corroborate the conclusions of Till (2018), and further support that water intake is an important contributor to maternal urinary fluoride levels.

90. Plaintiffs have shown, by a preponderance of the evidence, that a pregnant mother in the United States, under the condition of use (community water fluoridation of 0.7 mg/L, which is higher than the median water fluoridation levels in the Till (2018) data set of 0.56 mg/L found in Canada) produces a maternal urinary fluoride concentration level of at least **0.8 mg/L** for median water consumption or **1.89 mg/L** for 95th percentile water consumption.

a. As explained above, Till (2018) studied urinary fluoride levels in fluoridated areas of Canada, and identified a median (specific gravity adjusted) urinary fluoride level of 0.77 mg/L and a 95th percentile urinary fluoride level of 1.89 mg/L. Dkt. No. 432-4, Trial Ex. 108 at 25-26 (Table S4); Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 118:5-20 (Hu). Malin (2023) studied pregnant mothers living in Los Angeles, California, a fluoridated city, and similarly observed that those mothers had a median (specific gravity-adjusted) urinary fluoride level of 0.8 mg/L, and a 95th percentile level of 1.89 mg/L, in the third trimester. Dkt. No. 432-18, Trial Ex. 122 at 5 (Table 2); Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 124:1-16 (Hu). Dr. Hu testified credibly that the Malin (2023) cohort is representative of mothers in the United States as a whole, though if anything, this cohort would present *lower* fluoride exposure levels relative to other populations because data indicates Hispanic communities have a greater distrust of tap water relative to other communities, in part due to immigration from Mexico where tap water is distrusted. Dkt. No. 395,

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as Plaintiff's Demonstrative No. 4 at trial) to illustrate fully the trial testimony.

Jan. 31, 2024, Trial Tr. at 118:11-119:9 (Hu). Canada and the United States each take a similar approach to water fluoridation; both countries identify 0.7 mg/L as the optimal fluoridation level. *See* NTP Monograph at 1; Dkt. No. 396, Feb. 1, 2024, Trial Tr. at 245:1-22 (Lanphear). It follows that pregnant woman in the United States, exposed to fluoride under the condition of use at issue (community water fluoridation at a typical or optimal level of 0.7 mg/L) have an exposure level of **0.8 mg/L measured in maternal urinary fluoride** (median water intake) and **1.89 mg/L measured in maternal urinary fluoride** (95th percentile water intake), urinary fluoride levels that reflect the real world results of drinking water fluoride levels at the condition of use at issue in this case.

b. To be sure, maternal urinary fluoride reflects not only fluoride that a pregnant woman is exposed to from drinking fluoridated water from her community (the condition of use at issue), but also fluoride from other sources such as food and beverage and household items such as toothpaste; it reflects aggregate exposure to fluoride. *See* Dkt. No. 395, Jan 31, 2024, Trial Tr. at 105:10-25 (Hu); Dkt. No. 416, Feb. 12, 2024, Trial Tr. at 1404:19-21 (Barone); Dkt. No. 198-1 (Hu Trial Decl.). The EPA argues that because maternal urinary fluoride reflects *aggregate* fluoride exposure, rather than exposure attributed solely from community water fluoridation, maternal urinary fluoride is an inappropriate metric to use in assessing the risk of community water fluoridation. However, exposure level of fluoride expressed in the metric of maternal urinary fluoride is properly used in this risk assessment because:

i. Maternal urinary fluoride, though not a perfect metric in all respects, is a valuable metric in assessing risk associated with water fluoridation since it is a comprehensive metric, reflecting the true aggregate exposure to the chemical at issue. As Dr. Hu explained: "[T]he primary benefit [of using urinary fluoride as the metric of fluoride exposure] is that you're integrating fluoride exposure from whatever exposure source there is. So if it's dietary, if it's in the water, it's in the food, it's in the food that was cooked with the fluoridated water; if you happen to swallow toothpaste or if you're using other sources of fluoride, it will integrate all of it and express it in terms of what is the level of fluoride that's circulating in your blood and then gets filtered out into the kidneys. And that ultimately is the component of fluoride in the body that's

available to cross the blood-brain barrier to the brain and also to go to other target organs in the body." Dkt. No. 395, Jan. 31, 2024, Trial Tr. at 105:13-25 (Hu). Put differently, this metric reflects that water fluoridation does not occur in a vacuum; in the real world, fluoridating water means exposing women to fluoride *in addition to* the exposure a woman has to fluoride via other sources. Because dosage matters, it makes good sense to consider other sources of exposure to fluoride in deciding if adding to that exposure level presents a risk. *See* Dkt No. 400, Feb. 5, 2024, Trial Tr. at 676:12-21 (Barone) (recognizing that exposure and point of departure can be expressed in urine content in a risk assessment); Dkt. No. 402, Feb. 8, 2024, Trial Tr. at 1015:9-1020:13 (Savitz) (discussing pros and cons of using urinary fluoride as a measurement of water fluoridation and recognizing that urinary fluoride has a "number of positive features," including integrating exposure from different sources, that it is a measurement reflecting not just what is in that body on a given day but for a longer period of time, and explaining that he has used urinary fluoride as a metric in assessing another chemical, PFAS); Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 790:8-12 (Thiessen) ("there's no scientific reason why [the exposure level and hazard level] have to be milligrams per kilogram per day. They could also be milligrams per liter in the drinking water, they could also be milligrams per liter *in the urine*") (emphasis added).

ii. The EPA permits considering the *additive* risk posed by a chemical under the condition of use at issue when conducting a risk evaluation. To this end, Dr. Barone explained that in a situation where the condition of use is additive to other background sources, "you want to be able to understand, well, what's the background, be able to subtract the background; you want to be able to say what's the dietary component and what is the actual water intake component. And then if you have information on the other sources, potential sources, whether it's pharmaceutics or other inhaled or overly ingested pollutants having a similar kind of exposure, additive exposures, *you want to be able to capture that to the best of your ability*." Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 678:6-21 (Barone) (emphasis added). *See also* Dkt. No. 400, Feb. 5, 2024, Trial Tr. (Barone) at 567:18-568:2 ("Q. And the point of the exposure assessment is to identify what the human exposure level is under the specific conditions of use of the chemical being evaluated, right? A. It is – it is condition-of-use specific. Q. Now, it is condition-of-use

specific, but TSCA specifically permits EPA to consider aggregate exposures to the chemical, correct? A. *TSCA specifically allows for consideration of aggregate exposures*. It doesn't require us to quantify based upon aggregate exposures") (emphasis added). Indeed, rather than preventing a risk evaluator from considering aggregate exposure to a chemical in evaluating risk, Amended TSCA expressly identifies that a risk evaluator should describe whether *aggregate exposure* was considered and explain why, or why not. *See* 15 U.S.C. § 2605(b)(4)(F). Specifically, the statute provides: "[i]n conducting a risk evaluation under this subsection, the Administrator shall . . . describe *whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered*, and the basis for that consideration." 15 U.S.C. § 2605(b)(4)(F) (emphasis added).

iii. If water fluoridation was a minor contributor to overall exposure to fluoride, then it may be less appropriate to utilize an aggregate exposure metric in assessing risk of water fluoridation. If that were the case, much of the risk at issue would not derive from water fluoridation but another source; regulating water fluoridation would be of little consequence to the total exposure. But that is not the case. Instead, as described in depth below at ¶ 91(a), water fluoridation accounts for more than half of a pregnant woman's aggregate exposure level (*i.e.*, maternal urinary fluoride level). To this end, Dr. Thiessen credibly testified that fluoride content of the urine "will be driven by the fluoride content of the water," as "for most individuals, the intake is driven by the fluoridated water." Dkt. No. 402, Feb. 8, 2024, Trial Tr. at 934:18-22 (Thiessen). Drinking water fluoridation is highly consequential to a pregnant woman's overall exposure level and so it is wholly appropriate to use maternal urinary fluoride as the metric of exposure in assessing the risk of community water fluoridation. *See also* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 790:8-12 (Thiessen) ("[T]here's a consistent association between urinary fluoride and drinking water fluoride concentrations. As the concentration of fluoride in the drinking water increases, the fluoride concentration in the urine will increase."), 792:19-2793:16 ("[I]n most cases, the primary driver of the total fluoride intake [is fluoride concentration in the

drinking water]. So you can still make that hazard-to-exposure comparison.").[29]

91. To the extent that risk assessment requires determining the exposure level attributed solely to the condition of use (community water fluoridation), Plaintiffs have shown, by a preponderance of the evidence, that at least half of the maternal urinary fluoride levels observed, **0.4 mg/L** (median) (*i.e.*, 0.8 mg/L divided by two) maternal urinary fluoride and **0.945** mg/L (95th percentile) (*i.e.*, 1.89 mg/L divided by two) maternal urinary fluoride can be attributed to the condition of use (community water fluoridation):

a. As explained above, ¶ 89(a), Till (2018) observed that the maternal urinary fluoride levels were approximately **two-times higher** for pregnant women living in fluoridated regions compared to non-fluoridated regions. Dkt. No. 432-4, Trial Ex. 108 at 6, 25-26 (Table S4). Dr. Thiessen credibly testified that it is reasonable to conclude from Till (2018) that the 2x increase in maternal urinary fluoride levels in fluoridated areas can be attributed to community water fluoridation in those areas. *See* Dkt. 401, Feb. 6, 2024, Trial Tr. at 784:1-16 (Thiessen) ("The primary difference and the only main group difference that we're aware of is that one group is fluoridated and one is not. So a difference in the urinary fluoride would be attributable to the fluoride in the drinking water."); Dkt. No. 402, Feb. 8, 2024, Trial Tr. at 934:18-22 (Thiessen). And the EPA's expert witness agreed that the increase in maternal urinary fluoride levels can largely be attributed to intake of fluoridated water. Dkt. No. 416, Feb. 13, 2024, Trial Tr. at 1408:10-1409:11 (Barone) (explaining that the "parsimonious" explanation as to the 2x increase of maternal urinary fluoride levels observed in Till (2018) is that it is "due to intake, total intake,

[29] In Thippeswamy (2021), the researchers compared fluoride concentrations in urine, serum, and cord blood of women consuming water with designated "low" and "optimum" concentrations of fluoride to understand the relationship of these metrics. Dkt. No. 432-7, Trial Ex. 111 at 1. Thippeswamy (2021) did not observe a one-to-one correlation between urinary fluoride and water fluoride concentration, but concluded that "the low/optimum fluoride concentration in drinking water compared to urine . . . correlated significantly." *Id.* The strong relationship between the fluoride concentration in water and urinary fluoride is further corroborated by Green (2019). Green (2019) studied samples collected from the MIREC Cohort (Canadian women and offspring) and identified a moderate correlation between maternal urinary fluoride intake and water fluoride concentration. Dkt. No. 432-5, Trial Ex. 109 at 1, 5 ("The MUF, was moderately correlated with fluoride intake ($r = 0.49$; $P < .001$) and water fluoride concentration ($r = 0.37$; $P < .001$)."). Though not a one-to-one comparison, the correlation observed in these studies further corroborates Dr. Thiessen's testimony as to the relationship between water fluoride and urinary fluoride.

and that's probably both food and water . . . [a]nd water is a significant portion . . . of that"). Moreover, water fluoridation also contributes to fluoride exposure indirectly because commercial food and beverages are made using fluoridated water; this is known in the scientific community as the "halo effect" of water fluoridation. *See, e.g.*, Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 799:7:800:13 (Thiessen) (describing the "halo effect" of water fluoridation wherein individuals ingest water that has been fluoridated by way of beverages such as colas, juices, beer and wine, that were made using water from a fluoridated community); Dkt. No. 396, Feb. 1, 2024, Trial Tr. at 212:7-23 (Lanphear) (describing the "halo effect" of communities that fluoridate water, causing exposure of fluoride in surrounding areas by way of food and beverage). *See also* Dkt. No. 432-4, Trial Ex. 108 at 6-7 (describing the "diffusion or halo effect" . . . "which refers to the extension of fluoridation to residents of nonfluoridated communities as a result of foods and beverages that are commercially processed in fluoridated areas and consumed in nonfluoridated communities") (citing Griffin et al. 2001; Ripa 1993). Accordingly, it is appropriate to infer conservatively that approximately **half** of the maternal urinary fluoride observed in a pregnant woman's urine is attributed to community water fluoridation.[30] Here, that is **0.4 mg/L** (0.8 mg/L divided by two) (median) maternal urinary fluoride and **0.945 mg/L** (1.89 mg/L divided by two) (95th percentile) maternal urinary fluoride.

b. One concern regarding extrapolating water intake from maternal urinary fluoride is that fluoride intake is not necessarily equivalent with fluoride excretion; the absorption and excretion process adds complexity. For example, a pregnant woman will experience the breakdown of her own skeleton during pregnancy to form the fetal skeleton, releasing fluoride absorbed in her bones, resulting in an increase in excretion of urine not tied to additional fluoride consumption. *See* Dkt. No. 395, Jan. 1, 2024, Trial Tr. at 121:10-20 (Hu). To this end the EPA argues that because of the complexities regarding absorption and excretion of fluoride, use of a physiologically based pharmacokinetic ("PBPK") modeling[31] is necessary to convert maternal

[30] As noted below in Paragraph 91(b)(i), the EPA allows for assumptions, including, *e.g.*, absorption rates, when specific data is not available.

[31] PBPK model is "a computer model that estimates concentrations of a substance in other parts of

urinary fluoride levels to estimate the fluoride intake level. Because Plaintiffs have not done PBPK modeling, EPA argues, it is inappropriate to estimate exposure attributed to the condition of use from maternal urinary fluoride. *See* Dkt. No. 402, Feb. 8, 2024, Trial Tr. at 943:1-7 (Thiessen) (recognizing that PBPK models have not been identified to predict maternal urinary fluoride concentrations based on drinking water exposures.). The Court rejects the EPA's argument for the following reasons.

i. While PBPK modeling may be useful and perhaps ideal, it is not essential to conduct a risk evaluation. The Amended TSCA does not expressly mandate use of a PBPK model, but instead affords ample discretion in the methodologies and modeling the risk assessor may employ in assessing risk. *See* 15 U.S.C. § 2625(h) (describing factors to be considered determining the methodologies or models to employ when assessing risk and omitting any reference to a PBPK model).[32] And the EPA Guidelines expressly recognize that pharmacokinetic data may not always be available and instructs a risk assessor to be aware of

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the body based on physiological parameters like absorption" and is used to convert from excretion level to intake level. *See* Dkt. No. 402, Feb. 8, 2024, Trial Tr. at 943:1-7 (Thiessen).

[32] This section provides in full:

> In carrying out sections 2603, 2604, and 2605 of this title, to the extent that the Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science, and shall consider as applicable – (1) the extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information; (2) the extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture; (3) the degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented; (4) the extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and (5) the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models.

15 U.S.C. § 2625(h).

uncertainties posed by lack of such data. Specifically, the EPA Guidelines provide: "If data to be used in a risk characterization are from a route of exposure other than the expected human exposure, then pharmacokinetic data should be used, if available, to make extrapolations across routes of exposure. If such data are not available, the Agency makes certain assumptions concerning the amount of absorption likely or the applicability of the data from one route to another (U.S. EPA, 1992)." EPA Guidelines at 62. This is an implicit recognition that a risk evaluation can proceed without pharmacokinetic modeling when such data is not available. *See also* EPA Guidelines at 47 ("Pharmacokinetic data *may* be helpful in defining the dose-response curve, developing a more accurate basis for comparing species sensitivity (including that of humans), determining dosimetry at sites, and comparing pharmacokinetic profiles for various dosing regimens or routes of administration. The correlation of pharmacokinetic parameters and neurotoxicity data *may* be useful in determining the contribution of specific pharmacokinetic processes to the effects observed.") (emphasis added). Dr. Barone likewise testified that the EPA has conducted risk evaluations under Amended TSCA without PBPK modeling as such models are not always available, explaining: "[w]e used PBPK models in five of the first [ten] risk evaluations. And to varying degrees . . . In some cases we actually had the ability to . . . incorporate studies that included oral exposures, inhalation exposures and dermal exposures . . . so we could look at a wider range of exposures and to do that aggregation of exposures across routes. That's not always available to us, we don't always have those kinds of models available to us." Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 675:9-676:7 (Barone). *See also* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 576:12-17 (Barone), 578:8-10 (Barone) ("Q. And in EPA's 10 risk evaluations under TSCA, EPA has only departed from using the default uncertainty factor of 10 for intraspecies variability when it had an acceptable physiologically-based pharmacokinetic model for the chemical, correct? A. In the first ten that is a true statement."). Put simply, this lack of PBPK modeling is not fatal to Plaintiffs' proof.

ii. Though Plaintiffs do not present a PBPK model, Till (2018) and Malin (2023) provide real-world, observational data as to the exposure level of for the population at issue under the condition of use at issue. *See* ¶ 90. *See also* Dkt. No. 400, Feb. 5, 2024, Trial

Tr. at 678:6-21 (Barone) (describing that in assessing risk under a condition of use one endeavors to subtract the background exposure from the water intake component to understand the risk at issue, ideally through modeling, but ultimately "to the best of your ability"). And uncertainties posed by lack of modeling may be accounted for in subsequent steps of the analysis (*i.e.*, assessing overall confidence in data in the risk characterization, *see* ¶¶ 112-13 and when determining the appropriate uncertainty factor to employ when assessing the margin of exposure, *see* ¶ 101(b)). Under the present circumstances, there is sufficient data to support the exposure levels identifies notwithstanding lack of PBPK modeling.[33]

iii. As stated above, Till (2018) observed an approximately 2x increase in maternal urinary fluoride levels comparing the mothers in fluoridated relative to non-fluoridated communities across three trimesters of pregnancy. *See* Trial Ex. 108, Dkt. No. 432-4 at 6-7, 8-9; Dkt. No. 432-18, Trial Ex. 122 at 5-6 (Table 2 and Fig. 1). However, Till (2018) and Malin (2023) also observed that pregnant women's maternal urinary fluoride levels increased in *both* fluoridated and non-fluoridated areas in the third trimester of pregnancy relative to the first trimester. *See* Dkt. No. 432-4, Trial Ex. 108 at 8-9, Table 3; Dkt. No. 432-18, Trial Ex. 122, at 5-6 (Table 2 and Fig. 1). This would, at first blush, suggest that something other than fluoridated water contributed to increased maternal urinary fluoride levels in the third trimester, undermining the assumption that fluoridated water is a significant contributor to those levels. However, this observation is well accounted for. As explained previously, the increase in maternal urinary fluoride across both populations in the third trimester of pregnancy is believed to be caused by the breakdown of the maternal skeleton in later trimesters of pregnancy to facilitate the formation of the fetal bone – a process that releases fluoride. *See, e.g.*, Dkt. No. 395, Jan. 1, 2024, Trial Tr. at 121:10-20, 121:25-123:8 (Hu). This observation thus does not undermine the probative value of

[33] Though EPA does not bear the burden of proof in this context the Court does note that EPA has not explained why, if PBPK modeling is necessary to understand risk associated with water fluoridation and appropriate models are available, the EPA has not itself conducted this PBPK modeling. This is not legally relevant given the statutory framework, and does not bear on the Court's findings. However, to the extent that the EPA determines that PBPK modeling is necessary to engage in rulemaking, it may conduct this assessment to put a finer point on risk posed by the condition of use before taking regulatory action; there is nothing preventing EPA from doing so.

Till (2018) and Malin (2023).

92. The present recommended water fluoride concentration in the United States is 0.7 mg/L fluoride. NTP Monograph at 1. It follows that pregnant women living in a fluoridated community in the United States are typically exposed to fluoride levels of **0.7 mg/L** fluoride, measured in water fluoridation. Even more conservatively, the Till (2018) median water fluoride level of **0.56 mg/L** measured in water fluoride is also an appropriate, conservative exposure level to utilize in the risk evaluation. This is because the United States and Canada (where data for Till (2018) was collected) take a similar approach to water fluoridation. *See* Dkt. No. 433-4, Trial Ex. 129 at 16 (describing optimal water fluoride levels in Canada of 0.7 mg/L); Dkt. No. 396, Feb. 1, 2024 Trial Tr. at 245:1-22 (Lanphear) (describing optimal 0.7 mg/L water fluoride standard in Canada). Moreover, urinary fluoride levels in mothers from Los Angeles observed in Malin (2023) and Till (2018) are highly similar. *See* Dkt. No. 432-18, Trial Ex. 122 at 1, 9.

93. The EPA often expresses exposure and hazard level in mg/kg/day, but this is not necessary. What is vital, however, is that the exposure level and hazard level is in the same unit. Dkt. No. 400, Feb. 5, 2024, Trial Tr. (Barone) at 672:22-673:4 (testifying that what matters is that the "[e]xposure concentration in the denominator has to be in the same units as the hazard point of departure or hazard level in the numerator[;] [t]hey have to match up"). Dr. Thiessen likewise testified that "there's no scientific reason why [the hazard and exposure levels] have to be milligrams per kilogram per day. They could also be milligrams per liter in the drinking water, they could also be milligrams per liter in the urine. What matters is comparison of a hazard level and exposure level that are in the same units." Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 790:18-791:16 (Thiessen). Thus, the exposure and hazard level need not be expressed in mg/kg/day, but the units for each must match when conducting subsequent steps of the analysis.

94. For the reasons stated above, and in view of the record evidence, Plaintiffs have shown by a preponderance of the evidence that:

a. Pregnant mothers in fluoridated communities in the United States are typically exposed to fluoridation of drinking water at a concentration level of **0.7 mg/L**, or conservatively, **0.56 mg/L**. They have a median exposure level to fluoride of **0.8 mg/L** (measured in maternal

urinary fluoride), and at the 95th percentile have an exposure level to fluoride of **1.89 mg/L** (measured in maternal urinary fluoride).

b. To the extent that the exposure level used in this risk assessment must reflect exposure attributed solely to the condition of use of the chemical, approximately half of the maternal urinary fluoride levels discussed in Paragraph 87 are attributed to water fluoridation.

C. Step 3: Risk Characterization

a. *Framework*

95. At this step, the EPA calculates the risk presented by the chemical at issue by comparing the point of departure (*i.e.*, hazard level) with the human exposure level. *See* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 705:7-706:21 (Barone). To ensure a risk is not present, the EPA utilizes a Margin of Exposure (MOE) equation that compares a safe margin from the point of departure (benchmark MOE) with the actual margin between the exposure level and point of departure (MOE). *See id.* at 707:13-708:19.

96. The actual MOE is calculated by discerning the ratio of the point of departure and the human exposure level, *i.e.,* the point of departure divided by the exposure level. Dkt. No. 429-7, Trial Ex. 17 at 65. The benchmark MOE (*i.e.*, the safe or requisite margin) is the product of the applicable uncertainty factors (UFs) (*i.e.*, UF x UF). *See id.* at 2-3; Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 575:17-576:24 (Barone), 580:10-13 (Barone) ("Q. Now, the benchmark MOE is the product of all uncertainty factors that are found to be applicable to a given – to a given hazard, correct? A. To a given hazard, that's correct."), 580:24-581:19 (Barone) ("We don't add them. We multiply – if the uncertainty factor is the default of 10 for human variability, then we use that and multiply is by any other uncertainty factors."). For example, if there is an uncertainty factor of 10 for intraspecies variability, and an uncertainty factor of 10 for using a LOAEL as the point of departure, the benchmark MOE is 100 (10 times 10). *Id.* at 581:12-582:11. As another example, if the first uncertainty factor is 10, and the second uncertainty factor is 3, the benchmark MOE is 30 (10 times 3). *Id.*

97. If the actual MOE is lesser (*i.e.*, there is a smaller margin) than the benchmark MOE, then there is a risk present; if the actual MOE is greater (*i.e.*, there is a bigger margin) than the

benchmark MOE then a risk is presumed not to be present. *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 583:8-13 (Barone) (explaining that if the benchmark MOE exceeds the MOE between the hazard and exposure level a risk is present); Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 707:20-708:9 (Barone) (explaining the converse).

b. *Key findings*

98. A risk is present when using the BMCL of 0.28 mg/L (maternal urinary fluoride) as the point of departure, and whether calculating risk using either the median or high-end exposure levels; the exposure levels exceed the point of departure.

99. A risk is present when using the BMCL of 0.768 mg/L or even 1.536 mg/L (maternal urinary fluoride) as the point of departure, whether calculating risk using either the median or high-end exposure levels; the exposure levels exceed the point of departure.

100. Alternatively, a risk is present when utilizing the conservative 4 mg/L (water fluoride) as the point of departure; the actual MOE is less than the benchmark MOE.

c. *Underlying findings*

(a) BMCL: 0.28 mg/L and in the alternative, 0.768 mg/L and/or 1.536 mg/L (maternal urinary fluoride)

101. The appropriate benchmark MOE to use in calculating risk for the BMCLs identified by Dr. Grandjean is 10, which includes at least one UF of 10 to account for intraspecies variability:

a. A UF of 10 is utilized as a default practice in calculating risk to account for intraspecies variability, *i.e.*, the variability within the human species in reacting to chemicals.[34] *See* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 712:12-713:22 (Barone).

b. Absent use of physiologically based pharmacokinetic (PBPK) modeling to account for those variabilities, which could allow for the reduction of the UF from 10 down to 3, the EPA applies the UF of 10 in calculating the benchmark MOE. *See id.* at 712:24-713:22; Dkt. No. 401,

[34] Intraspecies variability can be compared with interspecies variability, which accounts for variability between different species (*i.e.*, animals and humans) when extrapolating from animal studies. Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 713:6-10 (Barone).

Feb. 6, 2024, Trial Tr. at 576:12-17 (Barone), 578:8-10 (Barone) ("Q. So the default uncertainty factor that EPA uses to account for intraspecies variability and uncertainty is 10, correct? A. That is the default. Q. And in EPA's 10 risk evaluations under TSCA, EPA has only departed from using the default uncertainty factor of 10 for intraspecies variability when it had an acceptable physiologically-based pharmacokinetic model for the chemical, correct? A. In the first ten that is a true statement.").

c. A PBPK model has not been performed to assess fluoride intake in pregnant women. Dkt. No. 402, Feb. 8, 2024, Trial Tr. at 943:1-16 (Thiessen); Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1396:17-1397:2 (Barone), 1397:20-23 (Barone) ("Q. And so in the nearly four years since the first trial in this case, plaintiffs still have not performed a PBPK model to extract a urinary fluoride value to an intake value, right? A. No, they haven't.").

d. Because there is no PBPK model utilized here, which would decrease uncertainty and allow from a downward departure of the default UF of 10, the default UF of 10 is appropriately used as the benchmark MOE in the present risk evaluation.

102. The median exposure level for pregnant women measured in urinary fluoride is 0.8 mg/L, and the 95th percentile is 1.89 mg/L. *See* ¶ 87.

103. The actual MOE for the BMCL of 0.28 mg/L at the median exposure level is 0.35 (0.28 mg/L divided by 0.8 mg/L) and 0.148 at the 95th percentile exposure level (0.28 mg/L divided by 1.89 mg/L). The actual MOEs, 0.35 and 0.148, do not exceed the benchmark MOE of 10; thus, the MOE is below the benchmark MOE and a risk is present. *See* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 707:20-708:9 (Barone) (explaining that a risk is not present where the actual MOE is *higher* than the benchmark MOE). Another way of looking at exposure/risk is taking the BMCL and adjusting it downward for risk factors. To account for a ten-fold risk factor of human variability, actual exposure should not exceed 1/10th of the BMCL of 0.28 mg/L – *i.e.*, 0.028 mg/L. However, the trial evidence establishes actual exposure of levels of 0.8 and 1.89 mg/L – this far exceeds that safety limit of 0.028 mg/L. *See also* Dkt. No. 198-4 at 75-77 (Thiessen Decl.) (providing MOE calculations).

104. The actual MOE for the BMCL of 0.768 mg/L at the median exposure level is 0.96

(0.768 mg/L divided by 0.8 mg/L) and 0.406 at the 95th percentile exposure level (0.768 mg/L divided by 1.89 mg/L). The actual MOEs, 0.96 and 0.406, do not exceed the benchmark MOE of 10; thus, the MOE is below the benchmark MOE and a risk is present. *See* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 707:20-708:9 (Barone). *See also* Dkt. No. 198-4 at 75-77 (Thiessen Decl.) (providing MOE calculations). Put differently, 1/10th of this BMCL is 0.0768 mg/L (0.768 mg/L divided by 10). Both the median and upper exposure levels of fluoride found in mothers' urine exceed this amount.

105. Even using the higher 1.536 mg/L BMCL to account for omission of the OCC Cohort data, *see* ¶ 73 (discussing exclusion of OCC Cohort data in deriving 0.768 mg/L BMCL using squared model in Grandjean (2022)), a risk is present. Using this figure, the actual MOE at the median exposure level is 1.92 (1.536 mg/L divided by 0.8 mg/L) and 0.813 at the 95th percentile exposure level (1.536 mg/L divided by 1.89 mg/L). 1.92 and 0.813 do not exceed 10; thus, the actual MOE is below the benchmark MOE and a risk is present. *See* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 707:20-708:9 (Barone). *See also* Dkt. No. 198-4 at 75-77 (Thiessen Decl.) (providing MOE calculations). Put differently, 1/10th of this BMCL is 0.1536 mg/L (1.536 mg/L divided by 10). Both the median and upper exposure levels in mothers' urine exceed this amount.

106. Even if the Court were to consider only half of the exposure level, directly attributable to water fluoridation, as opposed to other sources of fluoride (0.4 mg/L (0.8 mg/L divided by 2) (median) maternal urinary fluoride and 0.945 mg/L (1.89 mg/L divided by 2) (95th percentile) maternal urinary fluoride, a risk is still present. Both of these figures exceed the safe level using a BMCL of 0.28 mg/L (0.028 mg/L). *See* ¶ 103. And these figures also exceed the safe level considering the margin of error if the BMCL of 0.768 mg/L or 1.536 mg/L; the safe levels are 0.0768 mg/L and 0.1536 mg/L (1/10th of each BMCL), respectively. *See* ¶¶ 104-05.

(b) LOAL: 4 mg/L (water fluoride)

107. Alternatively, to the extent that the BMCLs identified previously are not appropriate points of departure, or maternal urinary fluoride is not an appropriate metric, a risk is present using a LOAL of 4 mg/L measured in water fluoride.

108. The appropriate UF applied in the benchmark MOE analysis using the LOAEL of 4

mg/L is 100 (10 x 10):

a. The UF of 10 is appropriately applied to account for intraspecies variability. *See* ¶ 101.

b. A second UF of 10 is also appropriately applied when using a LOAEL as the point of departure. Dkt. No. 440, Feb. 13, 2024, Trial Tr. at 1425:13-17 (Barone) ("Q. Right. If we were using a human study and only had a LOAEL, like was the case with PCE, you would, at that point, consider an additional uncertainty factor beyond the intraspecies variability uncertainty factor? A. Generally, yes. Yes, we would.").

c. Again, the benchmark MOE is calculated by multiplying the applicable UFs. Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 575:17-576:24 (Barone), 580:10-13 (Barone) (explaining that the benchmark MOE is the product of applicable UFs), 580:24-581:19 (stating that "[w]e don't add them[;] [w]e multiply").

109. Pregnant women in "optimally" fluoridated communities in the United States have an exposure level of at least 0.7 mg/L (water fluoride). *See* ¶ 86. Or conservatively, 0.56 mg/L derived from Till (2018), in the alternative. *See* ¶ 89(a).

110. The actual MOE for the LOAEL of 4 mg/L (water fluoride) is 5.71 (4 mg/L divided by 0.7 mg/L) or 7.14 (4 mg/L divided by 0.56 mg/L).

111. 5.71 and/or 7.14 do not exceed 100; the actual MOE is below the benchmark MOE and thus a risk is present. Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 583:8-13 (Barone) (explaining that if the benchmark MOE exceeds the MOE between the hazard and exposure level a risk is present). *See also* Dkt. No. 198-4 at 75-77 (Thiessen Decl.) (providing MOE calculations). Again, another way of looking at this is to take the LOAEL of 4 mg/L, and divide that by the two risk factors. To this end, 4 mg/L divided by 100 equals 0.04 mg/L, reflecting the tolerable concentration of exposure given the risk factors. Exposure to 0.7 mg/L in United States drinking water, or conservatively 0.56 mg/L (Till (2018)),[35] far exceeds that limit.

[35] The condition of use at issue in this suit is fluoridation of water at 0.7 mg/L. However, it is useful to consider the risk posed with the lesser exposure level of 0.56 mg/L given the findings of Till (2018). There, subjects in Canada – which has the same optimal level of water fluoridation as the United States – had a median community water fluoride level of 0.56 mg/L. It follows that

D. Step 4: Risk Determination

a. *Framework*

112. Once the risk has been identified, in the last step of the risk evaluation process the assessor determines if that risk is an *unreasonable* one. Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 735:11-19 (Barone).

113. In making the determination of whether the risk is unreasonable, the assessor considers several factors including: (1) severity of the hazard; (2) exposure-related considerations (*e.g.*, duration, magnitude, or frequency of the exposure, and size of the affected population); (3) other characteristics of the population that is exposed, including the susceptibility of subpopulations; (4) confidence in the information used to inform the hazard and exposure values; and relatedly, the (5) overall strength of the evidence and uncertainties and assumptions included throughout the risk assessment. *See* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 735:11-736:19 (Barone); Dkt No. 437-1, Trial Ex. 96, at 500 (PCE Risk Evaluation); Dkt. No. 437-3, Trial Ex. 98 at 271 (1,4-Dioxane Risk Evaluation).

b. *Key finding*

114. Based on the aforementioned factors, and in view of the record evidence, the risk at issue – reduced IQ in children posed by water fluoridation at 0.7 mg/L – is an unreasonable risk.

c. *Underlying findings*

115. Given the seriousness of reduced IQ, and the ample support in the record that the United States population is at risk of experiencing IQ decrements of over four IQ points, the **severity** of the hazard at issue (reduced IQ in children, *see* Section III.A.1.), weighs in favor of finding the risk at issue unreasonable:

a. The EPA has recognized that cognitive deficits including reduced IQ are critical chronic health effects, as exemplified by its in its risk evaluation of PCE under the Amended TSCA which identified cognitive deficits as the hazard warranting regulatory action. Dkt. No.

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some communities in the United States may have similar median water fluoridation levels. Thus, it is worth considering if a risk is present at this lower level of exposure, to understand the risk of setting an optimal fluoridation level of 0.7 mg/L as is the standard in the United States.

400, Feb. 5, 2024, Trial Tr. at 597:9-13 (Barone). Moreover, according to the EPA's Clean Air Science Advisory Commission, in the context of its analysis of lead: "[a] population loss of 1-2 IQ points is highly significant from a public health perspective." Dkt. No. 430-1, Trial Ex. 42 at 67000. To this end, a 1-to-2 point loss in IQ was the hazard that supported the identification of lead as a substance posing an unreasonable risk. *Id.* *See also* Dkt. No. 433-4, Trial Ex. 129 at 27 (recognizing that one study found that a reduction of one IQ point "has been shown to be associated with reduced educational attainment, employment status, productivity, and earned wages, reflecting substantial public health concerns").

b. In risk assessments, the EPA evaluates not only the hazard presented at median exposures levels, but considered the hazard posed to the 95th percentile (*i.e.*, high exposure populations). Dkt. No. 430-1, Trial Ex. 42 at 67000. And the EPA considers impact upon smaller, susceptible subpopulations in assessing the risk at issue. *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 587:7-18 (Barone) (testifying that the EPA considered impact on small, susceptible subgroup of population in regulating lead).

c. As Dr. Grandjean explained, women in the 95th percentile exposure level to fluoride exceed the BMCL for a 1-point loss in IQ by over a factor of four. *See* Dkt. No. 397, Feb. 2, 2024, Trial Tr. at 358:2-18 (Grandjean). Indeed, when considering high-end exposure levels, relative to Dr. Grandjean's BMCL identifying the dosage at which a 1-point IQ decrement is expected, fluoride presents a risk of a decrease in IQ ranging from 2.86 to 6.75 IQ points.[36]

116. **Exposure-related considerations** (*e.g.*, duration, magnitude, or frequency of the exposure, and size of the affected population) weighs heavily toward finding the risk at issue unreasonable; the exposure is continuous, and nearly all Americans are affected.

[36] According to Dr. Grandjean's analysis, an increase of 0.28 mg/L of fluoride exposure (measured in maternal urinary fluoride) is associated with a 1-point IQ loss in the mother's offspring (boys and girls). *See* Dkt. No. 432-15, Trial Ex. 119 (Grandjean (2023)) at 1-2, 9. Pregnant mothers in fluoridated communities in the United States have a median and 95th percentile exposure level to fluoride of 0.8 mg/L and 1.89 mg/L, respectively (measured in maternal urinary fluoride). *See* ¶¶ 86-88; Trial Ex. 122, Dkt. No. 432-18 at, Trial Ex. 122 at 9. Thus, fluoride presents a hazard of reduced IQ ranging from approximately 2.86 points at the median intake level,((0.8 mg/L (median exposure level) divided by 0.28 mg/L (dosage at which 1 IQ point decrease is observed)), *i.e.*, 2.857) to 6.75 points at the 95th percentile ((1.89 mg/L (95th percentile exposure level) divided by 0.28 mg/L (dosage at which 1 IQ point decrease is observed)), *i.e.*, 6.75).

117. The size of the affected population is vast. Approximately 200 million Americans have fluoride intentionally added to their drinking water at a concentration of 0.7 mg/L. *See* Dkt. No. 421 at 206-07 (undisputed). Other Americans are indirectly exposed to fluoridated water through consumption of commercial beverages and food manufactured with fluoridated water (*i.e.*, the "halo effect"). *See, e.g.*, Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 799:7:800:13 (Thiessen) (describing the "halo effect" of water fluoridation); Dkt. No. 396, Feb. 1, 2024, Trial Tr. at 212:7-23 (Lanphear) (similar). *See also* Dkt. No. 432-4, Trial Ex. 108 at 6-7 (describing the "diffusion or halo effect" . . . "which refers to the extension of fluoridation to residents of nonfluoridated communities as a result of foods and beverages that are commercially processed in fluoridated areas and consumed in nonfluoridated communities") (citing Griffin et al. 2001; Ripa 1993). Approximately two million pregnant women, and over 300,000 exclusively formula-fed babies are exposed to fluoridated water. Dkt. No. 421 at 209-210. *See also* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 815:6-816:23 (Thiessen). The number of pregnant women and formula-fed babies alone who are exposed to water fluoridation each year exceeds entire populations exposed to conditions of use for which EPA has found unreasonable risk; the EPA has found risks unreasonable where the population impacted was less than 500 people. *See* Dkt. No. 400, Feb. 5, 2024, Trial Tr. at 588:11-15 (Barone) (testifying that under TSCA the EPA had made unreasonable risk determinations for conditions of use that involve less than 500 people, and that "many are less than 500 people"). *See also* Dkt. No. 421 at 209-210 (EPA agreeing that "the exposed population for the condition of use of community water fluoridation exceeds the exposed populations of the first ten risk evaluations under Amended TSCA").

a. Individuals are exposed to fluoride through water intake every day; the parties do not dispute that frequency of exposure for most people is several times daily (*i.e.*, through drinking tap water). Dkt. No. 421 at 207 (undisputed).

b. And the duration of exposure to fluoridated water is continuous with its effects long-lasting. *See* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 813:18-20 (Thiessen) (describing that exposure to community water fluoridation is intended to be lifelong). To this end, fluoride remains in the body through years; for several years after cessation of fluoride exposure a woman

is likely to release fluoride into blood due to skeletal breakdown. Dkt. No. 397, Jan. 31, 2024, Trial Tr. at 370:6-371:12 (Grandjean); Dkt. No. 402, Feb. 8, 2024, Trial Tr. at 932:16-20 (Thiessen).

118. The **susceptibility** of exposed populations weighs heavily toward finding the risk at issue unreasonable. It is undisputed that large numbers of susceptible individuals are being exposed each year to fluoride through fluoridation, namely, approximately two million **pregnant women**, and over 300,000 exclusively formula-fed **babies**. Dkt. No. 421 at 209-210. *See also* Dkt. No. 401, Feb. 6, 2024, Trial Tr. at 815:6-816:23 (Thiessen).

119. The scientific literature in the record provides a high level of certainty that a hazard is present; fluoride is associated with reduced IQ. There are uncertainties presented by the underlying data regarding the appropriate point of departure and exposure level to utilize in this risk evaluation. But those uncertainties do not undermine the finding of an unreasonable risk; in every scenario utilizing any of the various possible points of departures, exposure levels and metrics, a risk is present in view of the applicable uncertainty factors that apply:

a. Regarding the point of departure, as discussed above, there is some uncertainty regarding the appropriate point of departure to utilize. Specifically, there is lack of certainty regarding the model fit to be utilized in the BMD modeling analysis, which determines the BMCL to utilize as a point of departure. *See* ¶ 72 (discussing use of linear vs. squared model to derive BMCL). However, under either scenario (whether using a linear or squared model), there is an insufficient safety margin between the exposure level and hazard level; a risk is present. *See* ¶¶ 102-106. Even assuming BMD modeling cannot be used for the data set and using a highly conservative LOAEL of 4 mg/L, a risk remains present by a substantial margin. *See* ¶¶ 107-111. Accordingly, the uncertainty regarding the point of departure (hazard level) is ultimately not consequential to the conclusion herein. The EPA has deemed a risk unreasonable even where it lacked high confidence in the hazard data. *See* Dkt. No. 421 at 211 (undisputed).

b. Regarding the exposure level, there is uncertainty presented by the fact that a PBPK model was not utilized to determine the precise amount of fluoride reflected in pregnant women's maternal urinary fluoride levels that derives from fluoridated water. *See* ¶ 91(b).

Uncertainty due to lack of modeling is offset by the fact that it is appropriate to view risk presented by water fluoridation in context of its additive effects on aggregate exposure, which is best reflected by real world maternal urinary fluoride levels. *See* ¶¶ 89-90. And this is particularly true where, as here, water fluoridation is known to be a significant contributor to maternal urinary fluoride levels, and indeed functions roughly as a 2x multiplier to those levels. *See id.* Further, here, there is real-world observational data showing what the maternal urinary fluoride levels of women that live in communities with fluoridation levels comparable to that of the United States; this data makes the PBPK model less critical to the analysis. *See* ¶¶ 89-91. The uncertainty from the lack of PBPK model weighs against finding the risk unreasonable, but not strongly so due to these mitigating circumstances. Moreover, when utilizing the conservative LOAEL as a point of departure, that metric is derived from water fluoride intake, and does not present the same uncertainty posed by using maternal urinary fluoride levels as the metric of hazard and exposure. Finally, the EPA has deemed a risk unreasonable even where it lacked high confidence in the exposure data. *See* Dkt. No. 421 at 211 (undisputed).

c. There is significant *certainty* in the data set regarding the association between fluoride and reduced IQ. Namely, there is a robust body of evidence finding a statistically significant adverse association between fluoride and IQ. A large majority of the 72 epidemiological studies assessed by the NTP Monograph observed this relationship including all but one of the 19 high-quality studies, *see* ¶¶ 34-36, and literature published after the NTP Monograph cutoff date observed the same relationship, *see* ¶ 37 – and countervailing evidence, for various reasons described previously, are of little impact on this repeated, and consistently observed association between fluoride and reduced IQ, *see* ¶ 39. Moreover, complete consistency amongst studies is not expected. *See* Dkt. No. 414, Feb. 9, 20240, Trial Tr. at 1172:23-1173:6 (Savitz). Notably, notwithstanding inherent difficulties in observing this association at lower exposure levels, studies assessing such levels still observed a statistically significant relationship between fluoride and reduced IQ. *See* ¶¶ 42-44. Again, to put the breadth of evidence supporting this finding in perspective, the EPA has identified a LOAEL based upon far less in other contexts. For instance, in the EPA's risk evaluation of Methylene, conducted pursuant to Amended TSCA,

the EPA used a LOAEL for developmental neurotoxicity, derived from the analysis of ***one study conducted upon mouse pups*** (Fredriksson et al., 1992). *See* Methylene Risk Evaluation at 262. Compare this with 6 (water fluoride) and 9 (urinary fluoride), high-quality, epidemiological studies of human populations underling the 4 mg/L LOAEL underlying the POD here. Dkt. No. 431-2, Trial Ex. 68 at 39, 41 (eTable 4). The scientific literature in the record provides a high level of certainty that a hazard is present; fluoride is associated with reduced IQ. The qualitative evidence is superior.

120. In sum, the first three factors weigh toward finding the risk unreasonable. Namely, the severity of the hazard weighs toward finding the risk unreasonable. The exposure-related considerations and exposure of susceptible populations weighs *strongly* toward finding the risk unreasonable; millions of susceptible individuals are exposed to fluoride and the exposure is frequent and long-lasting. The two final factors, confidence in hazard data and overall strength of the evidence and uncertainties, are largely neutral. Because the first three factors weigh strongly toward finding the risk unreasonable and the last two are largely neutral, the totality of the factors establish that the risk is unreasonable under the Amended TSCA. The Court thus finds that the Plaintiffs have established by a preponderance of the evidence that the risk at issue is **unreasonable**.

IV. CONCLUSIONS OF LAW

121. Plaintiffs have proven, by a preponderance of the evidence, that water fluoridation at the level of 0.7 mg/L – the prescribed optimal level of fluoridation in the United States – presents an "unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation under the conditions of use." 15 U.S.C. § 2620(b)(4)(B)(ii).

122. The Court thus orders the Administrator to initiate rulemaking pursuant to Subsection 6(a) of TSCA. *See id.* §§ 2605(a), 2620(a).

123. The Court defers ruling as to whether Plaintiffs are entitled to recovery of their costs of suit and attorneys and expert witness fees. Parties are ordered to submit a proposed supplemental briefing schedule regarding costs and fees within two weeks of the date of this order.

Defendant shall respond two weeks thereafter. The Court will take the matter under submission unless it orders a hearing.

The Clerk of Court is directed to enter judgment in Plaintiffs' favor.

IT IS SO ORDERED.

Dated: September 24, 2024

EDWARD M. CHEN
United States District Judge

United States District Court
Northern District of California

Washington Action for Safe Water
Bill Osmunson DDS MPH,
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425.466.0100
Issaquah, WA 98027

October 31, 2024

Dear Washington State Board of Health Members:

RE: #21 Rule Change Petition – addendum - additional evidence

This submission, addendum, is adding pictures and graphs that did not make it in our petition and evidence as the Board expressed their willingness to accept.

If the rule process is termed open, please add this to that review.

I am a dentist, retired after 46 years of practice in both low and high socioeconomic communities, Tribal clinic, and teaching cosmetic and functional neuromuscular dentistry, with master's degree in public health.

Fluoridation is part of both my professions and for the last decade and a half, I have donated my time to the Board of Health at no charge with no expectation of remuneration. Unlike the fluoridation lobby, I have no conflict of interest and my only intent is to stop the Board from harming the public. I am not a lawyer nor editor and my apologies for the typos. My head feels like it could explode trying to keep everything organized, summarized and condensed to save you time. This addendum is by no means fully definitive.

Dental caries can be serious, expensive and should not be dismissed as inconsequential. However, while we spend time and money on fluoridation which has little or no benefit, health education and other preventive measures are left with less support and the public is harmed.

OUTLINE

Our petition once again:

(8) The Board of Health does not recommend adding fluoridation chemicals to water with the intent to treat humans or animals.

Alternate wording:

(**8) In keeping with the Federal Safe Drinking Water Act, the Board of Health does not recommend chemicals, including fluoride compounds, be added to the water with the intent to treat or prevent disease in humans or animals.**

In the simplest of terms: The Court found fluoridation is an unreasonable risk. To assure safe drinking water as required by RCW, the Board and Department should stop promoting fluoridation and contact the Legislators and request RCW 57.08.012 be rescinded.

The Fluoridation Lobby, promoters of fluoridation, including the Board of Health, have denied any risk to the public from fluoridation other than mild cosmetic dental fluorosis. The Fluoridation Lobby's refusal to evaluate the lack of significant benefit and risks of harm is unethical and unscientific.

If one narrows the focus of a potential harm to just one variable and then dilute the evidence with enough extraneous cohorts and also demand absolute proof of harm, doubt for almost any topic can be achieved. In school we were taught that the word "never" and "always" in a true/false question would be false. Public health tends to speak in absolute terms of confidence when science does not.

The Fluoridation Lobby has a double standard demanding absolute proof of harm yet accepting lower quality observational evidence for efficacy.

With only one randomized controlled trial (RCT) of fluoride ingestion, and the singular RCT showing no statistical benefit, the study of harm which is done in conjunction with an RCT, becomes far more complex. Follow the money. When possible, give the public freedom. The benefit of fluoridation has been exaggerated and risks minimized.

FLUORIDATION VS FLUORIDE SUPPLEMENTS: If a person wants to ingest fluoride, they can contact their doctor or dentist and get a prescription (supplement) which is dose controlled, pharmaceutical grade, and made under Good Manufacturing Practices, although neither are FDA CDER approved.

The only reason, singular intent, to adding fluoride to water is to force compliance.

Freedom is the antithesis of the Fluoridation Lobby, those profiting and promoting fluoridation. . . which included me years ago. The public has not always taken kindly when they understand they are being medicated without their consent. Stopping fluoridation simply requires turning off the fluoride pump.

As an alternative to a prescription, a person can disregard the FDA warning on toothpaste and swallow a pea size of fluoridated toothpaste.

The Fluoridation Lobby has suggested fluoridation is similar to the addition of Vitamin D to Milk or the “enrichment” of bread, replacing vitamins removed in processing. Neither of those are highly toxic substances determined to be legend drugs. Dental caries is not caused by the absence of fluoride.

DEPARTMENT REVIEW OF FLUORIDATION: Our understanding is the Department is planning to do a review of fluoridation as we have requested. Thank you. This should include many streams of evidence including alleged benefit, risk/harm to the developing brain, thyroid, endocrine system, bones, kidneys, GI tract, cancer, mitochondria, pineal gland, teeth, in addition to laws, ethics, chemical purity, and Good Drug Manufacturing Practices as they relate to the entire population and subgroups such as age, race, and gender.

Confidence to remove your endorsement of fluoridation is needed. The National Toxicology Program experts took nine years to evaluate just one risk, and the U.S District Court eight years to review the same risk, but review can be done faster if the fluoridation lobby, like the tobacco lobby, does not delay, delay, delay. Over 500 water districts in the USA that we know of, along with most developed

countries and their health departments, have stopped or chosen not to fluoridate water after review of the science and ethics.

Asking the WA Department of Health to undertake a balanced unbiased review of fluoridation after decades of the Department and Board, staking their unreserved and unqualified reputation on promoting fluoridation, receiving funding in part for fluoridation, hiring employees to review, protect and promote fluoridation, advertising the benefits of fluoridation, and omitting the known and probable risks of fluoride ingestion, along with active blocking of the best science, is akin to asking a cat if the mouse should go free. Or akin to asking the fossil fuel industry to provide a balanced review of global warming or the tobacco lobby about the safety of smoking. Please excuse our doubt of the Department's ability to be scientific without bias. Remove your endorsement of fluoridation.

The Department is not an impartial jury, nor should the accused be the jury. Cherry-picking jury members with bias will ensure a desired outcome which may not protect the public. An impartial jury for fluoridation without vested interest or a financial stake, or balanced jury, is possible and necessary.

One of the tasks in science is to narrow the focus to, if possible, one variable. However, public health evaluation must stand back and evaluate all streams of evidence. We need to see the elephant in the room, not just one hair. Stand back and look at the entire evidence. Several experts in various specialties should be considered.

A "global" or big picture view of fluoridation, a public health evaluation, will make the evaluation faster and higher quality. The fluoridation lobby does not have quality research or FDA approval, and their only defense is to delay another 75 years profiting at the expense of the public's harm and attempt to maximize doubt over safety.

FLUORIDATION LOBBY- OPPONENTS OF THIS PETITION:

The Fluoridation Lobby (American Dental Association, AAP, AADOCR, AWWA, AFS, and those promoting fluoridation) attempts to protect policy rather than objectively review science, ethics and law.

It is not the job of the patient to prove that the drug they are being forced to ingest is safe. Without Food and Drug Administration Center for Drug Evaluation and Research (FDA) Drug Approval, the Board becomes the regulatory drug approval authority in Washington State (WA). Your words matter (just like the January 6 insurrection).

In response to the TSCA (Toxic Substance Control Act) Court ruling that fluoridation is an unreasonable risk, the Fluoridation Lobby blames others and points out that the Judge "*said that while he 'does not conclude with certainty that fluoridated water is injurious to public health,' there still is an 'unreasonable risk of harm.' The AAP and other experts have questioned the validity of the research on which Chen relied heavily in his ruling."*

First, good scientists should always question validity, just as we are doing. "Certainty" is a word seldom used in science, an extremely high bar. The Fluoridation Lobby suggests certainty is lacking, and we agree with the Court. The TSCA law requires confidence only to an "unreasonable risk" rather than absolute proof of harm which the Fluoridation Lobby wants.

The Fluoridation Lobby has a double standard, accepting lower quality research and uncertainty for evidence of benefit and requiring high quality certainty of harm. Harm is more difficult to study because we cannot intentionally cause harm, but we can and should have high quality research for benefit. After 75 years of fluoridation, the Fluoridation Lobby has had time to provide high quality studies of benefit and safety.

The Fluoridation Lobby almost never does research to evaluate whether their profit centers are harmful or lack safety. Safety evidence is generally placed on the manufacturer. In the case of fluoridation, the manufacturer would be the water purveyor authorities, an unreasonable expectation.

The Fluoridation Lobby is at fault for lack of high-quality research. Over the last 75 years the Fluoridation Lobby has had significant opportunity to ask the questions and provide randomized controlled trials of benefit (and quality safety studies) which could have been presented to the FDA CDER for fluoridation and/or supplement approval. However, the Fluoridation Lobby failed. There is only one RCT of fluoride ingestion evaluating benefit and it did not show significant benefit.

For safety, the Fluoridation Lobby, during the 9 years of the National Toxicology Program (NTP) review and 7 years of the Toxic Substance Control Act Court review of developmental neurotoxicity, the Lobby had plenty of time and did provide their best science, they failed to convince the Court.

The Lobby has been aware for at least 50 years that the FDA has rejected approval of fluoridation or fluoride supplements in part because the evidence of efficacy is, according to the FDA, “incomplete.” The Lobby could have completed the evidence years ago. Indeed, they have just started one small RCT study to evaluate possible benefit. Safety is not being adequately evaluated in that small study.

The Washington State Board of Health contacted the FDA in 2010 regarding gaining FDA approval. The FDA told the Board if the Board applied for approval, FDA would ban fluoridation. What about the word "ban" is so hard for the Board of Health to understand? Your mandate is to assure health, not industry profits.

Second, the Fluoridation Lobby provided their best evidence to the Court that fluoridation was safe and the Judge saw through their request for delay. The Lobby has had 75 years to get the research and has failed. Now they blame others for their failure. The Board must not continue to harm the public.

For example, when Judge Chen asked the EPA’s hired expert who was raising doubt on fluoridations developmental neurotoxicity*, “what would it take for you to change your mind?”* The EPA expert responded, *“one or two more studies.”*

Seriously? We have over 70 human studies reporting brain damage from fluoride. One or two more studies either way would not sway the evidence and

more studies have since been published confirming the majority of studies used by the NTP and Court. The precautionary principle is not part of the Fluoridation Lobby vocabulary.

The Dental lobby is not capable of rational introspection. For example, the black mercury fillings are strongly defended by the American Dental Association (ADA) and have been for over a hundred years. However, dentists cannot legally dump the filling material removed from people's teeth into the sewer because it is too toxic. Nor can the filling material be dumped into the trash because it is too toxic for the dump. Nor can the filling material be shipped in the U.S. Postal Service because it is too toxic for the postal workers. Nothing about the human mouth makes it safe. And we have had a better filling material for about 40 years. Yet the ADA staunchly defends the toxic fillings.

When hauled into court, the ADA defended itself by saying, the ADA has no duty to protect the public from products which may be harmful, we just provide advice.

Other authorities the Board has relied on like the CDC Oral Health Division, the U.S. Public Health Service, the EPA and many in academia follow the ADA who have the big bucks to market their belief in fluoride's "safe and effective". (Not all dentists and physicians fit in this mold such as the IAOMT and others).

The ADA and most dentists are not credible unbiased authorities. I hate to throw stones at my professions, because the stone hits me first as I promoted fluoridation years ago.

My Public Health Profession is just as bad. We are obedient soldiers. We promote and educate policy. Our job is not to question the policy, we are charged with implementing the policy. (Not all Public Health professionals fit in this mold, but the Board has historically been policy promoters and believers trusting the Department and have cherry picked-authorities rather than evaluating the empirical evidence and carefully verifying the evidence for themselves.) Endorsements are not empirical evidence.

II. EVIDENCE THE BOARD NEEDS TO REVIEW

A. OVERVIEW OF RISKS: As explained in our petition for rule change, the big picture is best seen starting with the National Research Council 2006 review of "Fluoride in Drinking Water A Scientific Review of EPA's Standards" (NTP 2006). Although dated, the review is still applicable and provides a bigger picture. (See NRC member comments further below)

B. THE COURT: Published experts and those providing sworn testimony to the U.S. District Court under the TSCA court case in 2024 (Court) must also be included. Recorded testimony from the Court is the highest quality of summary evidence for just one risk, lower IQ. Our petition covers the Court well and the Court is very clear, fluoridation is an unreasonable risk.

C. THE NATIONAL TOXICOLOGY PROGRAM (NTP): The Court ordered the release of the NTP's review of the developmental neurotoxic effects of fluoride. The NTP is our Nation's highest authority on toxins and stepped into the controversy where no other agency was brave enough to step in and protect the public from excess fluoride's harm. Their 700-page work was unjustly attacked, excessively peer reviewed, unethically blocked by HHS, and after 8 years still not fully published. A gold star goes to the NTP heroes and heroines. The National Toxicology Report is clear, fluoridation is not safe.

D. BEST AVAILABLE REVIEW OF BENEFIT: For evidence of efficacy, the FDA CDER is the top authority, charged by Congress to determine benefit and risk with dosage and label. Fluoride ingestion is not approved.

E. CURRENT EVIDENCE IN THE BOARD'S POSESSION OVER DECADES OF SUBMISSIONS: must be included in this eavaluation. Under an FOIA request in 2011, the Board provided us with many, many thousands of pages of evidence raising concern, risk, harm, ethics, lack of dosage control, lack of efficacy from fluoride ingestion, lack of Good Manufacturing Practices, lack of product purity, and the opposing position from the fluoridation lobby.

All the evidence previously presented to the Department and Board in your possession is part of this petition. (See attached WSBH January 10, 2011 letter)

Those thousands of pages are supported by the new evidence confirming concerns of harm, excess exposure, lack of significant benefit and lack of ethics. Significant research has been published confirming risk to all cells of the body. This petition addendum will summarize evidence and provide more current evidence in addition to responses to the Board's comments.

The Board/Department, would be wise to include for consultation scientists and experts such as:

1. Kathleen Thiessen PhD, one of the authors of the NRC 2006 review on EPA's "Fluoride in Drinking Water," and an expert providing sworn testimony to the Court in 2024, President and Senior Scientist at the Oak Ridge Center for Risk Analysis Inc.

2. Phillipe Grandjean MD, DMSc. (video) Author of over 500 peer-reviewed studies. Author of "Only One Chance: How Environmental Pollution Impairs Brain Development," reporting fluoride is one of 213 known brain-toxic chemicals that may lower the intelligence of generations of children. See link for some of his work on toxins such as mercury, PFASs, and fluoride.

3. Bruce Lanphear, MD, MPH is well published with over 350 studies, expert witness to the Court and several of his studies should be considered along with contacting him. Hall, Lanphear et al 2023,

4. Howard Hu MD, MPH, Professor Keck School of Medicine, USC, an expert witness to the Court and several of his studies should be considered along with contacting him.

5. Hardy Limeback BSc, PhD, DDS, member of the NRC 2006 review of fluoride, Editor, Comprehensive Preventive Dentistry, 2012, Wiley-Blackwell. Former Head of Preventive Dentistry, University of Toronto Dental School.

6. Michael Connett, lead lawyer for the Court case in the Toxic Substance Control Act.

For reasons why I changed my mind on fluoridation, watch my ppt with audio at https://youtu.be/rQHiIJLSujc

Or at the following Drop Box https://www.dropbox.com/scl/fi/pajvqu1k0a6usueh535q4/Fluoridation-Osmunson-9-2024-movie.m4v?rlkey=8dekyj3y5ah48sebe9vosrzsq&st=s8ro6tc7&dl=0

The 1 hour ppt video is a very condensed review of many, but not all, streams of evidence.

III. AUTHORITIES

Any one of the following authorities should stop the Board from promoting fluoridation and accept our petition for rule change or even better to recommend the cessation of fluoridation. Considering all the authorities below, the lack of benefit and safety is overwhelming. However, not every person at these agencies is going to join a consensus that fluoridation is an unreasonable risk. Freedom of speech must include various opinions which can make public health authorities require careful thought and review. "When authorities agree, hang on to your wallet."

Authorized regulatory authorities have more "weight of credibility" than endorsements of non-regulatory government agencies.

A. **Congress and WA Legislature defined "drugs"** as "articles intended for use in the . . . prevention of disease. . . . " 21 USC 321 (g)(1)(B). The sole intent of fluoridation is to prevent dental caries, a disease. Sodium fluoride is listed in the Pharmacopeia as a drug. Fluoride is not a nutrient or simply an inert mineral. Fluoride fits within the RCW definition of poison and exempt when regulated as a drug.

B. BOARD OF PHARMACY AND ATTORNEY GENERAL

1. **The Washington State Board of Pharmacy (BOP) in** June 4, 2009, letter to Bill Osmunson DDS MPH, (copy attached) June 4, 2009, Susan Boyer, for the Board of Pharmacy, responded, ***"Fluoride is a legend drug regulated under chapter 69.41".***

Ms. Boyer further states, *"the legislature has authorized water districts to fluoridate their water supplies in RCW 57.08.012. . . . By adopting a specific statute on the fluoridation of water supplies, the legislature has superseded the more general statutes in the legend drug act. . . ."*

Not so fast. Nothing in RCW 57.08.012 exempts the Board of Health or Pharmacy or Department from protecting the Health of the Public or to stop

promoting what is contributing to the harm of the public. Nor does RCW 57.08.012 exempt drug/poison laws, permit, or recommend use of police powers, nor the Board or Department to promote an unapproved drug mass medicated to everyone in drinking water without individual patient consent.

For example, RCW 69.38.010 defines a poison as "any substance designated by the state board of pharmacy which, when introduced into the human body in quantities of sixty grains or less, causes violent sickness or death." 60 grains = 3,889 mg. 15 mg of fluoride is likely to cause death in a child.[1] The Board of Pharmacy grasps the concept that 15 is less than 3,889 which defines fluoride as a poison and a poison is exempt from poison laws when regulated under drug laws but **not** exempt from the empirical evidence of fluoride's toxicity. Fluoride is highly toxic and the Legislature cannot change the toxic nature of fluoride. However, the Board of Pharmacy mistakenly appears to reason the legislature's authorization to fluoridate supersedes all other laws, science, ethics and federal laws and oversight.

a. Fluoridation has none of the required protections of a legend drug, and any one of the following is cause to accept our rule change and stop promoting fluoridation:

    i. A licensed doctor (sometimes called a legal intermediary)

    ii. Patient of the doctor's record

    iii. Specific dosage (not concentration) which has not been determined with quality studies

    iv. Patient's consent

    v. Arms-length dispensing

    vi. Label with dosage for various ages and/or weight and adverse risks

[1] Whitford G. (1996). Toxicology and Health Effects. Fejerskov et al, Fluoride in Dentistry, 2nd Edition. Munksgaard, Denmark. P. 171.

b. The fluoridation final drug manufacturer (water districts) for the protection of the public, are required, but do not have:

   i. Food and Drug Administration Center For Drug Evaluation and Research New Drug Application approval. The Board was told by the FDA if they tried to gain approval fluoridation would be banned. The Court in Rumsfeld v Doe ruled that even in time of war, a person (soldier) cannot be medicated with an approved drug off label. Ingestion of fluoride is not approved.

   ii. Good Drug Manufacturing Practices require a sterile/sanitized building and equipment costing millions of dollars with strict protocol and oversight.

   iii. Pharmaceutical Grade ingredients which would make fluoridation cost prohibitive. In contrast the chemicals added to the water are contaminated industrial ingredients which include lead, mercury, arsenic, beryllium, vanadium cadmium radium, radionuclides, silicon, and bauxite. The Board cannot “ensure” the fluoridated public water is safe.

Freedom of choice for a competent adult is only legally violated for the protection of the public, for a highly contagious lethal disease, with an approved drug. In recent history coercion was met with fierce opposition by some in the public. Just because the public is numb to fluoridation, is not evidence of approval. (Department’s survey of the public confirms many are opposed.)

Dental caries are not highly lethal, nor considered highly contagious. (See Kaul v. Chehalis, 45 Wn.2d 616, 277 P.2d 352 (1954), and AGO 1987 No. 3 – Jan 15 Authority to Fluoridate Water, Kenneth O. Eikenberry AG [attached]). Fluoride ingestion is not approved for treatment or prevention of any disease.

Ms Boyer’s 2009 letter continues, *"the legislature has authorized water districts to fluoridate their water supplies in RCW 57.08.012. . . By adopting a specific statute on the fluoridation of water supplies, the legislature has superseded the*

more general statutes in the legend drug act requiring a practitioner to dispense fluoride. Tunslall v Bergeson, 141 Wn.2d 201,211 (2000).”

At least three serious problems with the legal reasoning in the last paragraph above.

First: A constitutional right of self-determination supersedes RCW 57.08.012.

Second: there is a material difference between the education - reading, writing, and arithmetic, etc., a constitutional right - of incarcerated minor children in Tunstall v Bergeson, and the mass medication of everyone with a highly toxic contaminated poisonous unapproved FDA legend drug, industrial waste, without the patient’s consent, with known harm, unregulated dosage, disputed benefit in a non-drug contaminated manufacturing facility, and without label .

For example, just because the Legislature authorizes a road to be built does not mean all laws regarding safety such as signs, speed limits, and crosswalks are superseded and can be dispensed with. Such could not have been the intent of Legislators in RCW 57.08.012.

Third: RCW 57.08.012 authorizes fluoridation which is an unreasonable risk, appears in conflict with RCW 43.20.050[2] requiring the Board of Health to “assure” the water is safe.

The BOP lawyer in 2009 attempted to resolve that conflict by placing jurisdiction onto the local water districts, those with the least resources and experts to evaluate fluoridation’s risks and ethics. RCW 57.08.012 authorization does not absolve the Board and Department from asuring the water is safe.

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[2] **“RCW 43.20.050 Powers and duties of state board of health—Rule making—Delegation of authority—Enforcement of rules.**

(1) The state board of health shall provide a forum for the development of public health policy in Washington state . . . .”

(2) In order to protect public health, the state board of health shall:

(a) Adopt rules for group A public water systems, as defined in RCW 70A.125.010, necessary to assure safe and reliable public drinking water and to protect the public health.”

2. ATTORNEY GENERAL The BOP legal advice in their letter of 2009, fails to include the AG's letter of Smith Troy of Novembre 17, 1949, to John Kahl, MD, MPH,

"1. Where a local public water supply system adopts or intends to adopt the fluoridation method of treating water, the ***Department of Health*** *is responsible that the methods employed are not dangerous to the users of the water."*

Where are the studies on safety the Department of Health has relied on? None. Instead, the Department trusted the fluoridation lobby and for decades has been harming millions of developing brains and massive economic harm to individuals and the State of Washington.

The AG's letter continues:

"2. The Washington State ***Board of Health*** *should promulgate proper rules and regulations pertaining to fluoridation and should enforce such rules and regulations." . . . . "*

Section 1, chapter 116, Laws of 1901 [6001 Rem. Rev. Stat.] gives the Washington State Board of Health broad powers and duties as to the "preservation of the life and health of the people of the state."

Sections 290 and 291, chapter 249, Laws of 1909 [2542 and 2543 Rem. Rev. Stat.] and chapter 70, Laws of 1899 [9473, 9475, 9476 and 9477 Rem. Rev. Stat.] contain numerous provisions, both penal and otherwise, designed to insure the purity of water supplies.

For decades the **Board of Health** has failed to promulgate proper rules and regulations and the **Department of Health** has not made sure the methods are not dangerous to the users of water.

We have submitted 21 petitions for rule change to protect the public health and all previous ones have been denied in favor of blindly trusting the Fluoridation

Lobby money and cherry-picked science. The Board has even refused a forum to consider empirical evidence of risk, harm and lack of efficacy as RCW requires.

The 1949 AG letter continues*, " It is fair to conclude from the documents submitted by you that while the fluoridation of public water supplies is designed to bring about better teeth in the younger generation through the action of the fluoride as a caries prophylactic that the available evidence, while supporting such hypothesis, is at the present time presumptive only. Also, that the proper various amounts of fluoride concentration are yet to be determined for different geographical locations. Also, that the amount of fluoridation may prove injurious to the public if too great an amount be used. Also, that the application of fluoride should be carefully watched so that such will not prove harmful to the various persons who apply the same."*

Seventy-five years later the available evidence of benefit is still presumptive only, safety studies lacking, known harm is well accepted, and the proper various amounts are yet to be determined. Instead of the Board and Department carefully watching to make sure fluoridation is not harmful, the Board and Department have fought hard to protect the harmful policy rather than the public health.

The Board of Pharmacy's spurious and harmful interpretation of 57.08.012 is to suggest the public is protected only by a simple majority vote of the least informed non-scientific local commissioners (and/or voters), in effect, exempting fluoridation from toxicology and pharmacology experts, laws of nature, concentration of fluoride in water, all other applicable federal and state laws, including patient freedom of choice, FDA approval, doctor's prescription, Board and Department oversight, the Safe Drinking Water Act, dosage, label, good manufacturing practices, etc. Think Pontius Pilot.

Exemption from all other state and federal laws, regulatory agencies and scientific empirical evidence of nature are not stated or implied by RCW 57.08.012. In effect the BOP 2009 interpretation appears to place the local commissioners above Congress in the SDWA and FDA CDER in the Food, Drug, and Cosmetic, Act.

Requiring Commissioners to constantly evaluate the ever-changing science on the efficacy, safety, dosage, label and ethics of fluoridation is unreasonable. And further, RCW 57.08.012 does not exempt the Board or Department from evaluating the quality of research and any lacking research which would be needed to protect the public.

The National Toxicology Experts took 9 years to review one of many health risks of fluoride ingestion, including years of the fluoridation lobby delays, and the district court 7 years and hundreds of thousands of dollars to determine fluoridation is an unreasonable risk, lowering IQ.

In other words, the Board of Pharmacy lawyer, in conflict with the Washington State AG, appears to expect each group of commissioners to spend maybe years full time on each risk. Assuming the city is 10 times faster than the National Toxicology program and only spend 1,000 hours on each of 10 risks, each city would spend about 10,000 hours reviewing the science. Multiply that by the number of cities/water purveyors, who are or may add fluoridation and a million hours could be spent reviewing the science on fluoridation just in Washington State. Certainly, the legislators did not have that in mind when they passed RCW 57.08.012.

In practice, water purveyors do follow some Board and/or Department rules outside of RCW 57.08.012 and assume fluoridation is effective and without any risk in part because of the words of the Board and Department. The Board's words matter.

The WSBOH **July 22, 2010**, (Craig McLaughlin Ex. Dir) responded to our request for public information and responded in part:

"#1 Intent of Use: Fluoridation of drinking water in Washington State is permitted by statute. The Board has not to my knowledge taken a formal position either in support of or in opposition to fluoridation of drinking water. This agency, therefore, is not in possession of any records related to the Board's 'purpose and intent for supporting the addition of fluoride to public drinking water."

Seriously? The Board was clueless on intent of fluoridation? Impossible. Fluoridation is well known to the public to be administered with intent to prevent dental caries. Was the Board of Health the only entity which does not know why they promote fluoridation? The Board was (and still is) playing disingenuous games with the health of the public.

What was or is the Board's understanding of the total individual desired dosage of fluoride exposure? Silent.

What was or is the Board's understanding of the exposure which will cause harm? Silent.

Board of Health, April 14, 2008.

The Board of Health (and Pharmacy) were asked whether fluoride introduced into the body at 60 grains or less would cause violent sickness or death. Silent.

Board of Health, June 9, 2010.

"*Motion: The Board denies the petition for rule making . . . because the U.S. Food and Drug Administration has a memorandum of understanding with the U.S. Environmental Protection Agency clarifying that the latter agency has authority regulating tap water."*

The Board failed to ask the EPA or FDA the purpose of the memorandum, which regards water, not drugs. We asked the EPA and the EPA responded*, "The FDA, remains responsible for regulating the addition of drugs to the water supply for health care purposes."* Steve Neugeboren, Ass. General Counsel, Water Law Office EPA 2/14/2013. (Also stated August 2, 2012 from EPA Safe Drinking Water Hotline to Patrick Reeners, see attached December 28, 2012.)

Board of Health, March 2024, **petition #20 Denial.**

1. Ms. Hayes, responded for the Board, *"Board members were provided with all materials that were submitted relating to the petition."*

My memory is the Board and Department have over 26,000 documents on fluoridation which have been submitted previously. For judgment, all those must be included in our #21 petition. I was under the assumption I did not need to keep sending the Board information they already had in their possession and only needed to build on that evidence with the new evidence. My assumption was wrong. Thus, this memorandum is more extensive.

Ms. Hayes continues*, "Board staff provided background information about the scope and intent of the existing rule and current recommendations from the Department of Health and other organizations. . . ."*

Of course, the Fluoridation Lobby will defend their policy and profits. The Department is clearly biased and the "Board staff" failed to adequately inform the Board. "Organizations" (other than the FDA) tend to reference each other and are little more than endorsements. The Board avoids authorized agencies, such as the Food and Drug Administration Center for Drug Evaluation and Research and the Environmental Protection Agency's advice on the regulation of drugs or the National Toxicology Program, the Court, the Constitution of the USA and Washington State, or any laws raising doubt on the policy.

2. Ms. Hayes continues: *"Board members stated that they support the science around the use of fluoride as being beneficial and protective of oral health. . . ."*

   Board members evaluated endorsements rather than quality science. The Board failed to consider the science reporting harm and lack of benefit and fail to provide references of the science they rely on. Simply quoting the Fluoridation Lobby is not science. In part to protect profits, the Fluoridation Lobby refuses to admit any science reporting harm.

Questions of science the Board failed to answer and must answer include but not limited to:

a. What is the recommended daily dosage of fluoride to prevent dental caries for the fetus, infants, children and adults which will prevent dental caries? FDA should have that information but the FDA says the evidence of efficacy is incomplete. Please list the randomized controlled trials to support the dosage for efficacy. There is only one and it did not report statistical significance of efficacy.

b. What percentage of children are overdosed? (About 70% according to NHANES)

c. What is the safe daily dosage of fluoride for the fetus, infant and all ages. And what safety studies does the Board have to support a safe dosage for each age, race and gender?

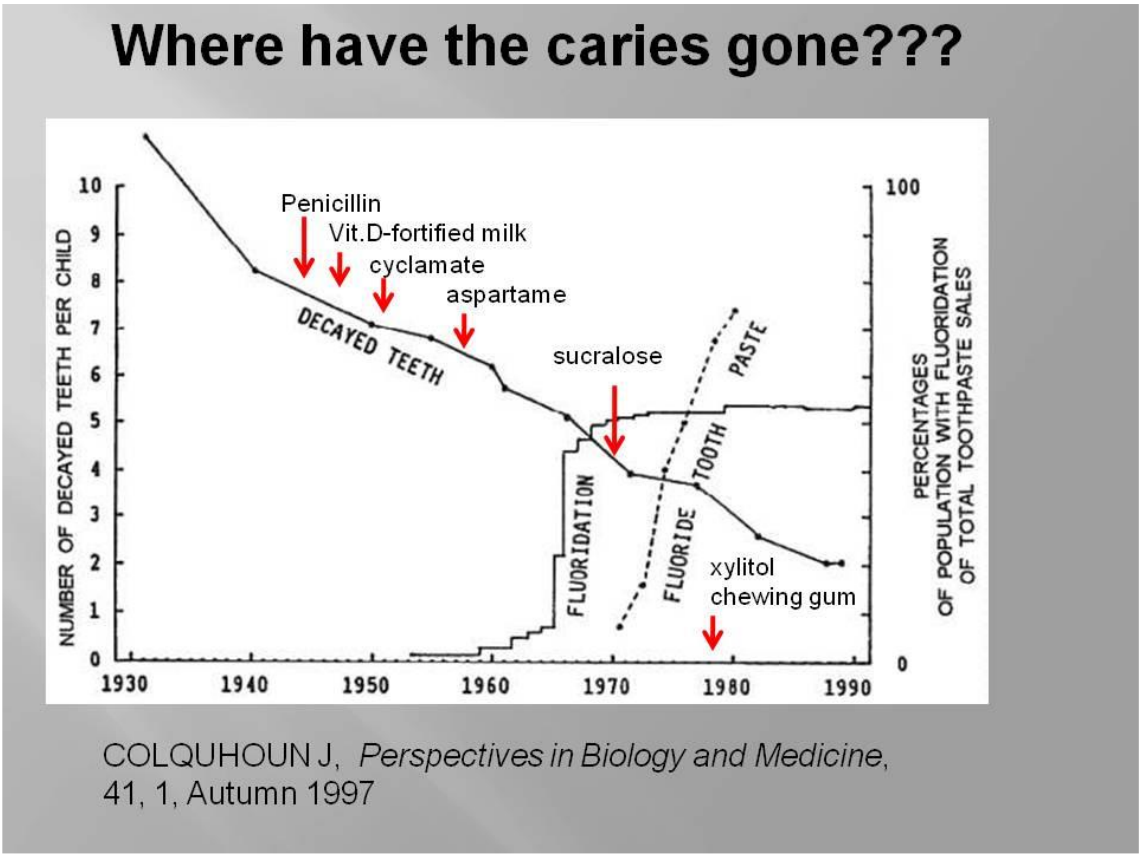
d. What is the range of fluoride daily exposure and what is the margin of error and intraspecies safety factor does the Board use?

e. What Federal Agency has jurisdiction over drug approval?

f. Are ethics of individual choice being violated?

g. Where have all the caries gone? The graph below demonstrates the difficulty of observational studies. Huge confounding unknown and speculated factors reduced dental caries rates prior to fluoridation. All of those have not been included as confounders in dental caries studies in part because they were unknowns.

   And unknowns did not occur in the same place at the same time to the same degree. However, we can agree fluoridation did not reduce dental caries prior to fluoridation starting.



3. Ms. Hayes continues: *"and (Board members) do not view **mild fluorosis** as harmful or generally resulting in neurotoxicity."*

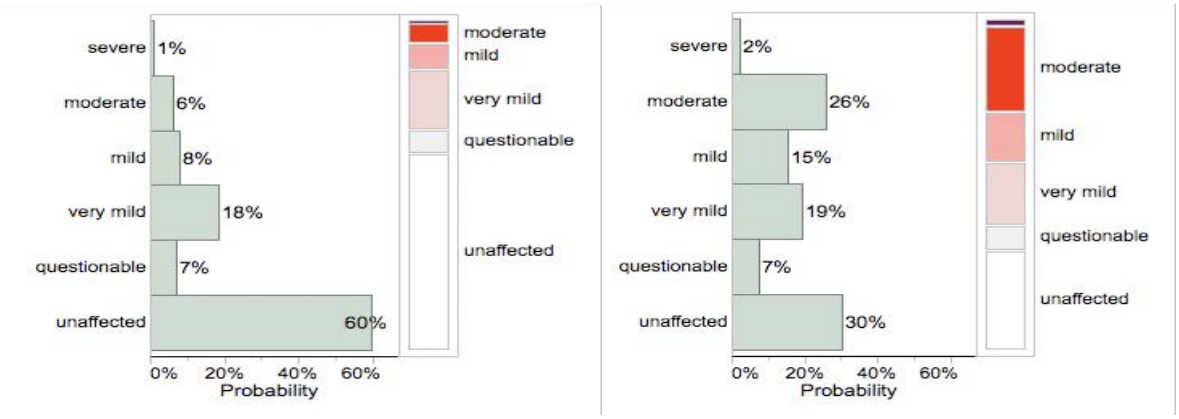
NHANES 2012 survey reported 28% in the USA have greater harm than mild dental fluorosis. Patients, the NTP, the Court, the EPA research, and science disagree with the Board that mild fluorosis is safe, not harmful. Certainly, a fractured tooth is harmful and costs to repair functional dental fluorosis costs more than cosmetic dental fluorosis.[3] And what evidence does the Board have that the TSCA Court is in error? Note, dental fluorosis does not cause neurotoxicity, they are both measures of over-exposure.

Is the Board referring to mild dental or skeletal fluorosis or both? And how many on the Board have diagnosed dental fluorosis or treated dental fluorosis? I previously sent research to the Board showing that 95% of patients with mild

[3] . Analysis of Costs for the Treatment of Dental Fluorosis U.S. Environmental Protection Agency, EPA/600/5-87/001 (NTIS PB87170817), 1987. Revised 2005. [EPA Link], Revised 08/02/2022 . EPA Science Inventory Accessed Dec. 27, 2022

dental fluorosis want the fluorosis treated.[4] If someone scratched your car, it would only be cosmetic, but it would indeed be damage. Cosmetic damage is damage.

Note the two graphs of NHANES 2000 data[5] with 40% of children showing dental fluorosis and in the right graph of 2012 showing 60% with dental fluorosis.



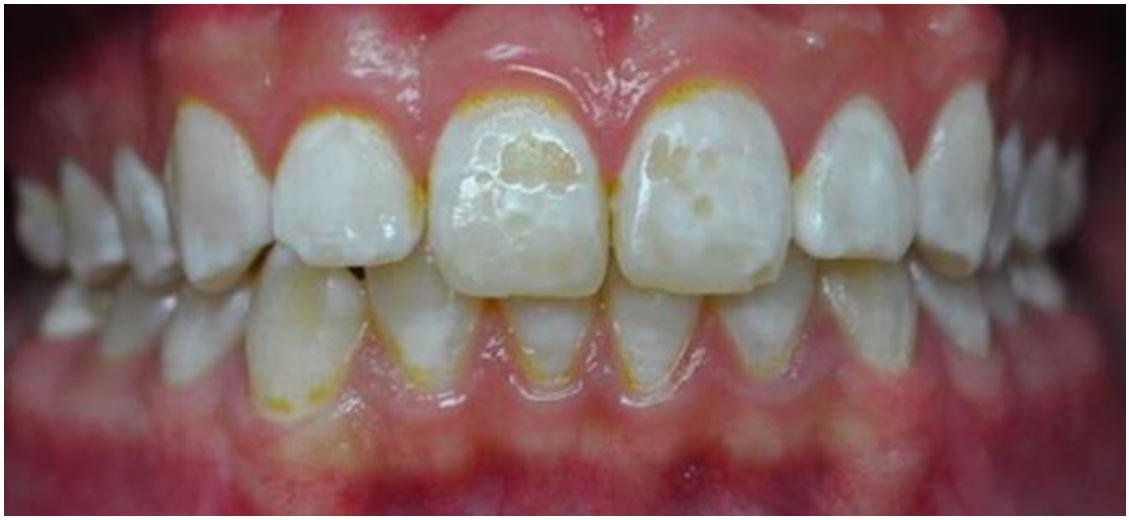
2000 NHANES 2012 NHANES

In 2000, 7% of children had moderate or severe dental fluorosis, exceeding the Board's concern. In 2012, 28% (one in 4) had moderate or severe fluorosis, exceeding the Board's lack of concern for even mild dental fluorosis. Dental fluorosis is a biomarker of excess fluoride exposure. If a patient has spots on the teeth, certainly they have spots in other parts of the body.

The patient below was raised on fluoridated water to make infant formula. Mom said he did not swallow toothpaste. The Board is ignoring patients like this.

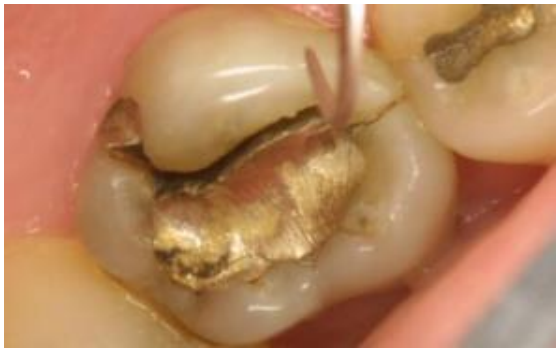
[4] Moimaz SA, Saliba O, Marques LB, Garbin CA, Saliba NA. Dental fluorosis and its influence on children's life. Braz Oral Res. 2015;29:S1806-83242015000100214. doi: 10.1590/1807-3107BOR-2015.vol29.0014. Epub 2015 Jan 13. PMID: 25590503.

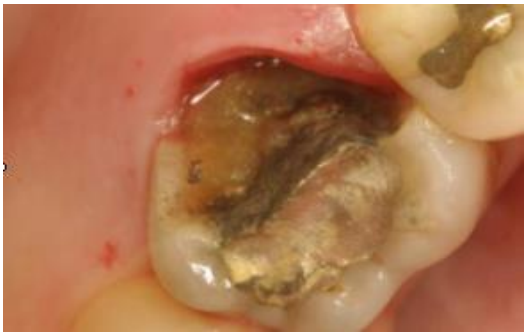
[5] Neurath C, Limeback H, Osmunson B, Connett M, Kanter V, Wells CR. Dental Fluorosis Trends in US Oral Health Surveys: 1986 to 2012. JDR Clin Trans Res. 2019 Oct;4(4):298-308. doi: 10.1177/2380084419830957. Epub 2019 Mar 6. PMID: 30931722. [PubMed]

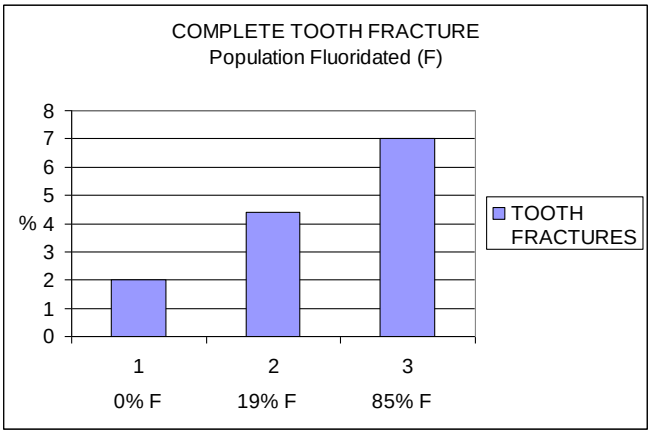


Fluoride appears to make teeth harder and harder teeth are more brittle. Although not proof of effect, when comparing the percentage of office visits for complete cusp fractures such as the pictures below, a clear increase (perhaps 350%) in the percentage of office visits for complete cusp fractures is apparent. More research is indicated. However, fractured teeth are a huge source of profitable income for dentists with possible root canals, crowns, posts, probable extractions, bridges and implants and replacement of those about ever 12 to 15 years. Explain why should dentists spend money on research which would limit the golden egg?

Seriously, dentists such as myself in the past, believed fluoridation was safe. Research on harm appeared pointless because fluoridation was declared safe, an established fact, always safe, written in stone, unquestioned safe. I was wrong.







Ms. Hayes continues: *"Members noted that they support fluoride in water systems. . . ."*

Please provide the scientific references, the peer reviewed empirical evidence, the randomized controlled trials which would be accepted by the FDA CDER, for Board Members support of fluoridation. There are none. Members support fluoridation based on endorsements, not quality science.

For 3,000 years many patients were observed to get better by draining out the bad humors (blood) and survivors provided testimonials confirming their bloodletting procedure was beneficial and the reason for their survival. Of course, those who died were "God's will" and silent.

I too gave credit to fluoridation when credit was not due. We often give incorrect credit for a health care procedure when the patient gets better in spite of our treatment, not because.

For example, my mentor was a missionary cardiovascular surgeon. When he went to a third world medical center as chief surgeon, the local surgeons asked him, "what do you want us to do?"

He responded, "keep doing what you have been doing, but bring me your diagnosis."

The three months prior his arrival the medical center had done over 100 appendectomies (my memory is 113). Most patients got better and survivors were so grateful for the skill of the surgeons. Those who died were silent.

The three months after the diagnosis was reviewed, the medical center did three appendectomies.

As a dentist I don't do appendectomies and asked, "why?"

He responded, "there are (my memory) 56 reasons for pain right here and 48 clear up in about 3 days," the same time as recovery from surgery.

A correct diagnosis, etiology, mechanism, and randomized controlled trials are science, rather than endorsements, observational studies and PR.

4. Ms. Hayes continues: *"with one member noting that in their community there are many people who do not have access to dental care or may not have good dental hygiene."*

Most all communities have low socioeconomic subpopulations to greater or lesser extent and access is almost always limited due to socioeconomic constraints along with fear and time. Health education is better than toxic chemicals. (We could use the fluoridation money for health education rather than poisoning people.)

However, the very people we are trying to help are not being helped by fluoridation and are the least able to compensate for reduced health and harm to their brain (and all cells) from excess fluoride.

The myth of fluoridation benefit, marketing by the Fluoridation Lobby has been persuasive but is not supported by higher quality science. See the Cochrane 2015 and 2024 report. Fluoridation does not correct for lack of dental care or poor dental hygiene or poor diet.

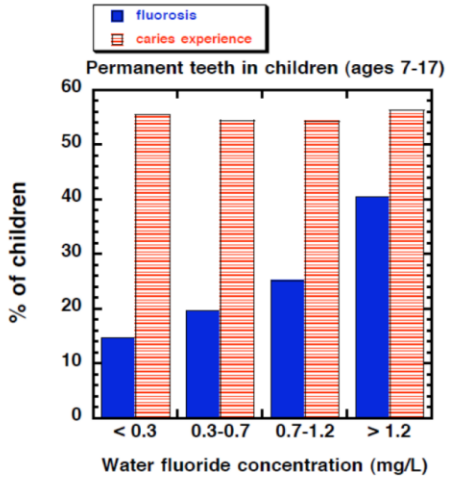
Ms. Hayes continues*: "Members stated that dentists and pediatricians are well positioned to advise parents about their individual use of fluoride for themselves and their children."*

Yes, we all agree dentists and pediatricians are well positioned to advise parents, although most are not current with the science, in part because they trust the Board and Department. And patient doctors are precisely why fluoride

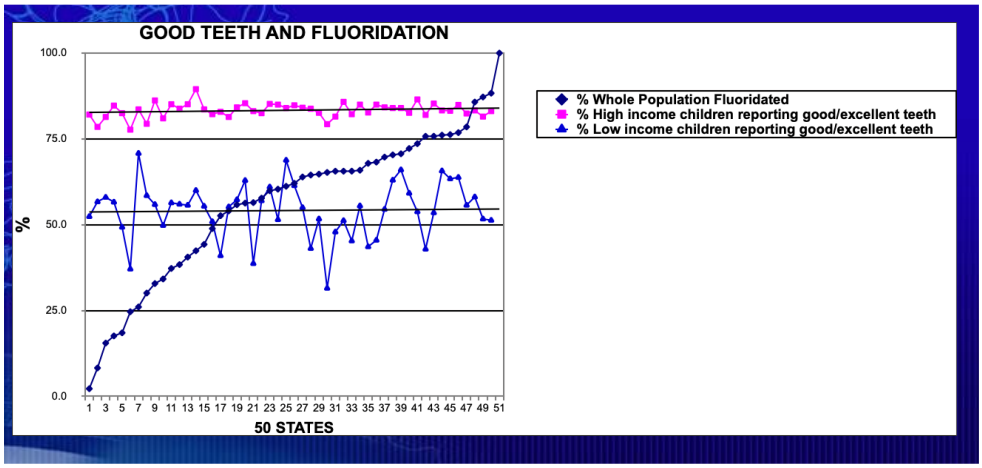
prescription supplements are better than fluoridating everyone in public water regardless of their age, health, total fluoride exposure from other sources or freedom of choice.

Note the study by Iida graphed below. As fluoride concentration in water increases, dental fluorosis (blue lines) increases, as we would expect. However, the red lines remain about the same showing little or no benefit.

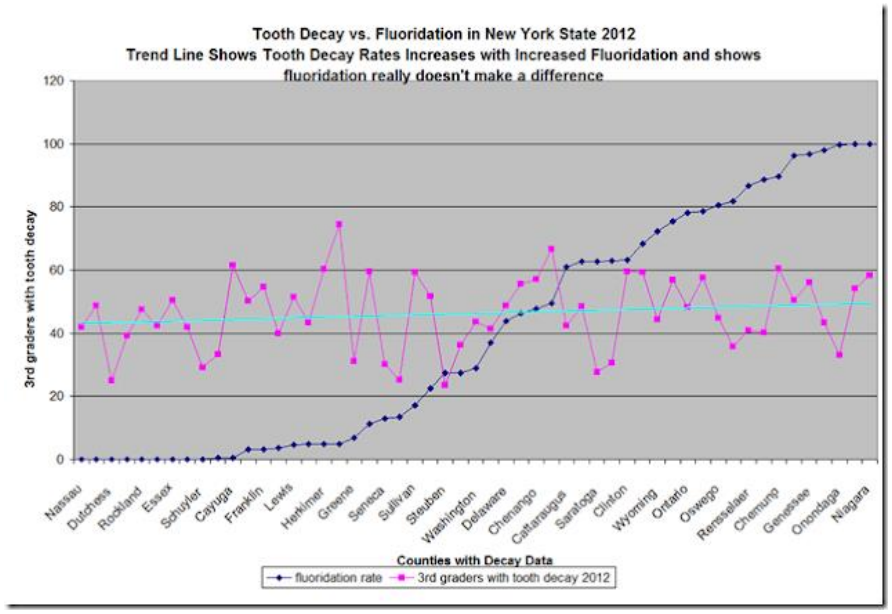
Iida, H., and Kumar, J.V. 2009. The association between enamel fluorosis and dental caries in U.S. schoolchildren. JADA 140:855-862.



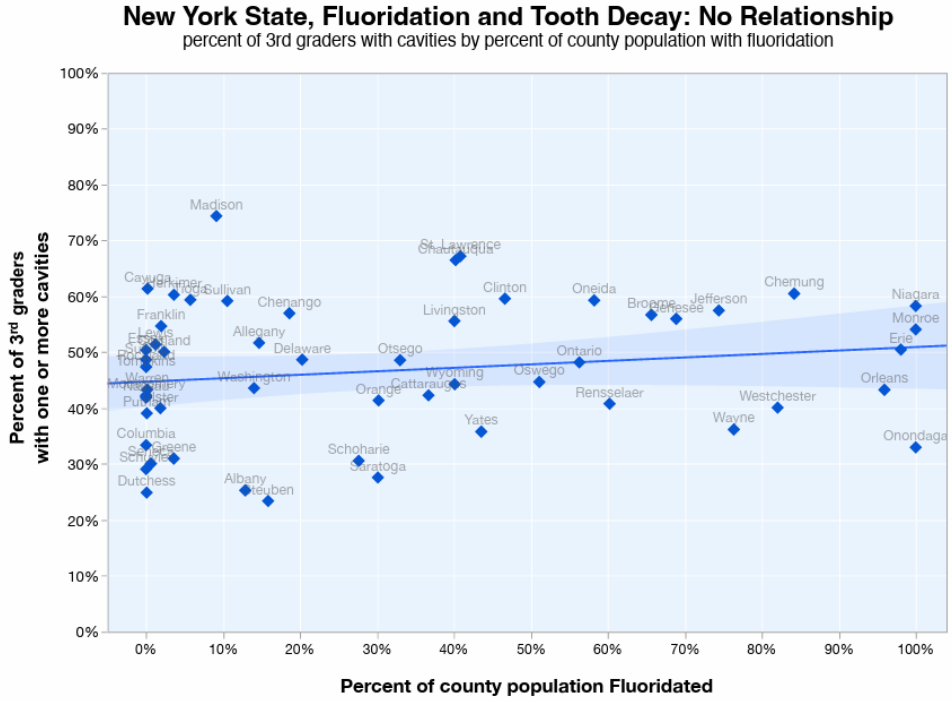
The graph below ranks the 50 states on the percentage of their whole population fluoridated, dark blue dots going from zero to 100%. The light blue line shows the percentage of low income reporting good/excellent teeth and the pink line shows the percentage of children with very good/excellent teeth. When I first made this graph the evidence jumped out at me, fluoridation had no common cause with good dental health and I had been giving credit to fluoridation for the difference in poor vs rich.



This next graph ranks the New York State Counties on each counties percentage of the population fluoridated and dental decay data. Fluoridation has no common cause with dental caries.

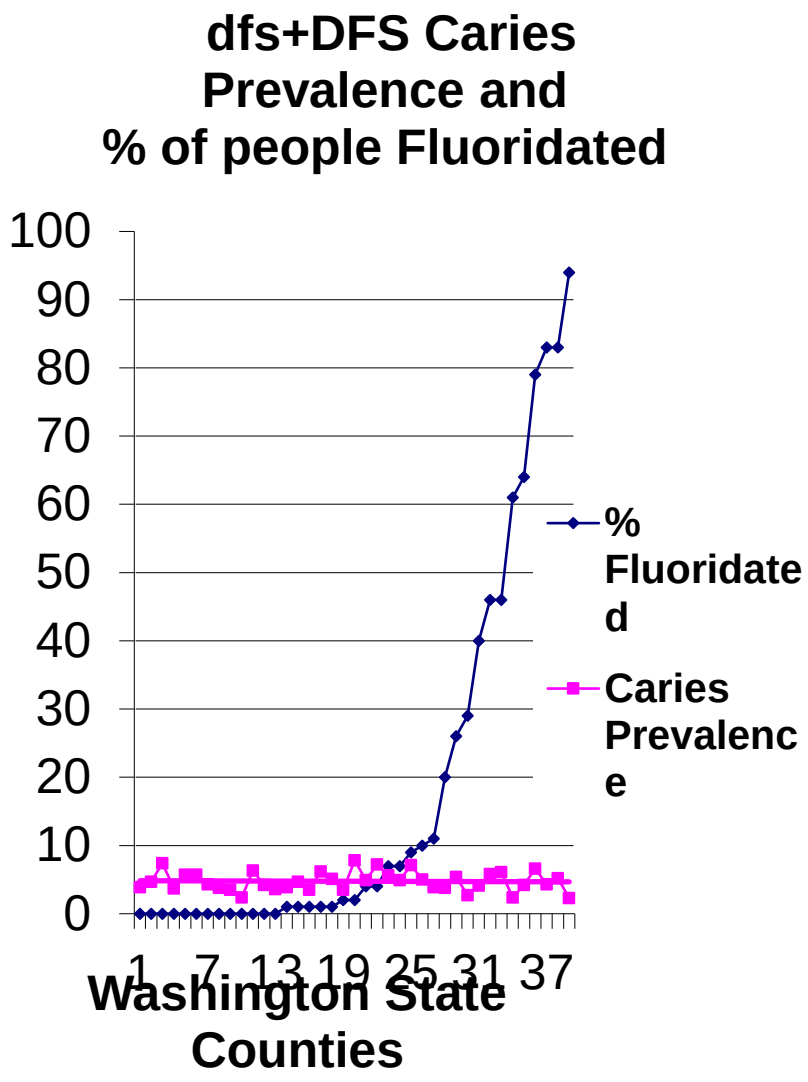


Plotting the percentage of NYS fluoridated and tooth decay does not see a public health benefit from fluoridation. In fact, the opposite trend becomes concerning. Too much fluoride can cause dental cavities and dental harm.



Data from NYS Department of Health.
Most recently available data. NYC data not available.
Fluoridation data for 2021 from:
https://apps.health.ny.gov/public/tabvis/PHIG_Public/pa/reports/PreventionAgendaTrackingIndicators-CountyMostRecentYearData.csv
Oral Health data for 2009-2011 from:
https://apps.health.ny.gov/public/tabvis/PHIG_Public/chirs/ and https://apps.health.ny.gov/public/tabvis/PHIG_Public/chirs/reports/#county

When Washington State Counties are ranked on their percentage of the population fluoridated and caries prevalence in the county plotted, we do not see a public health benefit from fluoridation.



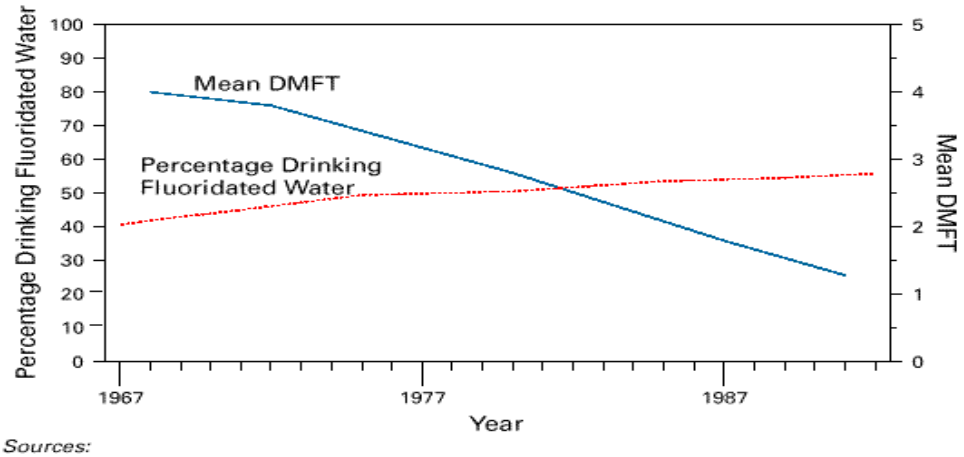
When I was in school in 1977, the first part of the current CDC graph below was shown to us. Decayed, Missing, Filled Teeth declined when more people received fluoridated water. Impressive.

However, just because two events happen is not proof of cause and effect or even relationship.

Rather strong evidence until one looks closer. Caries went from about 4 cavities down to just over 1.2 cavities/child for the entire USA population. About 17% more people were fluoridated with about a 70% reduction in caries. Wonderful, such marvelous results are not plausible. To achieve those results, fluoride would have needed to be administered to just the high-risk individuals and not random cities in the USA.

Failing to also consider the decline in dental caries prior to 1967 makes this a "gee whiz" distorted graph.

FIGURE 1. Percentage of population residing in areas with fluoridated community water systems and mean number of decayed, missing (because of caries), or filled permanent teeth (DMFT) among children aged 12 years — United States, 1967–1992



Sources:

1. CDC. Fluoridation census 1992. Atlanta, Georgia: US Department of Health and Human Services, Public Health Service, CDC, National Center for Prevention Services, Division of Oral Health, 1993.
2. National Center for Health Statistics. Decayed, missing, and filled teeth among youth 12–17 years—United States. Rockville, Maryland: US Department of Health, Education, and Welfare, Public Health Service, Health Resources Administration, 1974. Vital and health statistics, vol 11, no. 144. DHEW publication no. (HRA)75-1626.
3. National Center for Health Statistics. Decayed, missing, and filled teeth among persons 1–74 years—United States. Hyattsville, Maryland: US Department of Health and Human Services, Public Health Service, Office of Health Research, Statistics, and Technology, 1981. Vital and health statistics, vol 11, no. 223. DHHS publication no. (PHS)81-1673.
4. National Institute of Dental Research. Oral health of United States children: the National Survey of Dental Caries in U.S. School Children, 1986–1987. Bethesda, Maryland: US Department of Health and Human Services, Public Health Service, National Institutes of Health, 1989. NIH publication no. 89-2247.
5. CDC, unpublished data, third National Health and Nutrition Examination Survey, 1988–1994.

ADA awarded Kentucky with "50 Year Award" for 100% fluoridation 2003. However, 42% were edentulous (had no teeth), #1 in USA (2002 Mortality Weekly Report)

"With 1.6 to 4ppm fluoride in the water, 50% or more past age 24 have false teeth because of fluoride damage." JADA 1944

C. THE ENVIRONMENTAL PROTECTION AGENCY

1. **Congress** in the Safe Drinking Water Act prohibits adding anything to water with the intent to treat human disease. RCW 57.08.012 does not override Congress and the Safe Drinking Water Act.

The Environmental Protection Administration (EPA) was asked to explain their understanding of the Safe Drinking Water Act passed by Congress in 1974, which includes:

No national primary drinking water regulation may require the addition of any substance for preventive health care purposes unrelated to contamination of drinking water. " 42 USC 300g-1(b)(11):

The EPA explained:

"The Safe Drinking Water Act **prohibits the deliberate addition** of any substance to drinking water for health-related purposes other than disinfection of the water." FOIA Request HQ-FOI-01418-10

2. The Washington Office of Drinking Water states:

"We regulate Group A public water systems under state law and a formal agreement with the U.S. Environmental Protection Agency (EPA) for carrying out the federal Safe Drinking Water Act."

Neither the Washington Office of Drinking Water, the Department, the Board, or fluoridating water purveyors appear to be in compliance with the Safe Drinking Water Act as they claim.

3. Our petition is in keeping with the **Toxic Substance Control Act** (TSCA) of 1976 and updated June 22, 2016, called the Frank R. Lautenberg Chemical Safety for the 21st Century Act.

4. The U.S. Court ruled under the Toxic Substance Control Act that fluoridation of water **"poses an unreasonable risk of reduced IQ in children."**

5. An EPA study,[3] reported costs for treating functional dental fluorosis exceeded costs of treating cosmetic dental fluorosis. Looking back on my dental practice, I realize I made hundreds of millions of dollars both selling fluoride topical treatments and repairing functional damage to teeth from excess fluoride.

6. In 2006 the National Research Council[6] unanimously advised the EPA that their Maximum Contaminant Goal for fluoride was not protective and the EPA did not follow the NRC's advice. Concerns included.

    i. **Tooth damage**, **Rheumatoid and osteoarthritic-like pain**, **Bone cancer, Bone fractures**

Thyroid reduction -Diabetes -Obesity

    ii. **Kidney damage**

    iii. **Reproductive problems**

    iv. **Lower IQ --developmental neurotoxicity**

    v. **Allergies (overactive immune system)**

    vi. **Gastrointestinal disorders.**

Dental fluorosis is a biomarker of excess total fluoride exposure, but not the only result of excess fluoride exposure.

The Board must read the NRC 2006 report to the EPA and include it with our petition.

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[6]. Fluoride in Drinking Water A scientific Review of EPA's Standards, National Research Council of the National Academies. Link

The Environmental Protection Agency (once again) responded to the question of whether the EPA is responsible for the safety and efficacy of fluoridation, *"The FDA, remains responsible for regulating the addition of drugs to the water supply for health care purposes."* Steve Neugeboren, Ass. General Counsel, Water Law Office, EPA." 2/14/2013.

However, the FDA responded they do not regulate public water. Fluoridation is in a regulatory void. No regulatory authority assumes jurisdiction over determining the safety, ethics, dosage, label and efficacy of the fluoride drug.

The EPA scientists correctly determined and reported, *"In summary, we hold that fluoridation is an unreasonable risk. That is, the toxicity of fluoride is so great and the purported benefits associated with it are so small - if there are any at all - that requiring every man woman and child in America to ingest it borders on criminal behavior on the part of governments."* JW Hairy, Senior Vice-President, Headquarters Union, EPA 2001.

D. The Food and Drug Administration Center For Drug Evaluation and Research (FDA)

(a) The FDA on a fluoridated toothpaste label warns "Do Not Swallow" referring to a quarter milligram of fluoride the same dosage as one glass of water which the Board should also warn, "Do Not Swallow one glass of fluoridated water."

(b) The FDA (Food and Drug Administration Center for Drug Evaluation and Research) also warns the evidence of efficacy is incomplete and previously warned the WA Board of Health that if the Board tried to gain FDA approval, fluoridation would be banned. What about banned is hard for the Board to understand?

(c) The FDA notified 35 companies making fluoride supplements "there is no substantial evidence of drug effectiveness. . . . " In order to understand how much is needed to be effective, manufacturers must first determine whether it is effective at any amount. No quality evidence exists that fluoride ingestion

has any benefit. For almost 80 years the fluoridation lobby has marketed fluoride without quality evidence of benefit.

(d) The FDA testified to Congress in 2001, that fluoride is a drug.

(e) In a discussion that noted that they govern fluoride as a drug and that ingestion was associated with "dental fluorosis; bone fracture; reproductive, renal, gastrointestinal, and immunological toxicity; genotoxicity; and carcinogenicity," the FDA wrote in 1995 tha**t** "**Accordingly, because there is no consensus on the essentiality of fluoride, . . . the agency (FDA) is removing fluoride from the RDI list."** (Recommended Dietary Intake) - *Federal Register, Vol 60. No. 249, Dec 28, 1995*

(f) **Fluoridation is an unapproved drug.** In response to our request on whether fluoridation, fluoride, was an approved drug, **the FDA** responded, (July 22, 2009), *"A search of the Drugs@FDA database. . . of approved drug products and the Electronic Orange Book. . . does not indicate that sodium fluoride, silicofluoride, or hydrofluorosilicic acid has been approved under a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for ingestion for the prevention or mitigation of dental decay. . . . At the present time, the FDA is deferring any regulatory action on sodium fluoride products."*

(g) Commisioners/cities/water purveyors are the manufactures of fluoridated water. The WA State Board of Pharmacy Newsletter of July, 2008 (taken from a previous FDA Newsletter) stated, ***"Manufacturers of unapproved drugs are usually fully aware their drugs are marketed illegally, yet they continue to circumvent the law and put consumers' health at risk."***

(h) In a discussion that noted that they govern fluoride as a drug and that ingestion was associated with "**dental fluorosis; bone fracture; reproductive, renal, gastrointestinal, and immunological toxicity; genotoxicity; and carcinogenicity," the FDA wrote in 1995 that** "**Accordingly, because there is no consensus on the essentiality of fluoride, and because declaration of a percent DV for this nutrient would**

be of little value to consumers, the agency (FDA) is removing fluoride from the RDI list." *- Federal Register, Vol 60. No. 249, Dec 28, 1995*

(i) Regarding fluoride, *"The Food and Drug Administration Office of Prescription Drug Compliance has confirmed, to my surprise, that there are no studies to demonstrate either the safety or effectiveness of these drugs which FDA classifies as unapproved new drugs."* SOURCE: Letter from Dr. David Kessler, M.D., Commissioner, United States Food and Drug Administration, June 3, 1993 to Congressman Kenneth Calvert, Chairman, Subcommittee on Energy and Environment, Committee on Science, Washington, D.C.

(j) *"Fluoride, when used in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animal, is a drug that is subject to Food and Drug Administration (FDA) regulation."* SOURCE: United States Food and Drug Administration letter Dec, 2000, to Congressman Kenneth Calvert, Chairman, Subcommittee on Energy and Environment, Committee on Science, Washington, D.C.

E. Mother's Milk

One liter of **mother's milk** has the same amount of fluoride as one teaspoon of fluoridated water. Formula made with fluoridated water is about 175 times higher dosage of a highly toxic poison/drug as mother's milk. To limit the dosage of toxic poison/drug to the same as mother's milk, caregivers should only give a teaspoon of formula made with fluoridated water which is not enough for an infant's survival. Does the Board find mother's milk is flawed deficient in the fluoride poison/drug, or simply unaware?

The American Academy of Pediatrics has stated that mother's milk is the ideal nutrient for infants against which all other substitutes must be compared.

F. The **National Toxicology Program's (NTP)** concern, in their state of the science published report, is the fluoride in 2 liters (about quarts) of fluoridated water. The second section of the NTP, court ordered released as a draft and

final publication still blocked by HHS, does not show any intake of fluoride is safe and the NTP does not use the word safe.

A few of the studies reviewed by the NTP and Court include:

The following are 19 studies, published from 2017 to 2021, reporting an association of fluoride exposure to lower IQ in children. 10 studies from China, 3 from Mexico, 2 from Canada, one each from Egypt, India, Kenya and Sudan. Paul Connett, November 22, 2021.

1. 2021- China. 709 resident children in Tianjin, China, ages 6-13. Wang S, Zhao et al. 2021. The cholinergic system, intelligence, and dental fluorosis in school-aged children with low-to moderate fluoride exposure. Ecotoxicology and Environmental Safety.

   Conclusions: "… Our findings suggest low-to-moderate fluoride exposure was associated with dysfunction of cholinergic system for children. AChE may partly mediate the prevalence of DF and lower probability of having superior and above intelligence."

2. 2021- Mexico. 103 mother-infant pairs, tested at 12 months and 24 months. Funded by NIH & NIEHS. Cantoral A, et al. 2021. Dietary fluoride intake during pregnancy and neurodevelopment in toddlers: A prospective study in the progress cohort. NeuroToxicology.

   Conclusions: "In this prospective cohort study, higher exposure to fluoride from food and beverage consumption in pregnancy was associated with reduced cognitive outcome, but not with language and motor outcome in male offspring over the first two years of life."

3. 2021 – China. 952 resident children, 7 to 13 years old. Yu X, et al. 2021. Dietary fluoride intake during pregnancy and neurodevelopment in toddlers: A prospective study in the progress cohort. Environment International 155:106681.

   Conclusions: "Our study suggests that fluoride is inversely associated with intelligence. Moreover, the interactions of fluoride with mitochondrial

function-related SNP-set, genes and pathways may also be involved in high intelligence loss."

4. 2021 – China. 567 children, 6–11 years old. Zhao L et al. 2021. Fluoride exposure, dopamine relative gene polymorphism and intelligence: A cross-sectional study in China. Ecotoxicology and Environmental Safety 209:111826. [Epub ahead of print].

   Conclusions: "Our study examined the association between excessive fluoride exposure in prenatal and childhood periods and the intelligence of school-age children. We found that prenatal excessive fluoride exposure could cause lower IQ scores, especially the decreased odds of developing excellent intelligence. Meanwhile, a negative association between fluoride exposure and children's IQ scores was observed in children without prenatal exposure."

5. 2020 – China. 99 children, 8–12 years. 55 in dental fluorosis group (none with moderate or severe dental fluorosis, but all with mild) and 44 students without dental fluorosis. Lou D, et al 2020. Refinement Impairments of Verbal Performance Intelligent Quotient in Children Exposed to Fluoride Produced by Coal Burning. Biological Trace Element Research.

   Conclusions: "In conclusion, we believe that reducing fluoride intake with the assistance of the government can reduce fluorosis as well as the severity of intellectual impairment caused by fluorosis. Fluorosis in children can cause IQ impairment, especially the VIQ that is represented by language learning and vocabulary comprehension."

6. 2020 – Canada. 398 Mother-Offspring pairs. Fetus and Infants up to 3-4 year-olds. Funded by NIEHS. Till C, et al 2020. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. Environment International 134:105315. (Published in November 2019)

   Conclusions: "In summary, fluoride intake among infants younger than 6 months may exceed the tolerable upper limits if they are fed exclusively with formula reconstituted with fluoridated tap water. After adjusting for fetal

exposure, we found that fluoride exposure during infancy predicts diminished non-verbal intelligence in children…"

7. 2019 – China. 571 children, ages 7-13, randomly selected from endemic and non-endemic fluorosis areas in Tianjin. Wang M,. 2019. Thyroid function, intelligence, and low-moderate fluoride exposure among Chinese school-age children. Environment International 134:105229. [Epub ahead of print].

   Conclusions: The study suggests low-moderate fluoride exposure is associated with alterations in childhood thyroid function that may modify the association between fluoride and intelligence. In the current work, results demonstrated clearly that, across the full range of water and urinary fluoride concentrations and using a measure to focus on children's IQ scores, higher fluoride levels were associated with lower IQ scores."

8. 2019 – Canada. 512 Mother-Child pairs between the ages 3 and 4 years at testing. Funded by NIEHS. Green R, 2019. Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada. JAMA Pediatrics.

   Conclusions: "In this study, maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years. These findings indicate the possible need to reduce fluoride intake during pregnancy." Listen to discussion of JAMA editors on their process to publish this study.

9. 2018 -China. 323 children, ages 7 – 12 years. Urine fluoride levels and age-specific IQ scores in children were measured at the enrollment. Cui Y, et al. 2018. Dopamine receptor D2 gene polymorphism, urine fluoride, and intelligence impairment of children in China: A school-based cross-sectional study. Ecotoxicology and Environmental Safety, Sept 11;165:270 277.

   Conclusions: "Strengths of our study include using urine fluoride as an internal exposure index and thus minimizing the measurement error of exposure, adjusting up to 30 potential confounding covariates including

child age and gene polymorphismin regressing IQ on urine fluoride in children, and careful modeling with applications of cross-validation, bootstrap techniques, and sensitivity analysis. “In the overall participants, by LOWESS, the IQ decreased in a roughly linear manner as the log-urine fluoride increased (Fig. 1A). “The authors also determined a safety threshold of urine fluoride on intelligence impairment in the subgroup TT as 1.73 mg/L urine fluoride with a 95% CI of (1.51 mg/L, 1.97 mg/L).”

10. 2018 – Egypt. 1,000 children, 495 children, 4.6 – 11 years old. El Sehmawy AAEW, et al 2018. Relationship between Drinking Water Fluoride and Intelligence Quotient in Egyptian School Children. Occupational Medicine & Health Affairs, Aug 13: 6:3.

    Results: “In this study there’s a highly significant decrease in average IQ level in group of children with high fluoride level more than 1.5 mg /dL than the group of children with low fluoride level less than 1.5 mg /dL with the mean IQ was (96.25 ± 19.63) and (103.11 ± 28.00) for both groups respectively with p value ($p<0.001$), . . .”

11. 2018 – Kenya. 269 school children, 13-15 years Induswe B R. 2018. The Auditory Working Memory of 13-15-Year-Old Adolescents Using Water with Varying Fluoride Concentrations from Selected Public Primary Schools in North Kajiado Sub County. American Journal of Medicine and Medical Sciences, Jan; 8(0):274-290.

    Conclusions: “In conclusion, low fluoride in the water seemed to enhance the AWM (Auditory Working Memory). However, the AWM declined with an increase in the fluoride concentration in water.”

12. 2018 – Sudan. 775 primary students, 315 boys and 460 girls from 27 schools. Mustafa DE,. 2018. The relationship between the fluoride levels in drinking water and the schooling performance of children in rural areas of Khartoum State, Sudan (pdf). Fluoride 51(2):102–113.

    Results: “Negative correlation coefficients were found for the average score for all the subjects and for the overall score, with the result being

statistically significant in five out of the eight subjects and in the overall score (Tables 4 and 5). … significant correlations undoubtedly exit between the drinking water F level and the schooling performances in all the subjects except for one, technology, which might be due to the nature of the subject."

13. 2018 – China. 268 children, 8 -12 years of age: 134 children each from endemic fluorosis area and non-endemic fluorosis areas. Pang H, 2018. Relation Between Intelligence and COMT Gene Polymorphism in Children Aged 8-12 in the Endemic Fluorosis Area and Non-Endemic Fluorosis Area. Chinese Journal of Control of Endemic Diseases 32(2):151-152. Study in Chinese translated into English.

    Conclusions: "This study found that there was a great difference in the level of intelligence between children in the endemic fluorosis area and those in the non-endemic fluorosis area and such difference was statistically significant ($P < 0.05$). "The rate of mental retardation (IQ < 69) in children in the endemic fluorosis area was significantly higher than that in the non-endemic fluorosis area, and the difference was statistically significant ($P < 0.05$)."

14. 2018 – China. 2,886 resident children, 7 to 13 years. Yu X, et al (2018). Threshold effects of moderately excessive fluoride exposure on children's health: A potential association between dental fluorosis and loss of excellent intelligence. Environment International, Jun 2; 118:116-124.

    Conclusions: "In conclusion, chronic exposure to excessive fluoride, even at a moderate level, was inversely associated with children's dental health and intelligence scores, especially excellent intelligence performance, with threshold and saturation effects observed in the dose-response relationships. Additionally, DF severity is positively associated with the loss of high intelligence, and may be useful for the identification of individuals with the loss of excellent intelligence."

15. 2017 -Mexico. 299 Mother–Offspring pairs. Tests at age 4 and 6–12 years. Funding from NIH, NIEHS, and EPA. Bashash M, et al. 2017. Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico. Environmental Health Perspectives, Sept 19;125(9):097017.

    Conclusions: “In this study, higher prenatal fluoride exposure, in the general range of exposures reported for other general population samples of pregnant women and nonpregnant adults, was associated with lower scores on tests of cognitive function in the offspring at age 4 and 6–12 y.”

16. 2017 – Mexico. 65 Mother-Offspring infant pairs, aged 3–15 months, in an endemic hydrofuorosis area. Valdez Jiménez L, López Guzmán OD, Cervantes Flores M, Costilla-Salazar R, Calderón Hernández J, Alcaraz Contreras Y, Rocha-Amador DO. 2017. In utero exposure to fluoride and cognitive development delay in infants. Neurotoxicology Mar;59:65-70.

    Results: “In this study near to 60% of the children consumed contaminated water and the prevalence of children with IQ below 90 points was 25% in the control group (F urine 1.5 mg/g creatinine) in comparison with the 58% of children in the exposed group (F urine >5 mg/g creatinine) (OR = 4.1, CI 95% 1.3–13.2) (data unpublished). “Only 66.2% of the babies were at term. “We found higher levels of F in urine across trimester in premature compared with full term 2.4 vs 1.6 mg/l (1st); 2.3 vs 1.8 mg/l (2nd); and 4.1 vs 2.8 mg/l (3rd) (data not shown).”

17. 2017 – China. 118 newborns, 68 newborns to 12 months of age, from coal-burning fluorosis areas. Chang A, et al . 2017. Analysis on the Effect of Coal-Burning Fluorosis on the Physical Development and Intelligence Development of Newborns Delivered by Pregnant Women with Coal Burning Fluorosis. Chinese Journal of Control of Endemic Diseases, 32(8):872-873.

    Conclusions: “Comparison of the mental development index (MDI) and psychomotor development index (PDI) (assessed using the Standardized

Scale for the Intelligence Development of Children formulated by the Children Development Center of China [CDCC]) of newborns in the two groups at 3, 6, 9 and 12 months after birth showed that both the MDI and the PDI in the observation group were significantly lower than those in the control group (P< 0.05), which suggests that maternal fluorosis have a significant impact on the intelligence development of newborns."

18. 2017 -China. 284 children, 8 – 12 years: 167 were from coal burning-related endemic fluorosis areas and 117 were the control. Jin T, et al. (2017). Investigation of Intelligence Levels of Children of 8 to 12 Years of Age in Coal Burning-Related Endemic Fluorosis Areas. Journal of Environment and Health 34(3):229-231.

    Conclusions: "The intelligence of the 12-year-old group in the endemic area was lower than that of the control area, with the difference having statistical significance (Z = 3.244, P = 0.001)."

19. 2017 – India. 219 children, 12-14 year olds: 75 from low F area, 75 medium F area, and 69 from high F area. Razdan P, (2017). Effect of fluoride concentration in drinking water on intelligence quotient of 12–14-year-old children in Mathura District: A cross-sectional study. Journal of International Society of Preventive & Community Dentistry 7(5):252 258.

    Conclusions: "Concentration of Fluoride in the ingested water was significantly associated with the IQ of children. Outcome measures revealed that exposure to higher levels of F determined by dental fluorosis status of child inferred higher IQ deficit.

G. The U.S. Court (2024) found fluoridation unreasonable. About 3 IQ points are lost when the mother drinks 1 liter of water, and about 7 IQ points are lost when the mother drinks about 2 liters of water a day. Many mothers during the third trimester drink at least that or more.

To more fully understand the crushing effect lower IQ has on society, some social correlates of IQ (Herrnstein and Murray 1994) between those with less than 75 IQ and those with greater than 125 IQ are provided below.

IQ	< 75 IQ	>125 IQ
US population distribution	5%	5%
Married by age 30	72%	67%
Out of labor 1 month/year men	22%	10%
Divorced in 5 years	21%	9%
% of children 2/IQ in bottom decile (mothers)	39%	-
Had an illegitimate baby (mothers)	39%	2%
Lives in poverty	30%	2%
Ever incarcerated (men)	7%	0%
Chronic welfare recipient (mothers)	31%	0%
High School Dropout	55%	0%

Each IQ point represents about $500/year increase in wages.

(IQ and homelessness appears to have some relationship, but not well studied.)

The Court granted our request to have the NTP draft released and the Court ordered HHS to release the May 2023, National Toxicology Draft Report, "Association between fluoride exposure and children's intelligence: A systematic review and meta-analysis."

The report's meta-analysis includes more results than the first state of the science section and includes:

> *"RESULTS The meta-analysis of 55 studies (N = 18,845 children) with group-level exposures found that, when compared to children exposed to lower fluoride levels, children exposed to higher fluoride levels had lower mean IQ scores (pooled SMD: −0.46; 95% CI: −0.55, −0.37; p value < 0.001). There was a dose-response relationship between group-level fluoride exposure measures and mean children's IQ. The meta-analysis of*

studies that reported individual-level measures of fluoride and children's IQ scores found a decrease of 1.81 points (95% CI: −2.80, −0.81; p-value < 0.001) per 1-mg/L increase in urinary output. Overall, the direction of the association was robust to stratification by study quality (high vs. low risk of bias), sex, age group, outcome assessment, study location, exposure timing, and exposure metric. CONCLUSIONS AND RELEVANCE This meta-analysis confirms results of previous meta-analyses and extends them by including newer, more precise studies with individual-level exposure measures. The consistency of the data supports an inverse association between fluoride exposure and children's IQ."

The Board is well aware of the problems with lead ingestion and Needleman testified to Congress in 1991 which turned the tide on concern with lead. Needleman did a meta-analysis of leads toxicity and the following table compares the evidence of lead and fluoride.

The amount of lead exposure from 12 studies resulted in about 4 IQ point loss.[7] This compares with the NTP report on fluoridation with 55 studies and seven IQ point loss.[8]

Table comparing Needleman 1990 meta-analysis of Pb to NTP 2022 meta-analysis of F

	1990 meta-analysis of **Lead (Pb)**	2022 meta-analysis of **Fluoride (F)**
Reference	Needleman 1990	NTP 2022
Number of studies	12	55
Average exposure of all studies	30 to 60 ug/dL blood Pb	About 2 mg/L water F and 2 mg/L urine F
Average US population exposure at time of studies	15 ug/dL	0.9 mg/L urine F in fluoridated areas
Ratio of study exposure to population exposure	2x to 4x	2x
IQ point loss found in studies	-4 IQ points	-7 IQ points

[7] Needleman 1997 discusses a very rigged NAS committee that include Kehoe as a consultant [NAS/NRC 1972] and a much more balanced NAS committee that later corrected the errors of the first [NAS/NRC 1980]. Needleman1997 Patterson vs Kehoe on Pb.pdf

[8] https://www.c-span.org/video/?20139-1/lead-contamination-control-act-1991

The more fluoride a child is exposed to, the more brain damage they get. The Board needs perspective on the Court's ruling that fluoride is an unreasonable risk to the developing brain. The Court in the TSCA case only considered developmental neurotoxicity as measured by lower IQ. No other risk and no other measurement were used.

We would be foolish not to include other risks in our judgment and we would be foolish not to consider other measurements of lower IQ such as miscarriage, premature birth, infant mortality and a host of other neurological effects.

As the distinguished toxicologist and long-time director of NTP Linda Birnbaum stated along with two co-authors who have conducted the highest quality studies of fluoride and IQ [Lanphear 2020]: *"When do we know enough to revise long-held beliefs? We are reminded of the discovery of neurotoxic effects of lead that led to the successful banning of lead in gasoline and paint. Despite early warnings of lead toxicity, regulatory actions to reduce childhood lead exposures were not taken until decades of research had elapsed and millions more children were poisoned."*
See also Neurath 2020, Neurath 2021

Two tables are part of our submission and should be reviewed.
Table 1 contains the information from the 78 studies that found an association of fluoride exposure with the lowering of IQ. Participants included: **29,130 children and 689 adults.**
Table 2 contains the information from the 9 studies that found no association of fluoride exposure and the lowering of IQ. Participants included **4,363 children and 1,037 adults.**
NOTE: The IQ study #67 by Xu 2020 was retracted by the publisher on Nov 8, 2022. We have adjusted the number of each study to reflect that change. On Nov 9, 2022, another IQ study by Saeed et al. was published, for a total of 77 studies. (EC) (A new website is being built to handle the studies and not all links on the pages have been transferred.)

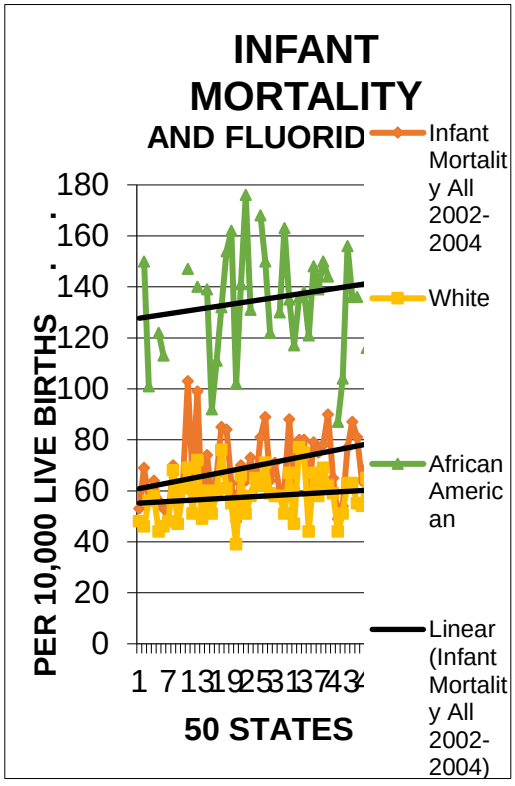
INFANT MORTALITY

IQ is just one measurement of developmental neurotoxicity. Miscarriage, premature birth, and infant mortality are other methods.

I once again ranked the states on the percentage of their whole population fluoridated and plotted infant mortality per 10,000 live births, about 15% increase in infant death. See graph below.

Data on infant mortality is readily available and the USA has a poor record compared to other countries trying to keep babies alive during their first year of life. Confounding factors need to be considered and more research is needed.

A study using U.S. Government records reported an increase in infant mortality (perhaps 20% increase) and premature births in fluoridated communities with soft water, such as Seattle water. See Figure 3 below.



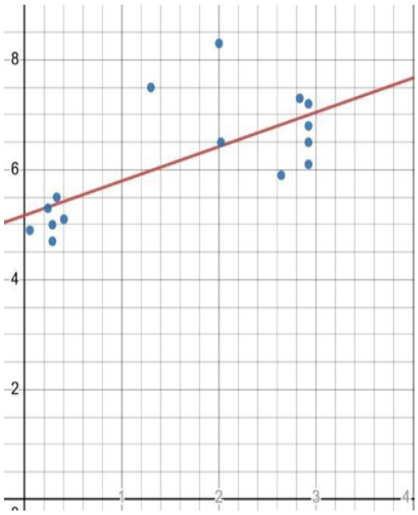
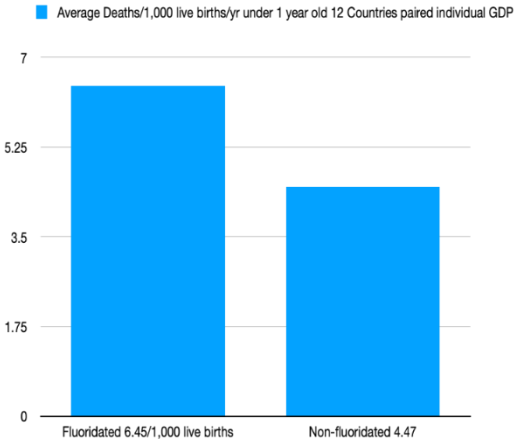


Figure 3: Infant mortality per 1,000 live births in hard water and soft water U.S. States on the vertical axis is plotted as a function of the ratio of the percent of the state population provided fluoridated water (0.7 ppm recommended) to water hardness as the calcium carbonate concentration (mg/L). Points were fitted with linear regression given by

$Y = 0.627X + 5.167$ ($r = 0.694$).

I recently compared six highly fluoridated countries paired economically (individual GDP) with six countries without fluoridated water or salt. Comparing these countries results in almost 30% increase in infant mortality. [9] Six countries is a small sample and fluoride is certainly not the only contributing factor for infant mortality.



The trend is serious and in keeping with the developmental neurotoxicity of fluoride as measured with lower IQ.

Preterm birth is defined as birth prior to 37 weeks of pregnancy. Damage to cerebral white matter is the most commonly recognized pathology of prematurity, say neuroscientists at the Dana Alliance for Brain Initiatives. “Babies born preterm face a range of potential neurological disruptions … The earlier the birth, the greater the risk that these disruptions will produce devastating and

[9] Six highly fluoridate countries were paired with six countries with no fluoridated water or salt and similar individual GDP’s or area. Infant mortality rates based on CIA.gov data, GDP per Capita - Worldometer (worldometers.info), and fluoride concentrations in water

potentially life-long cognitive, behavioral, and socialization deficits."[10] Preterm birth can be very expensive and devastating to a families budget even with insurance.

Hart reported, in 2009,

"Domestic water fluoridation was associated with an increased risk of PTB (9545 (6.34%) PTB among women exposed to domestic water fluoridation versus 25278 (5.52%) PTB among those unexposed, p < 0.0001)). This relationship was most pronounced among women in the lowest SES groups (>10% poverty) and those of non-white racial origin. Domestic water fluoridation was independently associated with an increased risk of PTB in logistic regression, after controlling for age, race/ethnicity, neighborhood poverty level, hypertension, and diabetes."

The fluoridation lobby demands proof of harm. One public health dentist told me he would promote fluoridation until it was proven people were falling over in the street dead from fluoridation. The fetus and infant do not walk down streets.

The Court in Doe v Rumsfeld, ruled even under emergency conditions of war the Government cannot force an individual to be medicated with a substance which has not been specifically approved for the purpose and manner it is intended. (Fluoridation is not FDA approved.)

H. The **2015 Cochrane** Review funded by the CDC reported, "There is insufficient information available to find out whether the introduction of water fluoridation program changed existing differences in tooth decay across

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1.[10] Patoine B. The vulnerable premature brain: Rapid neural development in third trimester heightens brain risks. Dana Foundation. May 2010. Available at https://www.dana.org/media/detail.aspx?id=27882.

socioeconomic groups. . . (or) stopping fluoridation. . . or preventing decay in adults, rather than children."

Once again, we need to keep in mind the Cochrane review lowered their usual standard and used observational studies rather than requiring randomized controlled trials.

The Cochrane reviews would not hold up to FDA standards. Thus, even the Cochrane reviews have serious limitations.

For example, some of the confounding factors for dental caries and some limitations of some observational studies:

A. Not one Randomized Controlled Trial

B. Socioeconomic status usually not controlled

C. Inadequate size

D. Difficulty in diagnosing decay

E. Delay in tooth eruption

F. Diet: Vitamin D, calcium, strontium, sugar, variables.

G. Total exposure of Fluoride

H. Oral hygiene

I. Not evaluating Life time benefit

J. Estimating or assuming subject actually drinks the fluoridated water.

K. Dental treatment expenses

L. Breast feeding and infant formula

M. Fraud or gross errors.

N. Genetics

O. Unknowns which crushed dental caries rates prior to fluoridation.

A second **Cochrane October 4, 2024** review, Cochrane systematic review, Water fluoridation for the prevention of dental caries, should also be considered with those limitations.

The review clearly states, *"We included 157 studies. All used non-randomised designs. Given the inherent risks of bias in these designs, particularly related to management of confounding factors and blinding of outcome assessors, we downgraded the certainty of all evidence for these risks. We downgraded some evidence for imprecision, inconsistency or both. Evidence from older studies may not be applicable to contemporary societies, and we downgraded older evidence for indirectness."*

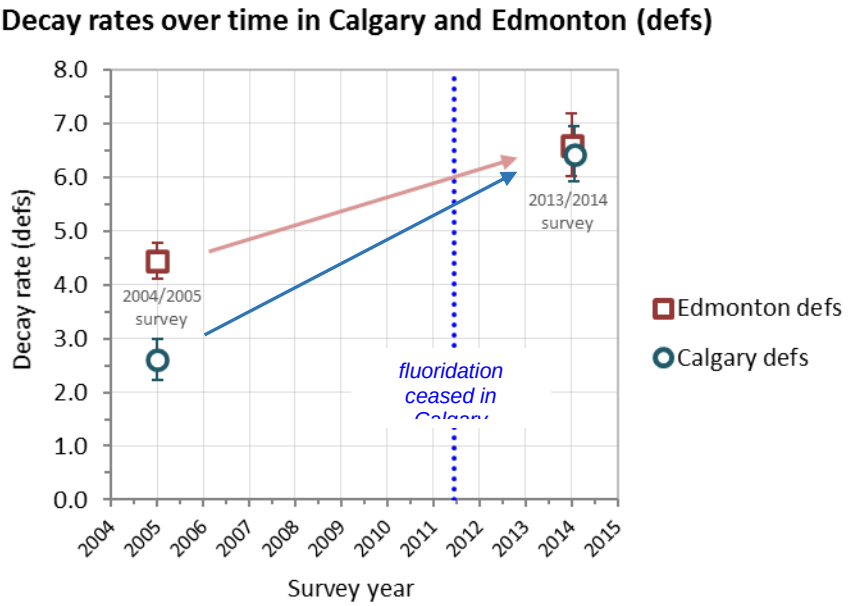
Twenty-one studies of fluoridation initiation were included and *"reported a slightly greater change in dmft* (baby teeth) *over time. . . approximately one-quarter of a tooth in favor; this effect estimate includes the possibility of benefit and no benefit."* (4% for baby teeth and 3% for adult teeth). *"Because of very low-certainty evidence, we were unsure of the size of effects . . . . " "Only one study, conducted after 1975, reported disparities according to socioeconomic status, with no evidence that deprivation influenced the relationship between water exposure and caries status."*

Judgment requires the Board to carefully weigh the lack of certainty for fluoridation's benefit against the known (such as cosmetic and functional dental fluorosis) and presumed risks (such as lower IQ), along with the lack of quality product being used to make the fluoridated water drug.

The Cochrane evaluation continues, *"Water fluoridation cessation (1 study). Because of very low-certainty evidence, we could not determine if the cessation of CWF affected DMFS. . . ."*

The Fluoridation Lobby has used Clagary's fluoridation cessation to argue there was an increase in dental caries when fluoridation stopped. The graph below compares Edmonton and Calgary dental caries rates over about 8 years.

Caries were increasing regardless of fluoridation and continued the same trend in both cities regardless of fluoridation. The increase is concerning; however, the increase cannot be placed on fluoridation cessation.



IV. MECANISM OF ACTION

A. Mechanism of Benefit is essential for drug approval and understanding. How does the fluoride ingested get to where the dental caries are forming from the inside of the tooth to the outside of the tooth?

Good question because a mechanism of action for fluoride benefit has not been determined. The tooth is highly resistant to the migration of fluoride through the tooth. In other words, fluoride can't get from the pulp chamber blood in the center of the tooth through the tooth to the outside of the tooth where the caries are forming. Teeth have been sectioned (like a loaf of bread) and fluoride concentrations measured at each section both in fluoridated and none fluoridated teeth. The concentration in the pulp chamber is indeed higher in fluoridated teeth, but is the same concentration throughout the dentin and enamel. Fluoride is not migrating through the tooth.

What about fluoride in the saliva? Saliva fluoride is a very low concentration, about 0.1 mg/L. Studies of fluoride at less than 700 mg/L have not produced positive results.

A Pubmed search of *"mechanism of fluoride ingested benefit*" gave 4 results, three remotely relevant provided here.

Limeback (1999)[11] *"The belief that fluoridated water reduces caries incidence by half stems from years of fluoridation studies where the caries rates of people in various fluoridated and non-fluoridated communities were compared. By their nature, the water fluoridation trials were not able to distinguish between the topical effects of the fluoride in the water and the systemic effects of the fluoride that is inevitably swallowed and incorporated into developing teeth. Some attempts have been made to estimate the contribution of systemic fluoride to the control of dental caries but researchers are discovering that the*

[11] Limeback H. A re-examination of the pre-eruptive and post-eruptive mechanism of the anti-caries effects of fluoride: is there any anti-caries benefit from swallowing fluoride? Community Dent Oral Epidemiol. 1999 Feb;27(1):62-71. doi: 10.1111/j.1600-0528.1999.tb01993.x. PMID: 10086928.

topical effects of fluoride are likely to mask any benefits that ingesting fluoride might have. In this updated review of the pre-eruptive vs. post-eruptive benefits of fluoride in the prevention of dental caries, a re-examination of the literature, which is often cited to support the notion that swallowing fluoride, either in water or in pill form, was done in recognition of the mounting evidence for the topical mechanism as being the primary mechanism for the prevention of dental caries. Maximum benefits from exposing newly erupted teeth to topical fluoride in the oral cavity may have been seriously under-estimated. This has obvious implications for the use of systemic fluorides to prevent dental caries and forces everyone working in the field to examine more closely the risks and benefits of fluoride in all its delivery forms."

Diesendorf (1997)[12] "*A review of recent scientific literature reveals a consistent pattern of evidence--hip fractures, skeletal fluorosis, the effect of fluoride on bone structure, fluoride levels in bones and osteosarcomas--pointing to the existence of causal mechanisms by which fluoride damages bones. In addition, there is evidence, accepted by some eminent dental researchers and at least one leading United States proponent of fluoridation, that there is negligible benefit from ingesting fluoride, and that any (small) benefit from fluoridation comes from the action of fluoride at the surface of the teeth before fluoridated water is swallowed. Public health authorities in Australia and New Zealand have appeared reluctant to consider openly and frankly the implications of this and earlier scientific evidence unfavourable to the continuation of the fluoridation of drinking water supplies."*

Zhao, et al (2021)[13] "*Dental fluorosis is characterized by hypomineralization of tooth enamel caused by ingestion of excessive fluoride during enamel*

[12] Diesendorf M, Colquhoun J, Spittle BJ, Everingham DN, Clutterbuck FW. New evidence on fluoridation. Aust N Z J Public Health. 1997 Apr;21(2):187-90. doi: 10.1111/j.1467-842x.1997.tb01681.x. PMID: 9161076. Pubmed

[13] Zhao L, Su J, Liu S, Li Y, Xi T, Ruan J, Liang KX, Huang R. MAP kinase phosphatase MKP-1 regulates p-ERK1/2 signaling pathway with fluoride treatment. Biochem Biophys Res Commun. 2021 Jan 22;542:65-72. doi: 10.1016/j.bbrc.2020.12.100. Epub ahead of print. PMID: 33493990. Pubmed

formation. Excess fluoride could have effects on the ERK signaling, which is essential for the ameloblasts differentiation and tooth development."

B. Mechanism of Action of Neurotoxicity

Zhao et al[14] in 2019 reported, *"Mechanically, pharmacological inhibition of mitochondrial fission exacerbated NaF-induced mitochondrial defects and cell death through promoting apoptosis despite partial autophagy restoration. . . . Collectively, our results suggest that mitochondrial fission inhibition induces mitochondrial abnormalities, triggering abnormal autophagy and apoptosis, thus contributing to neuronal death, and that the mitochondrial dynamics molecules may act as promising indicators for developmental fluoride neurotoxicity."*

Qiang et al (2017)[15] *". . . these data suggest that neuronal death resulted from excessive ER stress and autophagic flux dysfunction contributes to fluoride-elicited neurotoxicity."*

Xu et al (2023)[16] *"In conclusion, our results suggest that NaF exposure initiates excessive lysosomal stress response, resulting in elevated lysosomal pH, decreased lysosomal degradation, and blocked autophagic flux, which leads to neuronal apoptosis."*

Evidence of neurodevelopmental toxicity of any type – epidemiological or toxicological or mechanistic – by itself should constitute a signal sufficient

[14] Zhao Q, Niu Q, Chen J, Xia T, Zhou G, Li P, Dong L, Xu C, Tian Z, Luo C, Liu L, Zhang S, Wang A. Roles of mitochondrial fission inhibition in developmental fluoride neurotoxicity: mechanisms of action in vitro and associations with cognition in rats and children. Arch Toxicol. 2019 Mar;93(3):709-726. doi: 10.1007/s00204-019-02390-0. Epub 2019 Jan 18. PMID: 30659323. Pubmed

[15] Niu Q, Chen J, Xia T, Li P, Zhou G, Xu C, Zhao Q, Dong L, Zhang S, Wang A. Excessive ER stress and the resulting autophagic flux dysfunction contribute to fluoride-induced neurotoxicity. Environ Pollut. 2018 Feb;233:889-899. doi: 10.1016/j.envpol.2017.09.015. Epub 2017 Oct 31. PMID: 29100748. Pubmed

[16] Xu W, Hu Z, Tang Y, Zhang J, Xu S, Niu Q. Excessive Lysosomal Stress Response and Consequently Impaired Autophagy Contribute to Fluoride-Induced Developmental Neurotoxicity. Biol Trace Elem Res. 2023 Sep;201(9):4472-4483. doi: 10.1007/s12011-022-03511-0. Epub 2022 Dec 5. PMID: 36464725. Pubmed

to trigger prioritization and some level of action." - *The TENDR Consensus Statement (Targeting Environmental Neuro-Developmental Risks, 2016)*

Researchers: "New evidence questions existing policies about the safety of fluoride for babies' developing brains. Given that safe alternatives are available and that there is no benefit of fluoride to babies' teeth before they erupt or appear, it is time to protect those who are most vulnerable." - *Bruce Lanphear MD, PhD; Christine Till PhD; & Linda S. Birnbaum PhD in "It is time to protect kids' developing brains from fluoride." Environmental Health News (October 7, 2020)*

V. ETHICS OF FLUORIDATION should include: Individual autonomy, public health, social justice, informed consent and maintenance of trust.

Reviews of the ethics of fluoridation (Government of Canada) and others are generally consistent with the Nuffield Council on Bioethics: Concluding,

> "The principle of avoiding coercive interventions could be used to argue against adding anything to the water supply. However, we do not accept that this should always be ruled out, especially if the substance being added may bring health benefits. The acceptability of any public health policy involving the water supply should be considered in relation to:
>
> a. the balance of risks and benefits
>
> b. the potential for alternatives that rank lower on the intervention ladder to achieve the same outcome
>
> c. the role of consent where there are potential harms . . . ."

Regarding #1. The alleged potential benefit is a reduction in dental caries. The risks far outweigh benefit.

Regarding #2. Fluoride supplements are lower in the intervention ladder and can achieve the same outcome. Health education is lower in the intervention ladder and can achieve superior outcomes.

Regarding #3. Fluoridation is forced medication. Products are not labeled. Consent is violated and some potential harms have been listed and more below.

Democratic decision-making procedures are only applicable for benefits which are not violated by the first three.

VI. TOTAL FLUORIDE EXPOSURE

Although 30-70% of fluoride exposure is estimated to come from water, for easy figuring, using 50% is often reasonable; however, some drink very little water and the mean 1 liter/day, the 90th percentile about 2 liters/day and some drink 10 liters per day. Dosage just from water is uncontrolled.

And other sources are unlabeled. Where does the rest of the fluoride come from? The best source of information on total exposure, is the **2006 NRC** report on fluoride in drinking water. A few examples here:

A. Toothpaste is usually considered the second major source of fluoride. However, there are many extremes. My new toothpaste sample warns to keep out of the reach of children under 12 years of age and the last tube said 6 years of age.

   I was amazed, because I had told the FDA about my daughter at 11 years of age and one night late, I stuck my head into the bathroom to watch her brush her teeth. I warned her not to swallow and spit her toothpaste out, rinse and then spit and then rinse again.

   As she leaned over the sink, I watched her “Eve’s Apple” go up and down and then she spit. Her swallow reflex had her swallow first and then spit. We had to practice the spitting without the reflex of swallowing.

   The FDA was correct in changing the label and I would like to think I had a small hand in the change on at least some toothpaste labels to protect the public. Yes, sometimes authorities listen. (Then they are so smart!)

B. Other sources can include foods, pesticides, post-harvest fumigants, medications, general anesthesia, and environment.

Foods such as raisons, wine, grapes, tea, fries, burgers, rice, pudding, beef, fish, and many others can be high in fluoride.

Permissible Cryolite (sodiumfluoaluminate) 54% fluorine at 7 mg/kg is permitted on apples, beans, beets, broccoli, brussels sprouts, cabbage, cantaloupes, carrots, cauliflower, collards, cranberries, cucumbers, eggplant, grapefruit.

ProFume can have a fluoride residue of beef at 40 ppm, wheat flour 125 ppm, cheese 5 ppm, coconut 40 ppm, egg 850 and dried at 900 ppm, rice flour 98 ppm, vegetables 70 ppm, peanut 13 ppm and many other products.

The NOS standard permits fluoride for example, over 1,000 ppm in bone meal.

Measurements of total exposure must include concentrations of fluoride from all tissues especially saliva, serum, urine, nails, bones, teeth, brains, liver, kidney,

etc. In addition, synergistic chemicals may play a significant roll in the "implausible" increase in dental fluorosis. About 150 fluoridated pesticides had been identified by 2000..

Carbon fluoride compounds, forever chemicals, are beginning to be of concern because they may not be actually forever. Two of the most common compounds PFOA and PFOS are being phased out and replaced with shorter chain compounds marketed as safer but growing evidence suggests just as toxic and more mobile and persistent.

Although "forever" chemicals can last a thousand years to disappear from the environment, different reports put the half-life in humans at 1 or 2 to 9 or 15 years. For example, Desulfovibrio aminophilus and Sporomusa sphaeroides bacteria are capable of separating the carbon-chlorine bond in chlorinated PFAS compounds triggering a substantial spontaneous defluorination.

Although there is much we don't know, the fluorine ion and synergistic effects of the PFAS chemicals with fluoridation chemicals raises a red flag.

PFAS Toxicological research shows that per- and polyfluoroalkyl substances (PFAS) can disrupt hormonal, immune and reproductive systems, and can increase the risk of various cancers. A CDC report found 97 percent of blood samples taken from Americans contain PFAS. Although these have been called "forever" chemicals and bound so tight as to not break down, we now know that they do break down and release fluoride ions.

About 12,000 PFAS, synthetically manufactured chemicals exist and only about 100 have very much research. Even in this small subset, the ecological impacts, physiological effects, potential health concerns and synergistic adverse effects differ markedly.

Alexander et al, (2024)[17] **"**Exposure to per- and polyfluoroalkyl substances (PFAS) has been associated with several health outcomes, though few occupationally-exposed populations have been studied. We evaluated mortality and cancer incidence in a cohort of perfluorooctanesulfonyl fluoride-based specialty chemical manufacturing workers. . . . This study provides some evidence that occupational exposure to PFOS is associated with bladder and lung cancers and with cerebrovascular disease."

Li (2020)[18] "The reductive degradability and decomposition pathways of linear perfluorooctanesulfonate (L-PFOS) were investigated in a biomimetic system consisting of Ti(III)-citrate and Vitamin B_{12}. Biomimetic degradation of L-PFOS could well be described by a first-order exponential decay model. Accompanied by the release of fluoride ion, technical PFOS could not only be transformed to perfluorocarboxylates (PFCAs) and perfluoroalkylsulfonates (PFSAs) with perfluoroalkyl carbon chain length < C8 (thereafter referred as carbon-chain-shortened degradation products), but also be transformed to PFCAs with perfluoroalkyl carbon chain length ≥ C8 (thereafter referred as carbon-chain-lengthened degradation products). . . All carbon-chain-lengthened chemicals were first reported as the degradation products during the decomposition of L-PFOS, while carbon-chain-shortened compounds were first identified as the biomimetic reduction products of L-PFOS."

Singh et al (2019),[19] "Byproducts produced when treating perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) in water using a plasma treatment process intentionally operated to treat these compounds slowly to allow for

[17] Alexander BH, Ryan A, Church TR, Kim H, Olsen GW, Logan PW. Mortality and cancer incidence in perfluorooctanesulfonyl fluoride production workers. Am J Ind Med. 2024 Apr;67(4):321-333. doi: 10.1002/ajim.23568. Epub 2024 Feb 12. PMID: 38345456.

[18] Li F, Yang N, Yang Z, Cao W, Zhou Z, Liao X, Sun W, Yuan B. Biomimetic degradability of linear perfluorooctanesulfonate (L-PFOS): Degradation products and pathways. Chemosphere. 2020 Nov;259:127502. doi: 10.1016/j.chemosphere.2020.127502. Epub 2020 Jul 2. PMID: 32650169.

[19] Singh RK, Fernando S, Baygi SF, Multari N, Thagard SM, Holsen TM. Breakdown Products from Perfluorinated Alkyl Substances (PFAS) Degradation in a Plasma-Based Water Treatment Process. Environ Sci Technol. 2019 Mar 5;53(5):2731-2738. doi: 10.1021/acs.est.8b07031. Epub 2019 Feb 22. PMID: 30768259.

byproduct accumulation were quantified. Several linear chain perfluoroalkyl carboxylic acids (PFCAs) (C4 to C7) were identified as byproducts of both PFOA and PFOS treatment. PFOA, perfluorohexanesulfonate (PFHxS), and perfluorobutanesulfonate (PFBS) were also found to be byproducts from PFOS degradation. Significant concentrations of fluoride ions, inorganic carbon, and smaller organic acids (trifluoroacetic acid, acetic acid, and formic acid) were also identified.. . . “

VII. FLUORIDATION IS NOT COST EFFECTIVE

Summary of lower wages from 3 IQ loss, 2021 dollars,

The estimate here, including two risks is:

caries averted, less operational costs at	$8 PPPY.[20]
dental fluorosis treatment	-$126 PPPY.
developmental neurotoxicity lower wages	-$438 PPPY.

Net loss from Fluoridation of public water is -$556 Per Person Per Year for just two risks. This does not include costs for functional dental fluorosis, skeletal fluorosis or other risks as listed below. Neither for the harm to the patient nor the costs of treatment nor the costs to the State of Washington.

EPA research found "estimated costs for restoring function exceeds the cosmetic costs."

WHO reports, "In acute poisoning, fluoride kills by blocking normal cellular metabolism. Fluoride inhibits enzymes, in particular metalloenzymes involved in essential processes, causing vital functions such as the initiation and transmission of nerve impulses, to cease. Interference with necessary bodily functions controlled by calcium may be even more important."[21] Assuming fluoride has a threshold for everyone which is safe is presumptive.

Researchers have indicated water fluoridation is a crude and rather ineffective policy to prevent dental caries without a detectable threshold for dental damage. (Dong and European Commission, 2011) A detectible threshold of fluoride exposure for dental damage is possible and critical for the policy of fluoridation. Although the odds of developing dental fluorosis increased with increased water

[20] Ko L, Thiessen KM. A critique of recent economic evaluations of community water fluoridation. Int J Occup Environ Health. 2015;21(2):91-120.[*PubMed*] Adjusted for 2021 dollars.
[21] Environmental Health Criteria 36, Fluorine and Fluorides, p. 52. 1984

fluoride concentration, the potential for harm exists at all water fluoride concentrations and unique for different individuals.

Gu (2020)[22] “The pathogenesis of dental fluorosis is not totally clear, which may be a complex pathological process involving both genetic and environmental factors. The prevalence of dental fluorosis has an upward trend around the world, thus certain public prevention and treatment strategies need to be taken.”

Jarquín-Yñezá (2018)[23] “Conclusions: An association of rs 412777 polymorphism in the COL1A2 gene with dental fluorosis was found. Therefore, genetic variants represent a relevant risk factor to develop dental fluorosis, as it was proven in this study conducted in Mexican children.”

Suzuki (2015)[24] “We demonstrate that fluoride exposure generates reactive oxygen species (ROS) and the resulting oxidative damage is counteracted by SIRT1/autophagy induction through c-Jun N-terminal kinase (JNK) signaling in ameloblasts. In the mouse-ameloblast-derived cell line LS8, fluoride induced ROS, mitochondrial damage including cytochrome-c release, up-regula tion of UCP2, attenuation of ATP synthesis, and H2AX phosphorylation (γH2AX), which is a marker of DNA damage.”

Dental fluorosis is usually considered the singular causation, a biomarker, of excess fluoride in gestion prior to 6-8 years of age; however, other unknowns need to be explored to explain the significant increase in dental fluorosis.[25]

DENTAL FLUOROSIS IS BOTH COSMETIC AND FUNCTIONAL

[22] Gu LS, Wei X, Ling JQ. [Etiology, diagnosis, prevention and treatment of dental fluorosis]. Zhonghua Kou Qiang Yi Xue Za Zhi. 2020 May 9;55(5):296-301. Chinese. doi: 10.3760/cma.j.cn112144-20200317-00156. PMID: 32392970

[23] Jarquín-Yñezá L, Alegría-Torres JA, Castillo CG, de Jesús Mejía-Saavedra J. Dental fluorosis and a polymor phism in the COL1A2 gene in Mexican children. Arch Oral Biol. 2018 Dec;96:21-25. doi: 10.1016/ j.archoralbio.2018.08.010. Epub 2018 Aug 23. PMID: 30172079.

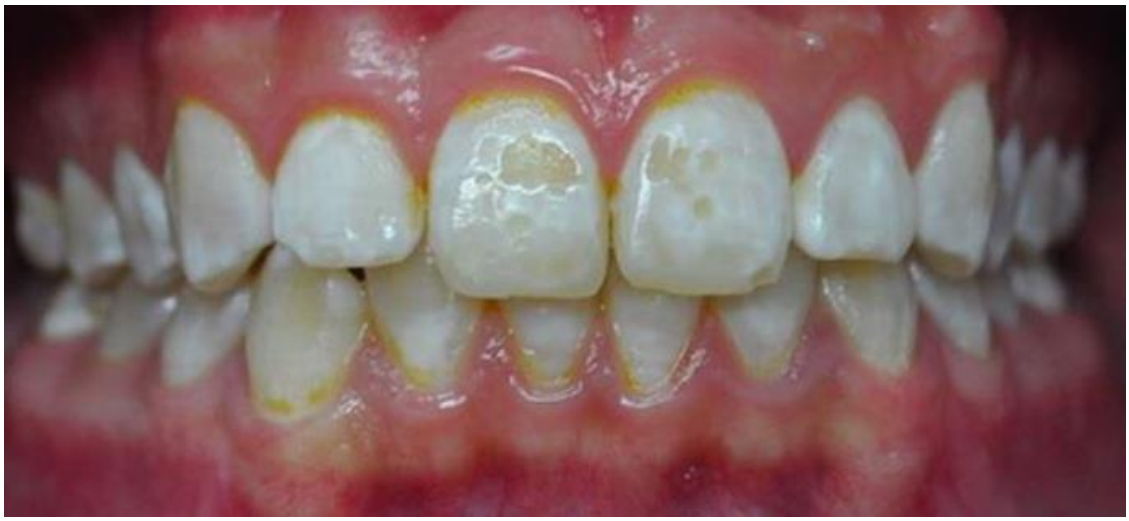
[24] Suzuki M, Bandoski C, Bartlett JD. Fluoride induces oxidative damage and SIRT1/autophagy through ROS-me diated JNK signaling. Free Radic Biol Med. 2015 Dec;89:369-78. doi: 10.1016/j.freeradbiomed.2015.08.015. Epub 2015 Sep 30. PMID: 26431905; PMCID: PMC4684823.

[25] Akpata ES. Occurrence and management of dental fluorosis. Int Dent J. 2001 Oct;51(5):325-33. doi: 10.1002/ 61 j.1875-595x.2001.tb00845.x. PMID: 11697585.

Collins. (1987)[26] “A mean cost for all consultants shows that the estimated costs for restoring function exceeds the cosmetic costs in all categories except the minimum later costs. This represents a new finding and raises an issue that has been overlooked or ignored by previous investigators and the profession. i.e .. that repair of the cosmetic discoloration was the only cost in volved; or that repair of dysfunction was never considered to be a problem.” (Emphasis supplied)

Collins study was funded by the EPA for the EPA and peer reviewed by the EPA to evaluate the cost of fluoride exposure from water at four concentrations. The six consultants do not appear to be blinded, they were chosen from locations with various fluoride concentrations. and do not ap pear to have been cosmetic dentists. Perhaps the consultants were functional dentists rather than cosmetic dentists and their focus was on functional restorations. Regardless, dental fluorosis is both cosmetic and functional damage.

“Damage is the cost, not the repair.” Without patient consent, compensation for damage with quality treatment costs is reasonable. Harm from fluoridation is not self-inflicted harm or patient negligence. The picture of severe fluorosis below is of my patient growing up on fluoridated bottled “Nursery Water” (DS Waters of America Inc.



[26] Collins, E., V. Segreto, H. Martin, AND H. Dickson. ANALYSIS OF COSTS FOR THE TREATMENT OF DENTAL FLUOROSIS. U.S. Environmental Protection Agency, Washington, D.C., EPA/600/5-87/001 (NTIS PB87170817), 1987.

Mom is confident he did not use fluoride toothpaste until about age 4 years old and did not swallow toothpaste. Estimated exposure is less than 1 mg per day when young to about 1 mg at age 4. Dosage estimated at 0.13+ mg/kg/day when 4 months old to 0.05+ mg/kg/day at 4 years. An increase in fluoride exposure when fluoridated toothpaste started would be expected. This severe dental fluorosis damage is known harm from excess fluoride.

In the picture above, the front four teeth have functional damage. Posterior teeth functional damage is not shown.

Akpata[27] reports, in some countries, exposure to apparently low fluoride concentrations in drinking water has resulted in severe dental fluorosis in some children.

In 1993, Riordan[28] reported 17.5% of 7 year-olds who do not have all their adult teeth were assessed by members of the public as a notable concern of dental fluorosis. Functional damage was not included. With dental fluorosis about twice as high now as1993, and currently NHANES twice reporting 70% of children with dental fluorosis, a conservative estimation of 17.5% of children have notable concern and functional damage is reasonable which would include a percentage of those with mild dental fluorosis and most with moderate and severe fluorosis.

Moderate and severe fluorosis appears to range from 3.6% (Beltran-Aguilar ages 12-15 years in 1999-2004) 6% (Ko) to 28% (NHANES 2012). Variation depends to some degree on the clinician's perception. Diagnosis is rather subjective.

Additional information the Board must consider includes: Health Effects of Fluoride,

While practicing in a low socioeconomic community, I almost never treated cosmetic issues. Moving to a high socioeconomic community I frequently treat

[27] Akpata ES. Occurrence and management of dental fluorosis. Int Dent J. 2001 Oct;51(5):325-33. doi: 10.1002/ j.1875-595x.2001.tb00845.x. PMID: 11697585.
[28] Riordan PJ. Perceptions of Dental Fluorosis. Journal of Dental Research. 1993;72(9):1268-1274. doi:10.1177/00220345930720090201

cosmetic concerns. When people have money, cosmetics becomes a greater concern and dentists tend to diagnose what their patients can afford or is covered by their insurance. There is no wonder why Delta Dental funds fluoridation when they assume benefit and do not cover cosmetic damage.

Micro-abrasion,[29] grinding away the outer layer of enamel, can improve superficial defects of dental fluorosis. Treatment estimated $500 to $2,500 per patient life time and may need additional vital bleaching. Some patients consider micro-abrasion additional damage, but certainly less than a typical crown or veneer.

Bleaching is more acceptable to some but tends to whiten all areas and a contrast in shade is, for some, not fully restored. Bleaching needs to be retreated and an estimate is $100 to $600 every 2 years. We use an estimated $100 PPPY (per person per year) for 60 years, $6,000 life time treatment costs. Statista survey reports 37 million in the USA had bleaching in 2020, about 14% of the age range of dental fluorosis.

Placing a value on the damage for patient perceived damage, assumed to be mostly in moderate to severe fluorosis found objectionable with high quality cosmetic and functional treatment is estimated at $1,000 to $2,500 per tooth, $1,200 is used here. The diagnosis of dental fluorosis is based on the two worst teeth, although 1 to 28 teeth can be damaged. If costs are not the controlling factor, a cosmetic patient will want several or all upper and lower teeth treated. An estimate of an average of 10 teeth at $1,200 per tooth damage both functional and cosmetic is at the high end of Collins EPA study and in keeping with high quality cosmetic restorative treatment. For a lifetime cost, the work is estimated to be replaced an average of every 12 years, or $1,000 PPPY, 60-year lifetime of $60,000 damage. Damage is determined by cost of damage.

See attachment for more details.

[29] Azzahim L, Chala S, Abdallaoui F. La micro-abrasion amélaire associée à l'éclaircissement externe: intérêt dans la prise en charge de la fluorose [Role of enamel microabrasion associated with external bleaching in the management of patients with den tal fluorosis]. Pan Afr Med J. 2019 Oct 4;34:72. French. doi: 10.11604/pamj.2019.34.72.20401. PMID: 31819788; PMCID: PM C6884726

VIII. PUBLIC HEALTH SERVICE AND SURGEON GENERAL

Public Health Service 2015 Report on Fluoridation:

The Federal Agency charged by Congress to evaluate the [30] [31] [32]
scientific evidence of both the safety and efficacy, risk/benefit, of a substance used with the intent to prevent disease is the Food and Drug Administration Center for Drug Evaluation and Research.

The Public [33]Health Service, PHS 2015 report did not directly address regulatory jurisdiction; however, the PHS 2015 includes the disclaimer, *"Although PHS recommends community water fluoridation as an effective public health intervention, the decision to fluoridate water systems is made by state and local governments."*

True, if the chemical is an approved drug. Local governments and the PHS are not authorized to circumvent the FDA CDER and make pseudo approvals for any substances used with the intent to treat or prevent human disease.

Likewise, the Washington State Board of Health attempts to delegate authority to local water commissioners. Determining the complex toxicological, pharmacological, and risk assessment task for fluoridation is dumped onto the least competent authority. . . often voters.

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[30] 21 USC 321 (g)(10)(B) Articles intended for use in the . . . prevention of disease . . . . FDA testified to Congress that fluoride is a drug, Congressional Investigation 2001, FDA CDER withdrew NDA for fluoride supplements in 1976

[31] A search of the Drugs@FDA database . . . does not indicate that sodium fluoride, silicofluoride, or hydrofluorosilicic acid has been approved . . . .2009 Best regards, Drug Information SH, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration

[32] FDA CDER ADVISES: Manufacturers of unapproved drugs are usually fully aware that their drugs are marketed illegally, yet they continue to circumvent the law and put consumers health at risk. http://www.nabp.net/publications/assets/OR082008.pdf Oregon Board of Pharmacy 8/08 Newsletter

[33] HHS and FDA admit that these additives and fluoridated waters are intended for use to prevent tooth decay disease but they refuse to exercise responsibilities under the Food Drug and Cosmetic Act (FDCA) to regulate these articles as drugs. 21 USC 393(a) and (b); 21 USC 321(g)(1). FDA states that the Safe Drinking Water Act (SDWA) relieves it of this responsibility. Dr. Wanda Jones 11-21-14 Letter Ms. McElheney. EPA administrates the SDWA and so has agency authority for its interpretation. EPA interprets the SDWA to not relieve HHS and FDA of their responsibilities "for regulating the addition of drugs to water supplies for health care purposes." Steven Neugeboren 2-14-13 Letter to Mr. Steel. However, EPA remains responsible for regulating total fluoride in public drinking water through setting a Maximum Contaminant Level (MCL) Goal and setting and enforcing a MCL. This Goal is required by the SDWA to be "set at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." 42 USC 300g-1(b)(4)(A).

Politicians are seldom scientists such as pharmacologists, toxicologists, or epidemiologists and their current paradigm is simple. If the PHS recommends fluoride, then the public assumes fluoride must be safe and effective and if a little is good, then more is probably better and also safe. The increase in fluoride exposure has been on a steady increase from many sources because of bias and lack of jurisdiction.

PHS 2015 MEMBERS WERE CHERRY PICKED and the BOH must not cherry pick members to review fluoridation:

The most striking flaw in the PHS 2015[34] report is the complete lack of the PHS, HHS, and all 27 members to insist the report mention Congress's intent, the law of the land. The FD&C Act, without exception, gave the FDA jurisdiction to determine risk/benefit/dosage/legend over substances used with the intent to prevent disease such as fluoride. The only member from the FDA CDER on the committee was a dentist from the Division of Dermatology and Dental Products, obvious bias and cherry picking by PHS 2015. Neither, unbiased drug approval experts, public legal counsel, stake holders, patients, concerned and being harmed with excess fluoride exposure were included as members. Cherry picking members of the committee ensured biased results and the only serious issue of benefit or risk considered was teeth: i.e. caries and fluorosis. Where is the minority report? Where are discussions and expert comments? PHS 2015 was not scientific, ethical or inclusive.

OCCURRENCE: *"Among children aged 6 months to 14 years, drinking water accounts for 40%-70% of total fluoride intake; for adults, drinking water provides 60% of total fluoride intake."*

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[34]. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries, US ..., Federal Panel on Community Water Fluoridation, Public Health Reports, Jul-Aug 2015, Vol. 130

The report took four years. New research was published, the committee cherry picked the new research with bias and without public comment.

Why is the fetus not included?

Why are infants on formula made with fluoridated water who are most at risk of excess fluoride, those under six months of age, not included?

PHS 2015. Over 200 million people in the USA are on artificially fluoridated water, many without consent.

EVALUATE WITHOUT BIAS: Some people are healthy, diseased, pregnant, unborn, new born, chemically sensitive, cancerous, diabetic, and/or dying patients and all are told by the PHS 2005 that artificial fluoridation is once again safe at 0.7 ppm.
The PHS 2015 evaluates “mean” and to the “90th” percentile exposure, not individual exposure. The dilute fluoride drug has no legend, dosage, cautions or warnings because there is no legend. Fluoride is a protected toxic contaminant with assumed pharmacological efficacy and safety. The bias of efficacy has in part kept NTP from careful honest scientific cancer research, evaluation, and classification. Each individual needs protection, not just the most healthy and industry.

EXCESS EXPOSURE: Dental fluorosis is a known biomarker of excess fluoride exposure and currently for children has increased to over 60% of children. We maintain deficiencies in the scientific data are more with downgrading the results of studies, bias and protecting the flawed intent of artificial fluoridation than a lack of adequate studies reporting carcinogenic risk of cancer and other harm.

RESEARCH DEFICIENCIES: Deficiencies in the most scientific data on safety are extensive. Deficiencies for *efficacy* include:

- Not one Randomized Controlled Trial (they are possible)
- Socioeconomic status usually not controlled

- Inadequate size
- Difficulty in diagnosing decay
- Delay in tooth eruption
- Diet: Vitamin D, calcium, strontium, sugar, variables.
- Lack of measured blood and/or urine, saliva fluoride concentrations
- Oral hygiene habits
- Not evaluating life time benefit
- Estimating or assuming subject actually drinks the fluoridated water.
- Dental treatment expenses • Breast feeding and infant formula
- Fraud or gross errors.
- Genetics and Dental office visits
- No determination on optimal desired target organ's fluoride concentrations
- The majority of dental caries declined prior to fluoridation use and no research accounts for those huge unknown confounding factors.

SAFETY: Research on safety of ingested fluoride is similar to research on safety of tobacco products in the 1960s and 1970s. Research by the tobacco companies usually claimed tobacco had no risks other than cosmetics to the teeth and dentists claim fluoride is generally safe with no risks except cosmetic effects to the teeth.

No margin of safety is applied. An uncertainty factor of 10 and intraspecific variation of 10 should be applied. In other words, Grandjean et al determined the baseline of safety is 0.28 mg/L fluoride in water. At least a factor of 10 should be applied for safety of minority subgroups for 0.028 mg/L. Mother's milk is about 0.004 mean fluoride concentration to 0.01 mg/L. Thus, a factor of 10 for water used to make infant formula is still above the concentration of fluoride in mother's milk.

The Fluoridation Lobby logic assumes fluoride only comes from water and has a direct pipeline to the teeth and does not go through the entire body to all tissues. However, dentists focus on teeth and nothing outside the mouth is part of the

practice of dentistry. The Board should not assume the CDC dental division or the American Dental Association will be protective of the whole body. Their focus is on the mouth and "owe no duty to protect the public from harmful products." And no one likes to consider that their most cherished beliefs, polices and advice causes cancer and harm, especially if they are profitable. We all tend to have bias to protect our traditions, beliefs and profits.

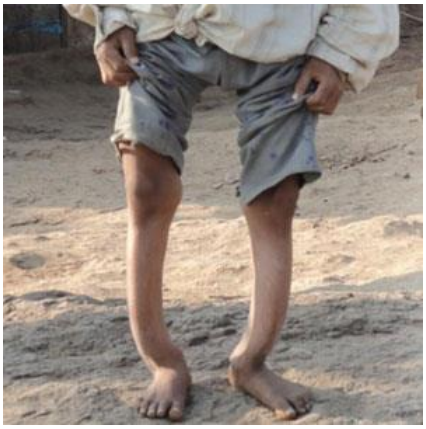
EPA IS LESS PROTECTIVE: As research has become clearer that fluoride causes harm at ever lower doses, EPA has done the opposite and actually raised their claim of fluoride's safety from 0.05 mg/kg/day to current NOAEL is 1 ppm (0.06 mg/kg/day) and LOAEL is 2 ppm. [35](6/1/1989) and in 2010 proposed and then implemented an RfD of 0.08 mg/kg/day.

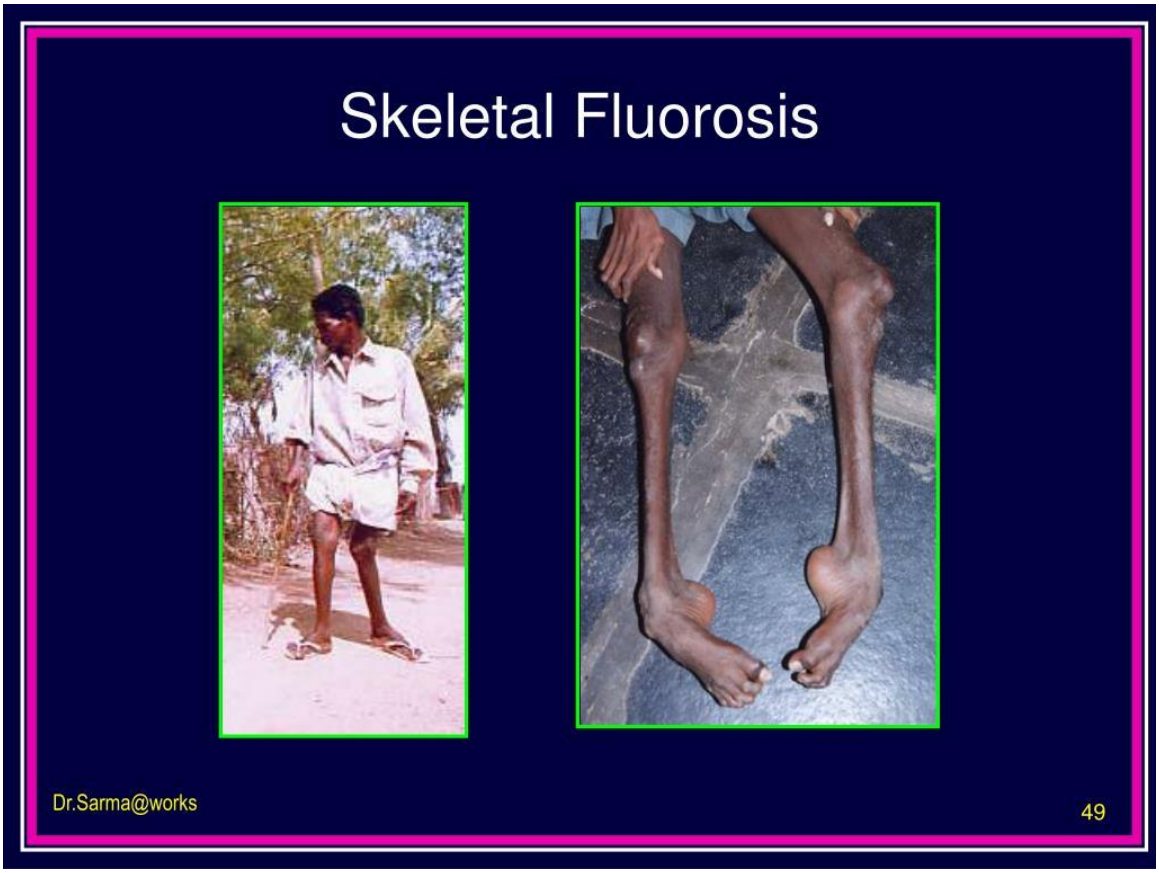
EPA is not basing their RfD on good science of safety, rather the reality of increased exposure from all sources and an attempt to protect the tradition of artificial fluoridation.

In some areas of the world, fluoride concentrations in water are very high. The EPA uses a point of departure, where EPA becomes concerned with excess fluoride exposure, to be severe dental fluorosis, like the pictures below. The EPA is not protective of the public and the NRC 2006 review of fluoride in water unanimously agreed EPA's fluoride concentrations are not protective and the Court agreed.

The Board and Department "trust" the EPA. The EPA standard is to protect against severe dental fluorosis and these pictures are what the EPA is trying to prevent. The EPA is succeeding; however, the Board must protect the public before this type of damage is caused.

[35] fluorine (soluble fluoride) (CASRN 7782-41-4)



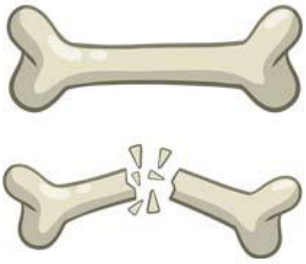


Earlier stages of skeletal fluorosis with symptoms more difficult to prove etiology. Back pain, fractured bones and teeth, poor sleep, stiffness and arthritic like pain in joints, abdominal pain and vomiting can be very difficult to determine and prevent the cause of the problem, etiology.

Symptoms and Signs of Skeletal Fluorosis

Lower back pain

Stiffness and pain in joints



Fractures

Poor sleep pattern

Reduced intelligence and cognitive functioning

Skin rash

Abdominal pain

Nausea and vomiting

Consider Total Fluoride Exposure, not just Fluoride from Water

A significant amount of research below focuses on ecological studies comparing water fluoridation with non-fluoridated communities.
However, water fluoridation can represent a wide range of a person's total exposure, 30%-70% (100% for infants) and an extremely crude form of measuring total exposure. A typical child swallowing candy tasting fluoride toothpaste twice a day can ingest more fluoride than provided in water fluoridation and 90%+ of toothpaste is fluoridated.

Usually, research does not include whether a child was actually drinking the fluoridated water or whether they were actually swallowing their toothpaste. Fluoride varnish at 22,600 ppm is glued on the teeth, not FDA CDER approved, and almost no research on fluoride varnish risks has been done. Fluoride appears to cause or contribute to cancer with gender, race, and age differences which need to be controlled in studies. Host susceptibility and synergistic effects with other chemicals has not been considered.

Measured Tissue Fluoride Concentrations: Researchers have called for actual measured fluoride concentrations of enamel, dentin, bones, brains, kidney, thyroid, liver, blood, serum, and urine concentrations to better measure actual body fluoride concentrations, but seldom are measurements actually taken of body tissues.

Optimal Target Organ Concentrations, Unknown: The Board has a focus on fluoride concentration for water. But fluoridation is not treating water. The intent is to treat teeth. The Board has failed to determine the optimal amount of fluoride for the tooth structure because the target organ has the same concentrations of fluoride in healthy and diseased tooth structure. No one claims the "optimal" concentration of fluoride in the tooth to prevent caries because no one knows. Therefore, no one knows the optimal fluoride concentration for total exposure or the serum to get the optimal concentration for the teeth.

If the Board or anyone intends to protect the fluoride concentration of the teeth to prevent dental caries, then the Board needs to first determine the optimal dentin and enamel fluoride concentration which prevents dental caries.

Too Little, Too Late: 18 years after the NRC 2006 committee unanimously advised the EPA their MCLG was not protective, the Board and EPA have still failed to protect the public; however, the USPHS published a recommendation for an artificial fluoride concentration of 0.7 ppm (mg/L). At first glance, the PHS 2015 recommendation [8] appears to be in the right direction but the reduction is "too little, too late" for those harmed and those who will be harmed.

. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries, US [8]
HHS, Federal Panel on Community Water Fluoridation, Public Health Reports, Jul-Aug 2015, Vol. 130 Referred here to as PHS 2015
rather than the EPA? Because Congress in the SDW Act authorizes the EPA to treat water but not people.

14% Population Reduction in Fluoride: PHS 2015 p.2 suggests lowering the fluoride concentration in water will result in *"a reduction of approximately 14% in total fluoride intake."*
The 14% is a "mean" or "average" and does not represent protection for the most vulnerable, chemically sensitive or drinking the most water or infants on formula made with fluoridated water or pregnant mothers on fluoridated water.
PHS 2015 continues,
"These estimates are based on intake among young children at the 90th percentile of drinking water intake for whom drinking water accounts for 40-70% of total fluoride intake."

Policy Over People: "*To protect the majority of the population, EPA uses the 90th percentile of drinking water intake for all age groups"* (page 3) and uses a 1:1 margin of safety, in other words, no margin of safety. The 90th percentile is about 2 liters of water/day for adults. Some adults (diabetics, athletes, etc) drink

as much as 10 liters a day, five times EPA's 90th percentile. HHS/PHS/Board of Health are recommending medicating 100% of the public, but they only consider exposure protection to 90%. 10% drinking the most water are discounted, ignored, abandoned and no a margin of safety is provided or caution, warnings, or dosage advice are provided.

Fluoridation harms some races more: In the 1950s when artificial public water fluoridation without cohort consent started, experts reassured the public that fewer than 10% of the public would get dental fluorosis. Dental fluorosis is a known biomarker of excess fluoride exposure during the time of life that the tooth was developing. PHS did not indicate what the optimal percentage of the population should show signs of a toxic overdose of fluoride. CDC MMWR Table 23, 2002 data reports moderate/severe dental [9]fluorosis 1.9% of Whites, 3.4% Blacks, and 4.8% Mexican-American.

Reports going back to the 1940s and 1960s[10] noting double the dental fluorosis among Blacks. NTP research must include age, gender and race data with actual measured evidence.

TABLE 23. Enamel fluorosis* among persons aged 6–39 years, by selected characteristics — United States, National Health and Nutrition Examination Survey, 1999–2002

Characteristic	Unaffected		Questionable		Very mild		Mild		Moderate/Severe	
	%†	SE§	%	SE	%	SE	%	SE	%	SE
Age group (yrs)										
6–11	59.81	4.07	11.80	2.50	19.86	2.12	5.83	0.73	2.71	0.59
12–15	51.46	3.51	11.96	1.84	25.33	1.98	7.68	0.93	3.56	0.59
16–19	58.32	3.30	10.21	1.70	20.79	1.78	6.65	0.67	4.03	0.77
20–39	74.86	2.28	8.83	1.23	11.15	1.22	3.34	0.58	1.81	0.39
Sex										
Male	67.65	2.63	9.99	1.45	15.65	1.52	4.58	0.54	2.12	0.39
Female	66.97	2.84	9.83	1.34	15.58	1.36	4.84	0.61	2.78	0.49
Race/Ethnicity¶										
White, non-Hispanic	69.69	3.13	10.43	1.62	14.09	1.56	3.87	0.60	1.92	0.48
Black, non-Hispanic	56.72	3.30	10.40	2.16	21.21	2.16	8.24	0.82	3.43	0.54
Mexican-American	65.25	3.89	8.95	1.29	15.93	2.24	5.05	0.72	4.82**	1.81
Poverty status††										
<100% FPL	68.02	3.21	10.67	1.64	14.29	1.73	4.07	0.69	2.97	0.66
100%–199% FPL	66.92	2.91	9.11	1.79	16.11	1.46	5.21	0.78	2.65	0.56
≥200% FPL	66.88	2.75	10.73	1.33	15.56	1.56	4.83	0.50	2.00	0.37
Total	67.40	2.65	9.91	1.35	15.55	1.37	4.69	0.49	2.45	0.40

* Using Dean's index. All estimates are adjusted by age (single years) and sex to the U.S. 2000 standard population, except sex, which is adjusted only by age.
† Weighted prevalence estimates.
§ Standard error.
¶ Calculated using "other race/ethnicity" and "other Hispanic" in the denominator.
** Unreliable estimate: the standard error is 30% the value of the point estimate, or greater.
†† Percentage of the Federal Poverty Level (FPL), which varies by income and number of persons living in the household.

[9] CDC MMWR August, 2005 / 54(03);1-44 Table 23 Emphasis added.

[10] 1965 George Waldbott, The Great Dillemma. www.whale.to/b/Waldbott_DILEMMA_ocr.pdf

Intent of the PHS 2015 recommendation is to *"reduce the chance of dental fluorosis — especially severe dental fluorosis—in the current context of multiple fluoride sources."* (PHS p. 4) The PHS 2015 appears to have tunnel vision focused on teeth, as though the fluoride ingested only goes to the teeth and skips the rest of the body.

EPA'S ERSCA: In response to the NRC 2006 report that the EPA MCLG (Maximum Contaminant Level Goal) is not protective, the EPA did an *Exposure and Relative Source Contribution Analysis* in 2010 and their Figure 8-1 is provided here.

EPA Decides NRC 2006 Is Wrong: Once again, the children above the black line are ingesting more fluoride than the EPA's proposed new RfD (Reference Dose) 0.08 mg/kg/day. However, the proposed RfD is a third higher dosage than current RfD which is **opposite** the NRC 2006 report's recommendation to be more protective. The EPA is attempting to protect fluoride by claiming it is safer to ingest even more fluoride. According to the EPA, about a third of children during the age of their highest risk for cancer are anticipated to exceed even this new RfD of 0.08 mg/kg/day.

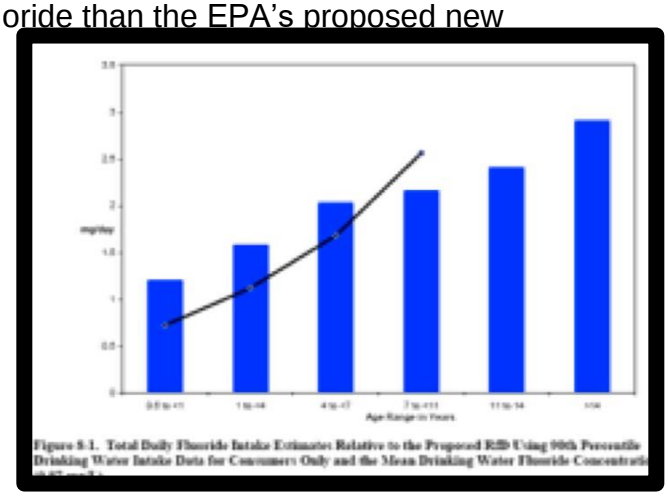


Figure 8-1. Total Daily Fluoride Intake Estimates Relative to the Proposed RfD Using 90th Percentile Drinking Water Intake Data for Consumers Only and the Mean Drinking Water Fluoride Concentratio

Infants Not Protected: In addition, the EPA does not include infants under six months of age, the most vulnerable. Many infants, our most vulnerable, ingest over 0.2 mg/Kg/day with formula made with fluoridated water (1 liter of formula made with fluoridated water at 1 ppm for a 5 Kg infant); whereas, mother's milk in most samples contains no detectable fluoride. Clearly, the EPA chose to protect fluoride over infants.

10% Ignored: the EPA only considers water consumption to the 90%, leaving 10% of the public drinking the most water essentially ignored. Some drink five times more than the 90th percentile.

No Margin of Safety: Still further, the EPA uses no margin of safety at 1:1.

FDA CDER's Concern: Some children and adults, swallow toothpaste. The FDA CDER uses 0.25 mg as their basis for the toothpaste label warning to use a pea size or smear of toothpaste and not to swallow. Children (10 Kg) learning to brush their teeth can swallow over 3 mg of fluoride in toothpaste a day, 0.3 mg/Kg/day.

Industry: Industries such as Cryolite and aluminum manufacturing workers are exposed to high concentrations of fluoride even without fluoridated water their cancer rates are high.

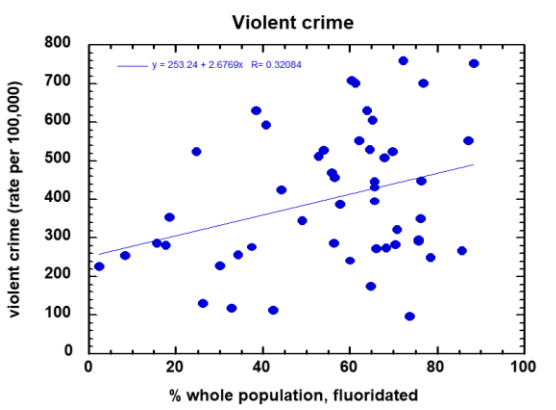
Desired Margin of Safety: The Board must use a margin of safety to protect all humans at all ages, genders, races, and potential synergistic toxic effects with other toxins. A margin of safety at 100 is reasonable, 10 is minimum, EPA uses no margin of safety.

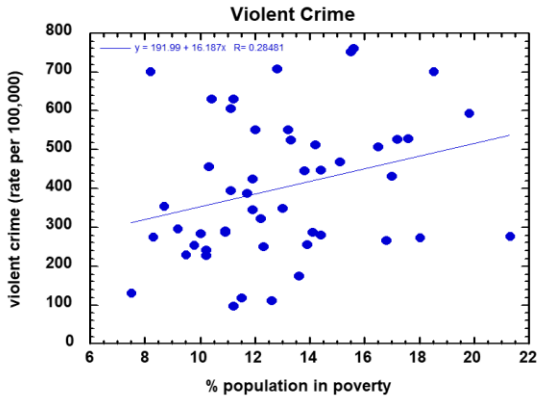
Fetus: Fluoride does not appear to be blocked by the placenta and the fetus appears to be at risk. In most samples of Mother's milk, fluoride is not detected, with mean fluoride concentration in non-fluoridated areas at 0.004 ppm.[18] Formula made with artificially fluoridated water has hundreds of times more fluoride than mother's milk. We must protect the most vulnerable. At least one animal study has found fluoride over exposure resulting in neurologic harm continues for at least 3 generations in mice. The legacy we are leaving our children, grandchildren and great grandchildren is of serious concern.

DESCENDANTS: Fluoride causes DNA damage and little research has been done on defects transmitted to the descendants of those harmed.

When IQ is lowered we should be able to detect social stresses such as increased incarceration, increased special education, homelessness, etc. These have not been well studied in relation to fluoridation.

Two preliminary observations include ranking the states on the whole population fluoridated and plotting data we do have such as violent crime. The graphs below do raise a need for more research.





A second look is to compare Washington State with 59% fluoridated (at the time) and Oregon with about a third less. Certainly there are many factors for crime, however, the data appears reasonably consistent with the theory.

Crime per 100,000		**WA 59% fluoridated**				**OR 19% Fluoridated**		
Violent	**Property**	**Murder**	**Rape**	**Robbery**	**Assault**	**Burglary**	**Larc.Theft**	**Veh. Theft**
WA	**331**	**3,758**	**2.9**	**40**	**97**	**191**	**801**	**2,525**	**424**
OR	**257**	**3,282**	**2.2**	**31**	**70**	**155**	**551**	**2,432**	**299**

SURGEON GENERAL

Based on FOI information for the TSCA Court case, the Surgeon General has gone silent on fluoridation recommendation.

IX. LACK OF BENEFIT:

Avoiding Bias: To reduce bias, we must briefly digress. The FDA is charged by Congress to determine the benefit of substances intended to prevent disease, rather than the NTP, CDC, EPA, HHS, NTP, ADA or Washington State Board Department of Health, commissioners or voters. Authorities must not assume ingested fluoride has benefit and view carcinogenicity with protective bias. The science does not support a significant current benefit from fluoride. A few examples:

FDA CDER Determination: The FDA has addressed a ”regulatory letter” to approximately 35 companies marketing combination drugs consisting of fluoride and vitamins. The letter states that these drugs are related to a product (Enziflur lozenges) for which FDA has withdrawn approval of a new drug application. The NDA for Enziflur was withdrawn because there is no substantial evidence of drug effectiveness as prescribed, recommended, or suggested in it’s labeling.

The FDA has therefore advised manufacturers of combination fluoride and vitamin preparations that their continued marketing is in violation of the new drug provisions of the Federal Food, Drug, and Cosmetic Act; they have, therefore, requested that marketing of these products be discontinued. [36]

Let us look closer at the false unscientific claims of the Board’s website, states:

“For water systems serving 20,000 people or more, every $1 invested in fluoridation saves $38 in dental treatment costs” Reference provided by the author, Jim Sledge, is perhaps to the “Washington State Board of Health” or himself.

[36] “NDA withdrawn for fluoride and vitamin combinations Drug Therapy June 1975

Current published research: Ko 2014 *"The U.S. Government states that $1 spent on CWF saves $38 in dental treatment costs. . . . Recent economic evaluations of CWF contain defective estimations of both costs and benefits. Incorrect handling of dental treatment costs and flawed estimates of effectiveness lead to overestimated benefits. The real-world costs to water treatment plants and communities are not reflected. . . . Conclusions: Minimal correction reduced the savings to $3 per person per year (PPPY) for a best-case scenario, but this savings is eliminated by the estimated cost of treating dental fluorosis." For example, the Board uses labor costs between $7 and $9/hour while real world labor is closer to $100/hour. And no risk or harm is factored in for the Government/Board claim of cost effective.*

"The results show that the reviewed original studies on economic evaluation of caries prevention do not provide support for the economic value of caries prevention."[37]

I am unaware of any fluoridation published studies of current 0.7 ppm fluoride concentration versus 1.0 ppm fluoride concentration in water. Even if fluoridation at 1.0 ppm were effective, that doesn't mean 0.7 ppm fluoride in water is equally effective. . . if at all.

The Board claims fluoridation is safe, without reference to any safety studies and this petition clear reports the National Research Council, the U.S. District Court, the National Toxicology Program/Office of Health Assessment and Translation, the Food and Drug Administration Center for Drug Evaluation and Research, most develop countries of the world, 97% of Europe, lack of known mechanism of

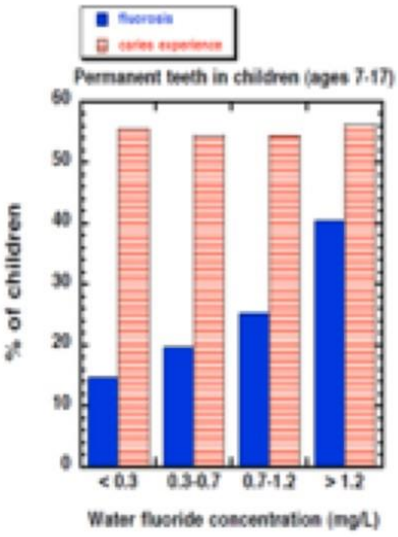
[37] Källestål C et al. Acta Odontol Scand. 2003 Dec;61(6):341-6. Economic evaluation of dental caries prevention: a systematic review.

action, and only one randomized controlled trial which did not report statistical benefit which did not include evaluating risks, do not find fluoridation safe.

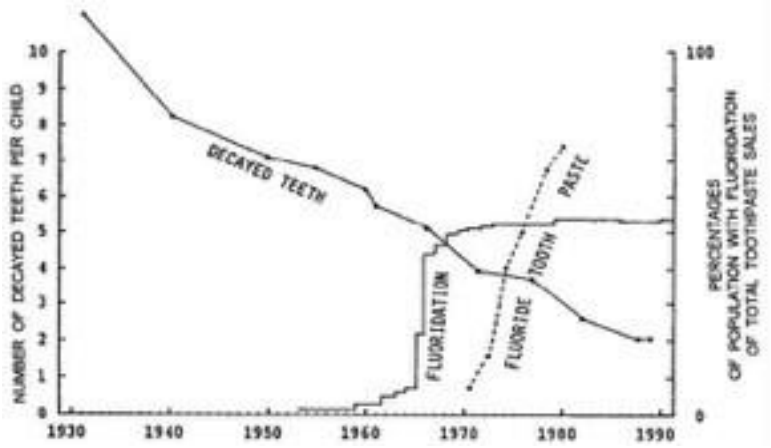
“A Benchmark Dose Analysis for Maternal Pregnancy Urine-fluoride and IQ in children . . . 0.2 mg/L” Grandjean 2022 What Grandjean is saying is water fluoride concentration should be reduced from 0.7 mg/L to 0.2 mg/L based on the studies we currently have. Other studies, like the NTP meta-analysis draft indicate no safe fluoride concentrations in water.

Research: Once again, the graph of Iida’s data is consistent with more than a hundred studies and demonstrates an increase in dental fluorosis (exposure) with higher concentrations in water and caries experience of perhaps a 1% to 2% dip between 0.3 and 1.2 ppm Fluoride. That is within the range of difficulty in diagnosis of caries, delay in tooth eruption from fluoride and many other confounding factors.

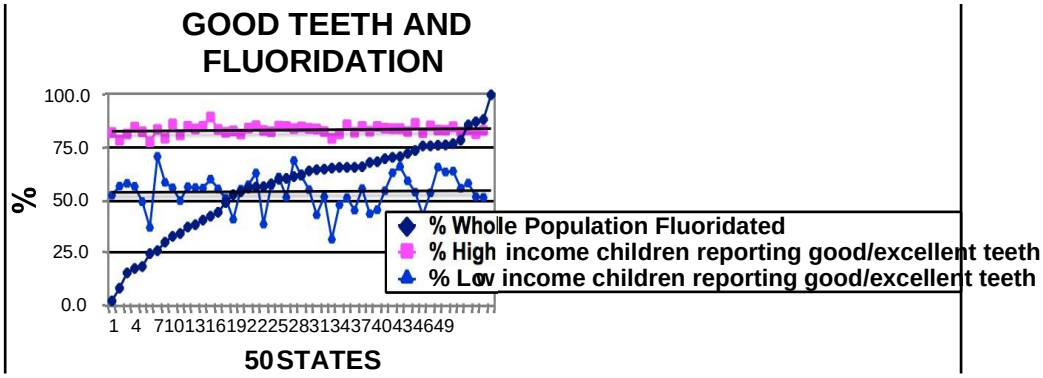
Iida, H., and Kumar, J.V. 2009. The association between enamel fluorosis and dental caries in U.S. schoolchildren. JADA 140:855-862.



Historic Decline in Caries Regardless of Fluoride: 1997 Colquhoun reported a [38]constant decline in dental caries in the USA before and after increases in fluoride exposure. No research controls for the huge confounding factor(s) crushing dental caries "prior" to artificial fluoridation, fluoride toothpastes and high fluoride intakes. Fluoride did not reduce dental caries for the population at large prior to fluoride supplementation.



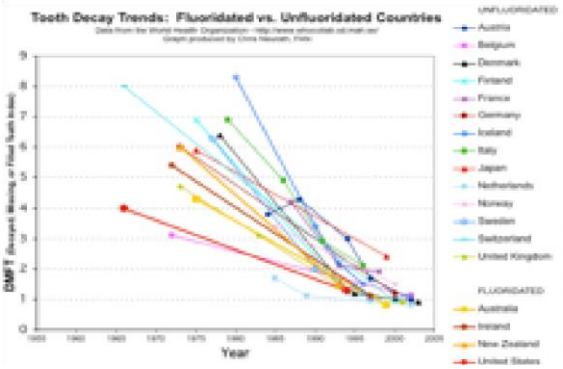
Population Comparisons: Ranking the 50 states on the percentage of whole population fluoridate and comparing with the reported good and excellent teeth, no common cause benefit with increased fluoride exposure is found. [39]

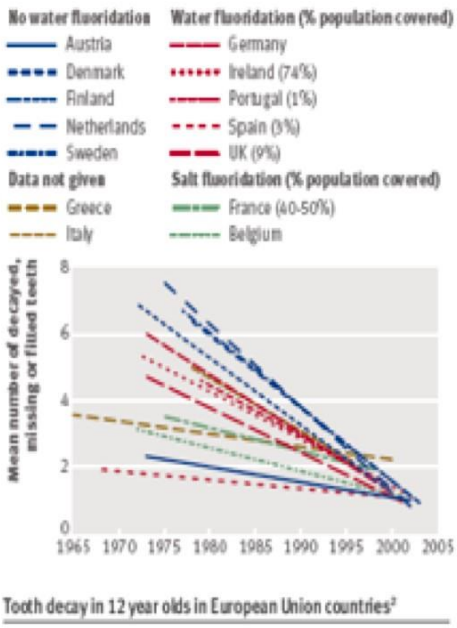


[38] Colquhoun J, Perspectives in Biology and Medicine, 41, 1, Autumn 1997

[39] U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. The National Survey of Children's Health 2003. Rockville, Maryland: U.S. Department of Health and Human Services, 2005

http://www.cdc.gov/oralhealth/waterfluoridation/fact_sheets/states_stats2002.htm http://pubs.usgs.gov/circ/2004/circ1268/htdocs/table05.html





International Comparisons: When considering WHO data on caries for developed countries, Neurath and later Chen reported all had decreased caries with or [40] [41]without fluoridation or fluoridated salt.

Judgment: Determining the effectiveness of a public health intervention must be demonstrated in the public at large. Fluoridation does not demonstrate efficacy in the public at large.

No Measured Evidence of Significant Reduction in Dental Treatment Costs: Savings in dental expenses are usually estimates based on assumptions, rather than measured evidence. Research does not find a lifetime mea- sured dental treatment cost reduction with fluoridated water for the population at large. Wild claims of "for every dollar spent on fluoridation, $38 on dental treatment are saved," are based on estimates of assumptions, modeling, and bias rather than measured evidence. Ko (2014) concluded,

"Minimal correction reduced the savings to $3 per person per year (PPPY) for a best-case scenario, but this savings is eliminated by the estimated cost of treating dental fluorosis."[15] There are not fewer dentists in fluoridated communities and dental insurance costs are not lower in fluoridated communities. Measured evidence of cost reduction in the public at large is

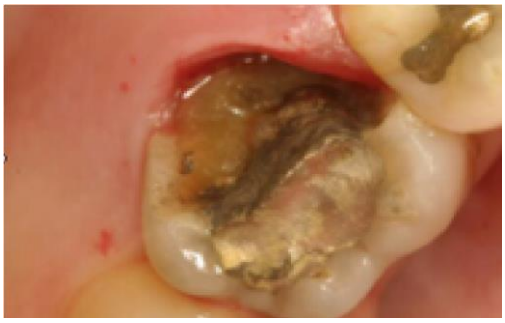
[40] http://www.fluoridealert.org/health/teeth/caries/who-dmft.html

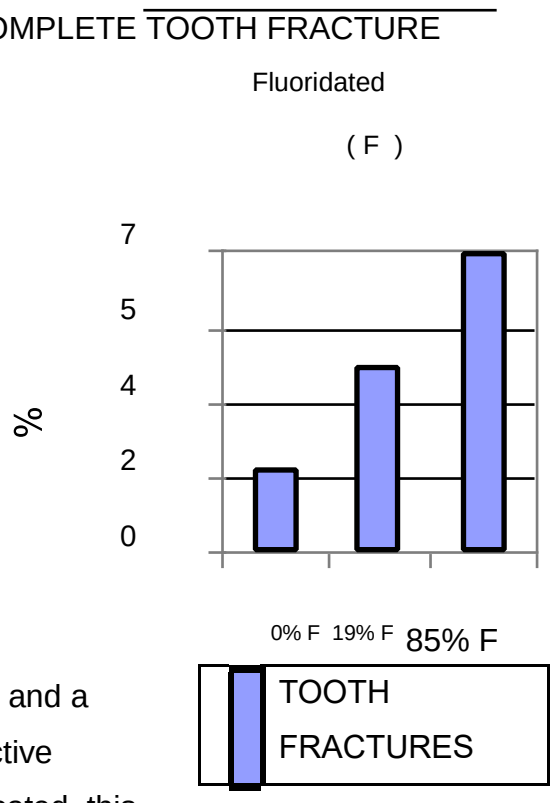
[41] Chen et al, BMJ 5 October 2007

generally not published because lack of benefit does not support policy. In small studies of low socioeconomic populations, cost savings have been reported but do not reflect the population at large and have serious limitations.

Harder Teeth Not Necessarily Better: In the first section we listed some confounding factors usually not included in research evaluating the efficacy of fluoridation. There is consensus that fluoride makes enamel and dentin and bones harder. Research also indicates an increased tooth and bone fracture rate with increased fluoride.

Comparing three studies on complete cusp fracture finds an increased complete cusp fracture visitation rate to dentists in areas with more artificial fluoridation. [42]





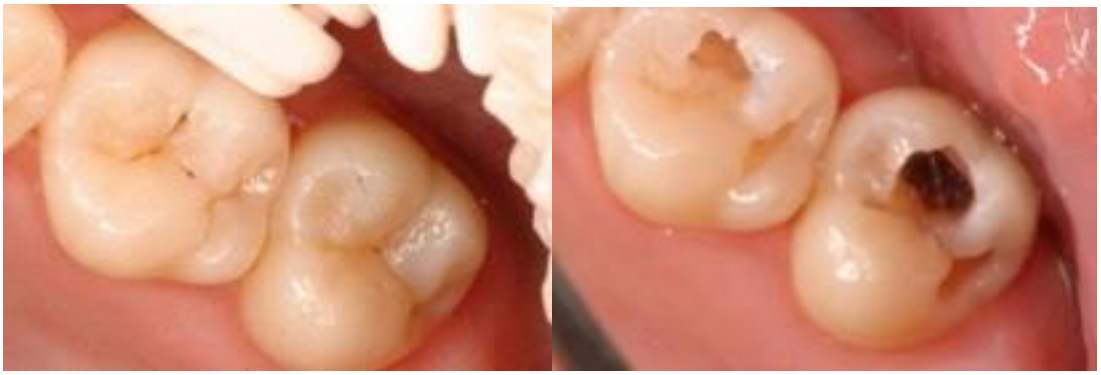
Two studies were by the same researcher and a complete cusp fracture is not a very subjective diagnosis. Although more research is indicated, this data along with other data from testing teeth should raise concern.

[42] Geurtsen Quintessence 2003 Patel Prim Dental Care 1995 Bader Com Dent Oral Epi 1996 and 2001 and JADA 2004 Vieira Eur J Oral Sci 2006 Fennis Int J Prosth 2002 Osmunson Fluoride 2007

Modern studies[43] find difficulty in measuring the benefits of fluoridation (no difference between fluoridated and non-fluoridated communities.) [44]

Not taking into account delayed tooth eruption makes early fluoridation studies "over-estimates of the benefits" [45]

An example of the difficulty with diagnosis and comparing dental caries is pictured below. The teeth clinically "look" like hard and strong, but the dental caries are very hard to detect with a delay in diagnosis which can skew research with a difficult confounding effect.



Diagnosis attempted in a school setting without proper lights and x-rays will not be accurate. And consistent diagnosis is difficult. Some dentists want to see certainty of a cavity, others will treat at the beginning of decalcification. Neither opinion is wrong, but consistency is hard to come by.

[43] Komarek et al, A Bayesian analysis of multivariate doubly-interval-censored dental data, Biostatistics 2005 6 pp 145-155

[44] Studies by: Brunelle, Angelilo, Clark, Ismail, Slade, Kumar and in Australia by Armfield JM. Spencer AJ 2004, a very large study found No difference in dental decay in permanent teeth

[45] Fluoride added to drinking water may have simply delayed caries in the past. Hardy Limeback DMD, Ph

NRC 2006 MEMBERS PERSPECTIVES:

A. Hardy Limeback comments 2015 [46]

"I served 3.5 years on the US National Academies of Sciences Subcommittee on Fluoride in Drinking Water.

The NAS is sometimes referred to as the "Supreme Court of Science," an organization that sets up unbiased (or balanced) committees to review scientific issues of concern to Americans. The committee on which I served examined the health effects of fluoride in drinking water. Our report, published March 22, 2006, can be found online.

Our committee was funded by the US EPA — we were charged NOT to examine the benefits of fluoridation but we certainly reviewed all relevant literature on the toxicity of fluoride, including those at low levels of intake, including the toxic side effects of fluoridation.

The EPA has still not made a ruling on the maximum contaminant level goal (MCLG) for fluoride, while the Department of Human Health Services, being concerned about the dental fluorosis that fluoridation is causing, has lowered its recommendation for levels of fluoride in drinking water to 0.7 mg/ L (ppm).
The American Dental Association and the Centers for Disease Control in the U.S. both agreed that fluoridated tap water should not be used to make up infant formula, since that increases the risk of dental fluorosis.
Health Canada and the US CDC, taking the recommendation of only pro-fluoridation experts, continues to recommend fluoridation (now at a lowered level of 0.7 ppm) despite mounting evidence that the optimum therapeutic level of fluoride in drinking water, if there is even any benefit at all, is at 0.35 ppm or less.
Our 2006 NRC (NAS) report also concluded that there is a likelihood that fluoride can promote bone cancer. On page 336 it is stated fluoride appears to have the potential to initiate or promote cancers, particularly of the bone, but the evidence to date is tentative and mixed (Tables 10-4 and 10-5). This alone should force the EPA to set a fluoride maximum contaminant level goal for fluoride in drinking

[46] Dr. Hardy Limeback BSc, PhD, DDS Professor Emeritus and Former Head of Preventive Dentistry, Faculty of Dentistry, University of Toronto

water at ZERO (as it did for arsenic). The EPA has not yet made a decision as to fluoride's carcinogenicity. I have personally conducted years of funded research at the University of Toronto on the topic of fluorosis (fluoride poisoning) and bone effects of fluoride intake. I am also the co-author of studies that show that too much fluoride accumulation in the dentin of teeth (the tissue that supports enamel) causes its properties to change as well. I suspect that a lifetime of fluoride accumulation on teeth causes them to be more brittle and fracture more easily."

B. Kathleen Thiessen was also a member of the NRC 2006 report, her comments (2011).

"The NRC (2006) did not consider fluoride to be clearly a carcinogen, the NRC also did not consider fluoride to be "clearly not carcinogenic." That leaves "possible carcinogen" and "probable" carcinogen as the only possibilities. The discussion of EPA guidelines and practice (NRC 2006, pp. 334-335, 342-343) would not have been relevant had the NRC considered "early not carcinogenic" to be a likely categorization. The question becomes one of how strongly carcinogenic fluoride is, and under what circumstances. The NRC (2006) specifically discussed the limitations of epidemiologic studies, especially ecologic studies (those in which group, rather than individual, measures of exposure and outcome are used), in detecting small increases in risk—in other words, most of the studies are not sensitive enough to identify small or moderate increases in cancer risk; therefore a "negative" study does not necessarily mean that there is no risk (see also Cheng et al. 2007). In particular, a "negative" study that does not address a key condition involved in a "positive" finding (e.g., the failure to include age-specific, individual exposure or to separate young and old people in the analysis) cannot be considered evidence of no risk.

Regarding the 1992 NTP study in particular (which was not made public until 2005), OEHHA should be aware of the caveats described by the NRC (2006, p. 319). In particular, the study did not have sufficient statistical power to detect a

low-level effect. In addition, the study did not show increased osteosarcoma with exposure to ionizing radiation, even though that was an expected outcome."

In humans, osteosarcomas tend to occur most commonly in young people (pediatric cases) or the very old (adult or geriatric cases), with a higher incidence in males than in females (Bassin et al. 2006). Sergi and Zwerschke (2008) indicate that 60-75% of cases are in patients between 15 and 25 years old. In the NTP 2-year study, fluoride exposure was begun when the animals were 6 weeks old (NTP 1990), as is typical for NTP and similar studies (Hattis et al. 2004). Puberty in the rat typically occurs at about 32 days of age in females and 42 days in males (e.g., Gray et al., 2004; Evans 1986). Thus, the age of 6 weeks in the 1990 NTP study probably corresponds to pubertal or post-pubertal animals. The cases of osteosarcoma in the rats were reported in the late stages of the test, and probably corresponded to geriatric osteosarcomas in humans. In Bassin's study, the age range for which the fluoride-osteosarcoma association was most apparent was for exposures at ages 4-12 years, with a peak for exposures at age 6-8 years (Bassin et al. 2006). Very likely, the fluoride exposures in most of the animal studies have started after the age corresponding to the apparent most susceptible age in humans, and thus these animal studies may have completely missed the most important exposure period with respect to initiation of the majority of human osteosarcomas. Therefore, the 1990 NTP study cannot be interpreted as showing no evidence of causation for pediatric osteosarcoma, although, properly interpreted, it does show evidence for causation of geriatric osteosarcoma. [47]

CANCER:"Regulatory Needs." Fluoride is in a regulatory "Vacuum."

JURISDICTION: Artificial fluoridation which represents roughly half individual fluoride exposure is repeatedly referenced in this nomination in part because of the intent of use as a drug, lack of legend, lack of dosage control, lack of FDA CDER oversight, lack of patient consent, the easiest exposure source to reduce

[47] Thiessen, KM, Member of the 2006 NRC committee reviewing fluoride in water for the EPA as written 2011 for the state of California. Thiessen works for Senes Oak Ridge Inc, Center for Risk Analysis.

by simply turning off the fluoride pump, and the easiest to do ecological comparisons of exposure.

Increases in cancer in artificially fluoridated communities raises significant concerns carcinogenic levels have been surpassed by some. Fluoride toothpaste, fluoride medications, and fluoride from pesticides, manufacturing and air contribute more than artificially fluoridated water for some individuals. Fluoride is ubiquitous, but governments have the greatest potential to reduce excess exposure if NTP no longer holds fluoride as a protected carcinogen.

X. CANCER

SPECIFIC ISSUE FOR REVIEW. FLUORIDE: CLEAR EVIDENCE OF KNOWN CARCINOGEN.

Some streams of evidence to consider when evaluating the carcinogenicity of fluoride.

1. Dosage of fluoride which is known to cause cancer in animals,
2. Different toxicities between primates and other animals,
3. Total fluoride exposure to include estimates and measurements of parental fluoride exposure and then pre-conception, fetus, birth to grave: saliva, serum, teeth, bone and other tissues, fluoride individual concentrations,
4. Risks and rates for race and gender at each time in life,
6. Exposure at each age and age of diagnosis of cancer,
7. With a margin of safety of 100.

The NRC 2006 report, "Genotoxicity and Carcinogenicity," should be carefully reviewed, starting with page 304. Below we review the failure of Kim/Douglass et al. to publish a reasonable review of their tax payer funded research. Comparing older with younger cohorts, comparing two cancers, and claiming fluoride has no effect on osteosarcoma rates, misled the PHS 2015 committee members.

More Research: The NRC 2006 report called for more research *"both cohort and case control designs would be feasible to address this question."*

No stronger evidence can be provided to the Board than researchers use fluoride to induce cancer and call fluoride a "known carcinogen." The question becomes one of dosage.

The Board of Health *"should not consider EPA's 2007 reports to be an adequate review of the carcinogenicity of sodium fluoride, and especially not a classification of fluoride as to carcinogenicity. It is merely a citation of a 1996 classification that is by now obsolete in view of additional information, together with a misinterpretation of the NRC review (NRC 2006) as being consistent with EPA's 1996 classification."* [48]

The NRC committee unanimously concluded that *"Fluoride appears to have the potential to initiate or promote cancers, particularly of the bone."* (NRC 2006, p. 336) even though the overall evidence is "tentative and mixed."

Referring to the animal studies, the committee said, *"the nature of uncertainties in the existing data could also be viewed as supporting a greater precaution regarding the potential risk to humans."* (NRC 2006, p. 317).

Fluoride has neurotoxicity, endocrine toxicity, reproductive and developmental toxicity, genotoxicity, immunotoxicity, adverse effects on metabolism, carcinogenicity, inflammatory toxicity, and is an enzymatic reactor. The question left is at what age, dosage and host susceptibility does the harm start for each person. Although the greatest negative economic impact from excess fluoride is a reduction in IQ, cancer kills.

Dose, Time and Host Make the Toxin

"More than 200 biologists, toxicologists, epidemiologists, nutrition researchers, and pediatricians determined that "[t]he timing of exposure -- with an emphasis on critical windows of susceptibility -- has therefore become a crucial factor to be considered in toxicological assessments" due to three primary aspects of consideration:

1. "the mother's chemical body burden will be shared with her fetus or neonate";

[48] Thiessen IBID, p 10.

2. “susceptibility to adverse effects is increased during development, from preconception through adolescence”;
3. “developmental exposures to toxicants can lead to life-long functional deficits and manifestations of increased disease risks.”

Fetuses and Infants are more vulnerable to toxins like fluoride because:

- The blood-brain barrier is not fully formed (Varner et al 1998)
- The placenta is unable to block toxins in maternal blood system from entering fetal blood system (Mullenix et al. 1995)
- The kidneys are not fully developed (Whitford et al. 1994)
- Children ingest 3-4 times more fluoride per body weight than adults (NRC 2006)
- http://www.rachel.org/lib/faroes_statement_text.070524.htm Grandjean P, Bellinger D, Bergman A, Cordier S, Davey-Smith G, Eskenazi B, Gee D, Gray K, Hanson M, van den Hazel P, Heindel JJ, B, Hertz-Picciotto I, Hu H, Huang TT, Jensen TK, Landrigan PJ, McMillen IC, Murata K, Ritz B, Schoeters G, Skakkebaek NE,
Skerfving S, Weihe P. The faroes statement: human health effects of developmental exposure to chemicals in our environment. Basic
Clin Pharmacol Toxicol. 2008 Feb;102(2):73-5. Available from:
http://www.ncbi.nlm.nih.gov/pubmed/18226057

MECHANISUM OF FLUORIDE’S CARCINOGENICITY

Mechanism of DNA Damage: Zhang (2008) *“Some recent studies have suggested that DNA damage may be a potential neurotoxic mechanism of fluoride. The tail length, as measured by an ocular micrometer, is increased in fluoride-treated human embryonic hepatocytes in a previous study carried out to investigate the geneotic effect of fluoride (Wang et al., 2004). In the present study, we performed OTM and percentage of DNA in the tail as indices of DNA damage. OTM, multiplication of the tail length and percentage of DNA in the tail,*

objectively and sensitively reflects the effect of fluoride on DNA damage. Our findings showed that fluoride-induced DNA damage and OTM was more a sensitive measure than percentage of DNA in the tail. The correlation analysis showed a positive correlation between ROS formation and OTM level (r2=0.583, P < 0.05), which indicated that ROS might play an important role in the course of DNA damage." [49]

Mechanism: Wang (2004) *"As cells were exposed to higher doses of fluoride, the percentage of L-02 cells with DNA damage increased. This result is consistent with other studies… Therefore, considering previous studies, we think that fluoride can cause lipid peroxidation, DNA damage and apoptosis, and that there is a positive relationship among these changes."* [50]

Mechanism: Aardema (1989) *"Based on these results and those previously reported for NaF and APC, it is proposed that NaF-induced aberrations may occur by an indirect mechanism involving the inhibition of DNA synthesis/repair."* [51]

Mechanism: Lasne (1988) *"Sodium fluoride was found to induce morphological transformation of SHE cells seeded on a feeder layer of X-irradiated cells at high concentrations (75-125 micrograms/ml). When the cells were seeded in the absence of a feeder-layer, the transformation frequencies increased in a dose-dependent manner with the concentrations of sodium fluoride ranging from 0 to the highly toxic concentration of 200 micrograms/ml. In the BALB/3T3 cell system, sodium fluoride was negative in the standard Kakunaga procedure, while through the experiment designed by table L8 (2(7] of the orthogonal method, an initiating-like effect and a weak promoting activity were detected within the concentrations ranging from a 25 micrograms/ml to a 50 micrograms/ml*

[49] Zhang M, et al. (2008). Effects of fluoride on DNA damage, S-phase cell-cycle arrest and the expression of NF-kappaB in primary cultured rat hippocampal neurons. Toxicology Letters 179(1):1-5.

[50] Wang AG, et al. (2004). Effects of fluoride on lipid peroxidation, DNA damage and apoptosis in human embryo hepatocytes. Biomedical and Environmental Sciences 17: 217-22.

[51] Aardema MJ, et al (1989). Sodium fluoride-induced chromosome aberrations in different stages of the cell cycle: a proposed mechanism. Mutation Research 223:191-203.

concentration which is highly toxic for BALB/3T3 cells. From these results, it is suggested that, besides a genetic mode of action, sodium fluoride could possibly act through a non-genotoxic mechanism." [52]

RATIONALE FOR LISTING FLUORIDE AS A KNOWN CARCINOGEN.

The "biological plausibility" of a fluoride-osteosarcoma link (and other cancers) is widely acknowledged in the scientific literature. When the connection between a chemical and a cancer is biologically plausible, studies that detect an association between the two are taken more seriously.

Three lines of plausibility in a fluoride/cancer connection:

1 Ames 1976, reported about 90% of organic compounds that were found [53]to be mutagenic are also carcinogenic.

2 Tissues such as bone, bladder, kidney, brain, are principal sites for fluoride accumulation in the body, and the rate of accumulation is increased during periods tissue turn over, such as for bone the development and osteoclastic osteoblastic activity.

3 Fluoride is a mitogen. For example, osteosarcoma is a cancer caused by an abnormal proliferation of the osteoblasts.

All tissues which come in contact with higher concentrations of fluoride should be considered for a fluoride cancer connection.

In short, fluoride's ability to induce mutagenic damage in fluoride-rich environments coupled with its ability to stimulate proliferation of osteoblasts provides a compelling biological basis by which fluoride could cause, or contribute to cancer. The only relatively "static" tissue high in fluoride appears to be dentin. Cancer of the dentin or enamel is not reported.

[52] Lasne C, et al. (1988). Transforming activities of sodium fluoride in cultured Syrian hamster embryo and BALB/3T3 cells. Cell Biology and Toxicology 4:311-24

[53] Ames, BN et al, Mutagens and carcinogens. Science, 194:132-133, 1976.

ISSUES, FACTS AND STUDIES:

The first aim of the Federal Caustic Poison Act is the protection of children.

Fluoride exposure is systemic, potentially affecting all tissues. Evidence is mounting that age and "timing" along with dosage, host health, race, and synergistic chemicals are all significant.

McCully (2020)[54] "Glyphosate, fluoride, and electromagnetic fields are examples of carcinogenic pollutants that promote loss and decomposition of the active site for oxidative phosphorylation, producing mitochondrial dysfunction and oxidative stress."

Known Carcinogen: Pal (2014): *Fluoride, a well-established environmental carcinogen, has been found to cause various neurodegenerative diseases in human. Sub-acute exposure to fluoride at a dose of 20mg/kgb.w./day for 30 days caused significant alteration in pro-oxidant/anti-oxidant status of brain tissue as reflected by perturbation of reduced glutathione content, increased lipid peroxidation, protein carbonylation, nitric oxide and free hydroxyl radical production and decreased activities of antioxidant enzymes. Decreased proteolytic and transaminase enzymes' activities, protein and nucleic acid contents and associated DNA damage were observed in the brain of fluoride intoxicated rats. The neurotransmitters dopamine (DA), norepinephrine (NE) and serotonin level was also significantly altered after fluoride exposure. Protective effect of resveratrol on fluoride-induced metabolic and oxidative dysfunctions was evaluated. Resveratrol was found to inhibit changes in metabolic activities restoring antioxidant status, biogenic amine level and structural organization of the brain. Our findings indicated that resveratrol imparted antioxidative role in*

[54] McCully KS. Environmental Pollution, Oxidative Stress and Thioretinaco Ozonide: Effects of Glyphosate, Fluoride and Electromagnetic Fields on Mitochondrial Dysfunction in Carcinogenesis, Atherogenesis and Aging. Ann Clin Lab Sci. 2020 May;50(3):408-411. PMID: 32581036.

ameliorating fluoride-induced metabolic and oxidative stress in different regions of the brain. [55]

Known Carcinogen: McCully (2009) *". . . Depletion of thioretinaco ozonide from cellular membranes is suggested to underlie the carcinogenic and atherogenic effects of fluoride and other electrophilic carcinogens."* [56]

Known carcinogen (increase incidence): Marigold (1969) explained that [57] fluoride has a paradoxical action on cancer. Some of the most effective anti-cancer drugs have contained fluoride and yet other inorganic fluoride compounds are powerful carcinogens such as dimethylaminoazobenzene who's cancer-producing ability is enhanced seven times as much as by substitution of fluoride with other halogens.

Known carcinogen (chronic exposure - shorter life span): Taylor (1954) carried [58]out a total of 12 experiments involving 645 mice. The data indicated that drinking water containing as little as 1ppm of fluoride shortened the life span of cancer-prone mice by an average of 9%, regardless of whether they died of cancer or another disease. In contrast, 1953, Fleming transplanted sarcoma 37 into young adult mice and guinea [36] pigs. For a few weeks, one group received 20 ppm NaF in drinking water and another 1,000 ppm intraperitoneally while controls received no fluoride. The fluoride treated animals lived longer, lost less weight and had tumors inhibited by fluoride. One striking difference between Taylor's and Flemming's studies is "time and dosage," Taylor had chronic low dose exposure while Flemming had acute high dose.

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[55] Pal S, Sarkar C, Protective effect of resveratrol on fluoride induced alteration in protein and nucleic acid metabolism, DNA damage and biogenic amines in rat brain Environ Toxicol Pharmacol. 2014 Sep;38(2):684-99. doi: 10.1016/j.etap.2014.07.009. Epub 2014 Jul 23.

[56] McCully KS, Chemical pathology of homocysteine. IV. Excitotoxicity, oxidative stress, endothelial dysfunction, and inflammation., Ann Clin Lab Sci. 2009 Summer;39(3):219-32

[57] Marhold, J. and Matrka, M.: Ca=inogenicity and Oxidation of Fluoro- Derivatives of Dimethylaminoazobenzene. Fluoride 2:85, Apri11969.

[58] Taylor, A.: Sodium fluoride in Drinking Water of Mice. Dental Digest, 60:170, 1954.

Known carcinogenic: Taylor (1965) reported observations from 54 experiments, 991 [37] mice bearing transplanted tumors and 58 experiments with 1817 eggs implanted with mouse cancer tissue. Sodium fluoride accelerated the growth of cancer tissue. Taylor's work has been repeatedly confirmed. Note: Talyor's [38] first study was criticized because he did not control the fluoride in animal feed, probably CaF. His subsequent work did control for total fluoride exposure and the results were confirmed.

Known Carcinogen: Suzuki (1991) *"We tested the induction of mutagenic effects by in vivo and in vitro bone marrow micronucleus tests. A significant increase in micronucleated polychromatic erythrocytes was observed 24 H after intraperitoneal injection of sodium fluoride at a dose of 30 mg/kg body weight. In the in vitro micronucleus test, the frequency of micronucleated polychromatic erythrocytes was increased significantly at concentrations of 2 and 4 MM. These results indicate that the micronucleus test may be useful in evaluating the cancer risk of sodium fluoride."* [39]

Known Carcinogen: Pati (1987) *"Genotoxicity of Sodium fluoride was evaluated in mice in vivo with the help of different cytogenetic assays. The frequency of chromosome aberration was dose – and time*

[36] Fleming, H,S.: Effect of fluorides on the Tumors 37 After Trans- plantation to Selected Locations in Mice and Guinea Pigs. Journ. of Dent. Res. 32:646, October 1953

[37] Taylor, A.: Effect of Sodium fluoride on Tumor Growth. Proceedings of the Society for Experimental Biology and Med. 119:252-5, 1965.

[38] *See, e.g.,* Irwin H. Herskowitz & Isabel L. Norton*, Increased Incidence of Melanotic Tumors in Two Strains of Drosophila Melanogaster Following Treatment with Sodium Fluoride*, 48 GENETICS 307 (1963); Chong Chang, *Effect of Fluoride on Nucleotides and Ribonucleic Acid in Germinating Corn Seedling Roots*, 43 PLANT PHYSIOLOGY 669 (1968); Danuta Jachimczak &

Bogumila Skotarczak*, The Effect of Fluorine and Lead Ions on the Chromosomes of Human Leucocytes in Vitro*, 19 GENETICA POLONCIA 353 (1978); John Emsley et al*., An Unexpectedly Strong Hydrogen Bond: Ab Initio Calculations and Spectroscopic Studies of AmideFluoride Systems*, 103 J. AM. CHEM. SOCY 24 (1981); John Emsley et al*., The Uracil-Fluoride Interaction: Ab Initio Calculations including Solvation*, 8 J. CHEMICAL SOCY CHEMICAL COMMUN. 476 (1982); A.H. Mohamed & M.E. Chandler, *Cytological Effects of Sodium Fluoride on Mice*, 15 FLUORIDE 110 (1982); Toshio Imai et al., *The Effects of Fluoride on Cell Growth of Two Human Cell Lines and on DNA and Protein Synthesis in HeLa Cells*, 52 ACTA PHARMACOLOGICA ET TOXICOLOGICA 8 (1983); Takeki Tsutsui et al., *Cytotoxicity, Chromosome Aberrations and Unscheduled DNA Synthesis in Cultured Human Diploid Fibroblasts Induced by Sodium Fluoride*, 139 MUTATION RES. 193 (1984); Takeki Tsutsui et al., *Induction of Unscheduled DNA Synthesis in Cultured Human Oral Keratinocytes by Sodium Fluoride*, 140 MUTATION RES. 43 (1984); Takeki Tsutsui et al., *Sodium Fluoride-induced Morphological and Neoplastic Transformation, Chromosome Aberrations, Sister Chromatid Exchanges, and Unscheduled DNA Synthesis in Cultured Syrian Hamster Embryo Cells*, 44 CANCER RES. 938 (1984); Carol A. Jones et al., *Sodium Fluoride Promotes Morphological Transformation of Syrian Hamster Embryo Cells*, 9 CARCINOGENESIS 2279 (1988); Marilyn J. Aardema et al., *Sodium Fluoride-induced Chromosome Aberrations in Different Stages of the Cell Cycle: A Proposed Mechanism*, 223 MUTATION RES. 191 (1989); Takeki Tsutsui et al*., Cytotoxicity and Chromosome Aberrations in Normal Human Oral Keratinocytes Induced by Chemical Carcinogens: Comparison of Inter-Individual Variations*, 5 TOXICOLOGY IN VITRO 353 (1991).

[39] Suzuki Y, Li J, Shimizu H. (1991). Induction of micronuclei by sodium fluoride. Mutation Research 253(3):278.

– dependent but not exactly route-dependent. Fractionated dosing induced less aberration. Incidence of micronucleus and sperm abnormality increased with dose. Relative sensitivity of the three assays has been found to be: Sperm abnormality > Chromosome aberration > Micronucleus. The present results have revealed the mutagenic property of NaF." [59]

Known Carcinogen: Tazhibaev (1987)*"The test animals were fed with low-grade food during 2-5 months under conditions of acute and chronic action of hydrogen phosphide and hydrogen fluoride induced by inhalation, that resulted in the pronounced impairment of the chromosomal apparatus of the bone marrow cells in the rats. A principal possibility has been established of modification of the hydrogen phosphide and hydrogen fluoride cytogenetic effect by the alimentary action. In particular, it has been found that the effect is significantly higher when the rats are fed with a low-grade ration than under conditions of balanced nutrition."* [60]

NTP mutagenic: According to the National Toxicology Program "the preponderance of evidence" from laboratory "in vitro" studies indicate that fluoride is a mutagenic compound. Many substances which are mutagens, are also carcinogens. As is typical for in vitro studies, the concentrations of fluoride that have generally been tested were usually, but not always, higher (millimolar levels) than the concentrations found in human blood (micromolar levels). In Khalil (1995), the authors found a statistically significant mutagenic effect at a concentration of just 1 micromole (0.019 ppm). This is similar to blood fluoride concentrations among individuals living in *fluoridated* communities. More recent research has found effects at 24 uM (Zhang 2009) and 34 uM (Tiwari & Rao 2010).

The relevance of the in vitro findings are further amplified by the fact that there are certain "microenvironments" in the body, such as the bones (3,708 ppm Eble

[59] Pati PC, Bhunya SP. (1987). Genotoxic effect of an environmental pollutant, sodium fluoride, in mammalian in vivo test system. Caryologia 40:79-87.

[60] Tazhibaev ShS, et al. (1987). [Modifying effect of nutrition on the mutagenic activity of phosphorus and fluorine compounds]. Vopr Pitan. Jul-Aug;(4):63-6.

DM 1992 JPHD), teeth, kidney (50 fold increase over plasma, NRC 2006), bladder, and pineal gland (21,000 ppm, Luke 1997; 2001), where the cells can be exposed to fluoride levels many times higher than the fluoride levels found in the blood (between none detected and 0.01 ppm).

Bone mineral is regularly broken down by osteoclasts as part of the bone remodeling process, the fluoride sequestered in bones (and other tissues) may be periodically released, exposing bone cells to increased fluoride concentrations. This might help explain why fluoride has been associated, in both human and animal studies, with osteosarcoma (bone cancer). One in vitro study, for example, found that 10 to 19 ppm fluoride caused mutagenic effects in bone cells after 24 to 48 hours of exposure. (Mihashi 1996). According to the authors:

Known Carcinogen: *"Significant increases in the frequencies of chromosome aberrations were induced in a dose- and treatment time-dependent fashion when NaF was administered to [rat vertebral bone] cells at 0.5 and 1.0 mM [=9.5 to 19 ppm] for 24 and 48 h. The results indicate that NaF is genotoxic to rat vertebrae, providing a possible mechanism for the vertebrae, as a target organ of NaF carcinogenesis."* [61]

Known Genetic Damage: Humans and apes have been found to be more susceptible to fluoride-induced genetic damage than rodent cells. (Kishi 1993). Chromosome breaks occurred in human and ape cells at fluoride concentrations (19 to 114 ppm) that had no effects on rodent cells. (Note: Fluoride varnish is 22,600 ppm)

Known Mutagenic: 1990 NTP *"In summary, sodium fluoride is mutagenic in cultured mammalian cells and produces transformation of Syrian hamster cells in vitro. The reports of in vivo cytogenetic studies are mixed, but the preponderance of the evidence indicates that sodium fluoride can induce chromosome aberrations and sister chromatid exchanges in cultured mammalian cells. These mutagenic and clastogenic effects in cultured cells are supported by positive*

[61] Mihashi M, Tsutsui T. (1996). Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. Mutation Research 368(1):7-13.

effects in Drosophila germ cell tests that measure point mutations and chromosome breakage. In vivo tests in rodents for chromosome aberrations provide mixed results that cannot readily be resolved because of differences in protocols and insufficient detail in some study reports to allow a thorough analysis. The mechanism(s) by which these effects result from exposure to sodium fluoride is not known." [62]

Preponderance of Evidence: 2001 Bassin *"The effects of fluoride as a mutagen, carcinogen, and antimutagen are inconsistent, but the preponderance of evidence in cultured mammalian cells indicate that sodium fluoride can induce chromosome aberrations and sister chromatid exchanges."* [63]

Capable: 1993 Environment Canada *"Fluoride (as sodium fluoride) should be considered capable of inducing chromosomal aberrations, micronuclei, and sister-chromatid exchanges in vitro in mammalian cells, although the results from such studies have been inconsistent."* [64]

Genotoxic: 1991 HHS *"Genotoxicity studies are highly dependent on the methods used… Despite the apparently contradictory reports appearing in the published literature, fluoride has not been shown to be mutagenic in bacteria (Ames test). In some studies fluoride has been reported to induce gene mutations in both cultured rodent and human cells. Fluoride has also been reported to transform rodent cells in vitro. Although there is disagreement in the literature concerning the ability of fluoride to be a clastogen (induce chromosome aberrations) in cultured cells, it has been suggested that fluoride can cause chromosome aberrations in rodent and human cells. Fluoride induced primarily chromatid gaps and chromatid breaks, indicating that the cells are most responsive in the G stage of the cell cycle, i.e., after chromosome duplication in*

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[62] National Toxicology Program [NTP] (1990). *biochemical responses of cells treated with fluoride. Sodium fluoride inhibits both protein and DNA synthesis in cultured mammalian cells. The inhibition of DNA synthesis may be a secondary effect of the* Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3f1 Mice. Technical report Series No. 393. NIH Publ. No 91-2848. National Institute of Environmental Health Sciences, Research Triangle Park, N.C.

[63] Bassin EB. (2001). Association Between Fluoride in Drinking Water During Growth and Development and the Incidence of Ostosarcoma for Children and Adolescents. Doctoral Thesis, Harvard School of Dental Medicine. p. 15.

[64] Environment Canada. (1993). Inorganic Fluorides: Priority Substances List Assessment Report. Government of Canada, Ottawa.

preparation for cell division. Negative results reported in some cytogenetic studies are likely the effect of inadequate test protocols…. Although the mechanism(s) by which these cellular effects result from exposure to fluoride is not known, a number of possible mechanisms have been proposed to explain the genetic activity observed. These mechanisms have been based on the observed reactions of fluoride in solution with divalent cations or necleotides, or the physiological and inhibition protein synthesis, or a result of the direct inhibition of DNA polymerase. Fluoride can react with divalent cations in the cell so as to affect enzyme activities that are necessary for DNA or RNA synthesis, or chromosome metabolism or maintenance; it may react directly with DNA as part of a complex; or it ca disrupt other cellular processes such as cell differentiation or energy metabolism." [65]

Airborne Fluoride: *"Fluoride has displayed mutagenic activity in studies of vegetation, insects, and mammalian oocytes. There is a high correlation between carcinogenicity and mutagenicity of pollutants, and fluoride has been one of the major pollutants in several situations where a high incidence of respiratory cancer has been observed. For these reasons, the relation between airborne fluoride and incidence of lung cancer needs to be investigated."* [66]

Chromosomal anomalies and Primary DNA Damage: Tiwari (2010) *"Our study*
has supported the role of As [arsenic] and F [fluoride] as potent genotoxic agents, since in vitro exposure of both caused increased chromosomal anomalies along with primary DNA damage, in human peripheral blood cultures." [67]

Known Carcinogen: Zhang (2009) *"Twenty four agents were used to evaluate this screening assay. We selected the agents, ranging from DNA*

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[65] Department of Health and Human Services. (1991). Review of fluoride: benefits and risks. Report of the Ad Hoc Subcommittee on Fluoride. Washington, DC. p. 70. (There is also an abbreviated report)

[66] Marier J, Rose D. (1977). Environmental Fluoride. National Research Council of Canada. Associate Committe on Scientific Criteria for Environmental Quality. NRCC No. 16081.

[67] Tiwari H, Rao MV. (2010). Curcumin supplementation protects from genotoxic effects of arsenic and fluoride. Food & Chemical Toxicology 48(5):1234-8.

alkylating agents, oxidative agent, radiation, DNAcrosslinking agent, nongenotoxic carcinogens, precarcinogenic agents, which included . . . sodium fluoride, acrylamide . . . . The results showed that all 20 tested known carcinogenic and genotoxic agents were able to induce gadd153-Luc expression at a sublethal dose.. . . .” [68]

Known Genotoxic, Mutagenic, Teratogenic: Ercivas (2009)*“In this study we concluded that NaF, in 5 and 10 lg/ml NaF concentrations cause genotoxic alterations. So genotoxic, mutagenic and teratogenic effects of NaF need to be carefully screened and evaluated together with other long-term effects using in vitro and in vivo animal test models.”* [69]

Known Genotoxic: Kleinsasser (2001) *“For fluoride concentrations of 2 ppm to 35 ppm, non vital cells of less than 10% could be shown. After incubation with 71 ppm and 213 ppm Olaflur, there were 15% and 43% of damaged cells, respectively. Weak genotoxic effects on mucosal cells as well as on lymphocytes could be demonstrated at all concentrations tested. In fluoride concentrations of 213 ppm genotoxicity increased to max.”* [70]

Known DNA Damage: Chen (2000) *“To investigate the effects of fluoride on DNA damage*
as well as the effects of selenium and zinc against fluoride respectively or jointly in pallium neural cells of rats, single cell gel electrophoresis was used to detect the DNA damage of neural cells prepared in vitro. The results showed that the degree of DNA damage in the fluoride group and the selenium group were significantly greater than that in control group (P < 0.01). The damage in the fluoride group was even more serious. The damage in the fluoride + selenium group and fluoride + zinc group was slighter than that in the fluoride group but

[68] Zhang R, et al. (2009). A stable and sensitive testing system for potential carcinogens based on DNA damage-induced gene expression in human HepG2 cell.Toxicology In Vitro. 23(1):158-65.

[69] Erciyas K, Sarikaya R. (2009). Genotoxic evaluation of sodium fluoride in the Somatic Mutation and Recombination Test (SMART). Food & Chemical Toxicology 47(11):2860-2.

[70] Kleinsasser NH, et al. (2001). [Cytotoxicity and genotoxicity of fluorides in human mucosa and lymphocytes]. Laryngorhinootologie 80(4):187-90.

with no significant difference. The extent of DNA damage in the fluoride + selenium + zinc group was significantly slighter than that in the fluoride group(P < 0.05). It suggested that fluoride and selenium could induce DNA damage in pallium neural cells of rats respectively." [71]

Known Genotoxic Rivedal (2000) *"In the present work, 13 compounds [chlordane, Arochlor 1260, di(2-ethylhexyl)phthalate, 1,1,1-trichloro-2, 2-bis(4-chlorophenyl)ethane, limonene, sodium fluoride, ethionine, o-anisidine, benzoyl peroxide, o-vanadate, phenobarbital, 12-O-tetradecanoylphorbol 13-acetate and clofibrate] have been tested for their ability to induce morphological transformation and affect intercellular communication in Syrian hamster embryo (SHE) cells… In vitro morphological transformation of SHE cells is now one of the most frequently used cell transformation systems. Around 500 chemicals have been tested in this system, and a good correlation has been obtained with the ability of compounds from different chemical groups to cause tumours in animals and humans. The SHE cell transformation assay also responds to tumour promoters and carcinogens not detected by tests for genotoxicity… [N]ine of the 13 tested substances (TPA, o-vanadate, DEPH, phenobarbital, Arochlor 1260, clofibrate, o-anisidine, limonene and NaF) are considered positive for induction of morphological transformation."* [72]

Known Genotoxic: Mihashi (2000)*"Significant increases in the frequencies of chromosome aberrations were induced in a dose- and treatment time-dependent fashion when NaF was administered to [rat vertebral bone] cells at 0.5 and 1.0 mM for 24 and 48 h. The results indicate that NaF is genotoxic to rat vertebrae, providing a possible mechanism for the vertebrae, as a target organ of NaF carcinogenesis."* [73]

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[71] Chen J, et al. (2000). [Effects of selenium and zinc on the DNA damage caused by fluoride in pallium neural cells of rats]. Wei Sheng Yan Jiu. 29(4):216-7.

[72] Rivedal E, et al. (2000). Morphological transformation and effect on gap junction intercellular communication in Syrian hamster embryo cells as screening tests for carcinogens devoid of mutagenic activity. Toxicology In Vitro 14(2):185-92.

[73] Mihashi M, Tsutsui T. (1996). Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. Mutation Research 368:7-13.

Known Genotoxic: Khalil (1995) *"The genotoxic effects of inorganic fluorides were investigated by treating cultured rat bone marrow cells with varying concentrations (0.1-100 microM) of potassium fluoride (KF) and sodium fluoride (NaF) for different durations (12, 24 and 36 h) and measuring the incidence of cells with aberrations and number of breaks per cell. Both forms of fluoride were found to be weak mutagens relative to the positive control N-methyl-N-nitro-N-nitrosoguanidine (MNNG). A specificity of fluoride ion in inducing chromosome aberrations (CA) was indicated by the observation that both NaF and KF behaved almost equivalently in this study and at significantly higher variations from the results with potassium chloride (KCl) and sodium chloride (NaCl)."* [74]

Known Mutagen: Gritsan (1993)*"The testing of hydrogen fluoride (HF) for its mutagenic activity by fumigation of barley seedlings showed that the mutation rate was linear with dose. It was found that the cytogenic effects of gaseous fluoride on grain crops was correlated with the fluoride content in plant tissue."* [75]

Chromosome Aberrations - early cell cycle dependent: Hayashi (1993) *"A significant increase in the incidence of chromosome aberrations was observed only in cultures treated with NaF during early and/or middle S phases of cell cycle. These results suggest that cytotoxicity and clastogenicity of NaF to cultured human diploid fibroblasts are cell cycle dependent, and that the cells in early and middle S phases are more sensitive to the effects."* [76]

Species Dependent Kishi (1993) *"Conflicting evidence has been reported concerning the mutagenicity of sodium fluoride (NaF), especially clastogenicity at concentrations of more than 1 mM. NaF is known to induce chromosome aberrations at these concentrations in human cells, but not in most rodent cells. We considered that such species-specific difference in chromosomal sensitivity*

[74] Khalil AM. (1995). Chromosome aberrations in cultured rat bone marrow cells treated with inorganic fluorides. Mutation Research 343:67-74.

[75] Gritsan, NP. (1993). Cytogenetic effects of gaseous fluorides on grain crops. Fluoride 26: 23-32.

[76] Hayashi N, Tsutsui T. (1993). Cell cycle dependence of cytotoxicity and clastogenicity induced by treatment of synchronized human diploid fibroblasts with sodium fluoride. Mutation Research 290: 293-302.

would be derived from the phylogenetic distance between rodents and man. To clarify the role of interspecies differences, we investigated the chromosomal sensitivity to NaF in cell lines from various primates, which diverged into many species, including rodent-like prosimians and human-like great apes. The results showed that the clastogenicity of NaF was limited to human and great ape cells. . . . ."[77]

Induction of mutagenic effects: *"We tested the induction of mutagenic effects by in vivo and in vitro bone marrow micronucleus tests. A significant increase in micronucleated polychromatic erythrocytes was observed 24 H after intraperitoneal injection of sodium fluoride at a dose of 30 mg/kg body weight. In the in vitro micronucleus test, the frequency of micronucleated polychromatic erythrocytes was increased significantly at concentrations of 2 and 4 mM. These results indicate that the micronucleus test may be useful in evaluating the cancer risk of sodium fluoride."* [78]

Induce mutations: *"Sodium fluoride was found to induce gene-locus mutations at the thymidine kinase (tk) and hypoxanthine guanine phosphoribosyl transferase (hgprt) loci in human lymphoblastoid cells."* [79]

Aberrations dependent on cell cycle: Suzuki (1989) *"Inducibility of chromosome*
aberrations of the cells following treatment with sodium fluoride was also dependent upon the phase of cell cycle." [80]

Promotes Cancer: Jones (1988) *"Sequential treatment of Syrian hamster embryo (SHE) cells with a chemical carcinogen followed by sodium fluoride (NaF) resulted in a higher yield of morphologically transformed cell colonies than*

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[77] Kishi K, Ishida T. (1993). Clastogenic activity of sodium fluoride in great ape cells. Mutation Research 301:183-8.

[78] Suzuki Y, Li J, Shimizu H. (1991). Induction of micronuclei by sodium fluoride. Mutation Research 253:278.
[79] Crespi CL, et al. (1990). Sodium fluoride is a less efficient human cell mutagen at low concentrations. Environmental Molecular Mutagenesis 15:71-7.

[80] Suzuki N, Tsutsui T. (1989). [Dependence of lethality and incidence of chromosome aberrations induced by treatment of synchronized human diploid fibroblasts with sodium fluoride on different periods of the cell cycle]. [Article in Japanese] Shigaku. 77(2): 436-47.

treatment of the cells with carcinogen alone… This enhancement/promotion of cell transformation by NaF was only expressed after the cells had been pretreated with either directacting carcinogens or procarcinogens." [81]

Clastogenic: Albonese (1987) *"Chromosomal aberrations were recorded for all the concentrations used. . . .The authors conclude that sodium-fluoride may be considered to be clastogenic in these cells."* [82]

Genetic Damage: Caspary (1987) *"While the results in this paper demonstrate the ability (of fluoride) to induce genetic damage in cultured mammalian cells, the potential risks to animals or man are not addressed."* [83]

Genotoxic and suggested carcinogenic: Tsutsui (1984) *"Mass cultures of cells treated with NaF (75 or 100 micrograms/ml) for 24 hr, followed by continuous cultivation for 35 to 50 passages, developed the ability to grow in soft agar and to produce anaplastic fibrosarcomas when injected into newborn hamsters. In contrast, no morphological and neoplastic transformation was observed in untreated cells. Furthermore, a significant increase in chromosome aberrations at the chromatid level, sister chromatid exchanges, and unscheduled DNA synthesis was induced by NaF in a dose- and time-dependent manner. These results indicate that NaF is genotoxic and capable of inducing neoplastic transformation of Syrian hamster embryo cells in culture. A potential for carcinogenicity of this chemical, which is widely used by humans, is suggested. However, the carcinogenic risk of this chemical to humans may be reduced by factors regulating in vivo dose levels."* [84]

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[81] Jones CA, et al. (1988). Sodium fluoride promotes morphological transformation of Syrian hamster embryo cells. Carcinogenesis 9: 2279-84.

[82] Albanese R. (1987). Sodium fluoride and chromosome damage (in vitro human lymphocyte and in vivo micronucleus assays). Mutagenesis 2:497-9.

[83] Caspary WJ, et al (1987). Mutagenic activity of fluorides in mouse lymphoma cells. Mutation Research 187:165-80.

[84] Tsutsui T, Suzuki N, Ohmori M. (1984) Sodium fluoride-induced morphological and neoplastic transformation, chromosome aberrations, sister chromatid exchanges, and unscheduled DNA synthesis in cultured syrian hamster embryo cells. Cancer Research 44:938-41.

DNA Damage: Tsutsui (1984) *"A significant increase in the frequency of chromosome aberrations at the chromatid level was observed in treated cells in a dose-dependent manner… These results suggest that NaF causes DNA damage in human diploid fibroblasts in culture."* [85]

DNA Damage: Tsutsui (1984) *"The effect of treatment of cultured human oral keratinocytes with sodium fluoride (NaF) has been investigated with respect to induction of unscheduled DNA synthesis (UDS)… Significant levels of UDS were induced in a dose-related fashion by NaF treatment. The results suggest that NaF causes DNA damage in cultured human oral keratinocytes."* [86]

Neoplasm: Greenberg (1982) *The results of this investigation indicate that young leukocytes chronically exposed to elevated fluoride levels have the potential for an irreversible shift toward the formation of neoplasm."* [87]

Chromosome damage at artificial fluoridation concentrations: *"Human leucocytes in the cultures in vitro were exposed to the action of lead and fluorine ions… Both factors caused structural and quantitative aberrations in the chromosome set, which seems to indicate their mutagenic character. It is noteworthy that the smallest of the applied concentrations of fluorine ions (3.15 x 10-5M) is equal to the concentration of these ions in the running water of Szczecin, given for the prevention of caries."* [88]

[85] Tsutsui T, Suzuki N, Ohmori M, Maizumi H. (1984). Cytotoxicity, chromosome aberrations and unscheduled DNA synthesis in cultured human diploid fibroblasts induced by sodium fluoride. Mutation Research 139:193-8.

[86] Tsutsui T, Ide K, Maizumi H. (1984). Induction of unscheduled DNA synthesis in cultured human oral keratinocytes by sodium fluoride. Mutation Research 140(1): 43-8.

[87] Greenberg SR. (1982). Leukocyte response in young mice chronically exposed to fluoride. Fluoride 15: 119-123.

[88] achimczak D, Skotarczak B. (1978). The effect of fluorine and lead ions on the chromosomes of human leucocytes in vitro. Genetica Polonica 19: 353-7.

Mutagenic agent: Mohamad (1977) *"These findings indicate that HF in addition to being a mutagenic agent is also able to reduce crossing over in certain chromosome segments."* [89]

Genetic damage: Gerdes (1971) *"Two strains of Drosophila melanogaster were treated with sub-lethal levels of gaseous hydrogen fluoride for six weeks. Egg samples were collected at various times for hatchability determinations. Adults reared from these samples were evaluated for fecundity and fertility. Treatment with HF caused a marked reduction in hatchability and fecundity in the more sensitive strain. Male fertility was depressed but female fertility remained stable over the test period. The reduction of these parameters in the offspring of populations subjected to low levels of atmospheric HF contamination for prolonged periods suggests that HF causes genetic damage."* [90]

Genetic aberrations: Gerdes (1971) *"Results indicate that treatment increased the incidence of genetic aberrations as measured by at least two parameters."* [91]

Known mutagen: Mohamed (1970) *"These findings indicate that HF is a mutagenic agent."* [92]

DNA damage: Wu (1995) *"In recent years, SCE analysis has been considered to be a sensitive method for detecting DNA damage. There is a clear relationship between a substance's ability to induce DNA damage, mutate chromosomes, and cause cancers.The SCE frequency in the human body in peripheral blood lymphocytes is very steady, and does not vary with age or sex. Any increase of the SCE frequency is primarily due to chromosome damage. Thus using a method to detect SCE for exploring the toxicity and harm caused by fluoride is of*

[89] Mohamed AH. (1977). Cytogenetic effects of hydrogen fluoride gas on maize. Fluoride 10: 157-164.

[90] Gerdes RA, et al. (1971). The effects of atmospheric hydrogen fluoride upon Drosophila melanogaster. II. Fecundity, hatchability and fertility. Atmospheric Environment 5:117-122.

[91] Gerdes RA. (1971). The influence of atmospheric hydrogen fluoride on the frequency of sex-linked recessive lethals and sterility in Drosophila Melanogaster. Fluoride 4: 25-29.

[92] Mohamed AH. (1970). Chromosomal changes in maize induced by hydrogen fluoride gas. Canadian Journal of Genetics and Cytology 12: 614-620.

great importance. The results in this paper showed an obvious increase in the SCE frequency of the patients with fluorosis, indicating that fluorine had some mutagenic effects, and could give rise to DNA damage." [93]

The Oral Health Research Institute at the Indiana University School of Dentistry has repeatedly failed to find any evidence of genotoxic effects from fluoride exposure, whether in fluoride-exposed humans or animals. (Jackson 1997; Li 1995; Dunipace 1995; Jackson 1994).

Chromosome aberrations*:* Joseph (2000) *"Our results indicate that there is a significant increase in the frequencies of chromosome aberrations and SCE in one of the village populations exposed to a fluoride concentration higher than the permissible limit.The lymphocytes of these residents were also more susceptible to a clastogen such as Mitomycin-C than the other populations and displayed a significant increase in chromosome aberrations."* [94]

Chromosome aberrations Meng (1997)*"Our study here provides evidence that the air pollutants at the phosphate fertilizer factory, in which HF and SiF4 are the main chemicals, could induce both CA (chromosomal aberrations) and MN (micronuclei) in human blood lymphocytes in vivo.Our earlier observation on sister-chromatid exchanges (SCE) of peripheral blood lymphocytes from this same population showed that the mean SCEs/cell of the workers was significantly higher than that of the controls (p < 0.01). The results of our studies imply that even if the concentration of the chemical pollutants in the air is low (e.g. F 0.50-0.80 mg/m 3), it may cause damage to genetic material at the chromosomal level…it is suggested that chromosomal abnormalities induced by fluoride could be the results from interaction with the enzymes responsible for DNA synthesis or repair, rather than directly with*

[93] Wu DQ, Wu Y. (1995). Micronucleus and sister chromatid exchange frequency in endemic fluorosis. Fluoride. 28(3):125-127.

[94] Joseph S, Gadhia PK. (2000). Sister chromatid exchange frequency and chromosome aberrations in residents of fluoride endemic regions of South Gujarat.Fluoride33(4):154-158.

DNA." [95]

Mutagenic Agent: Wu (1950 *"The results in this paper showed an obvious increase in the SCE frequency of the patients with fluorosis, indicating that fluorine had some mutagenic effects, and could give rise to DNA damage.The fact that the SCE frequency of the healthy people in the endemic regions was also higher than that of the controls in the non-endemic regions suggests that early harm by fluorine can be cytogenetically detected in the sub-clinical patients with fluorosis who could not be given an early diagnosis clinically. Under normal circumstances, the incidence rate of micronucleus is very low, usually 0-2%. The normal value checked in this paper is 0-2%, which agrees with that reported in the literature. The results show that the mean value of the micronucleus rate of the fluorine-toxic patients was 1.94 + 0.86% (range 1-15%) which is 2-3 times more than that of 0.57 + 0.44% in the controls…To sum up, the rise of SCE and MN in the peripheral blood lymphocytes of the fluorine-intoxicated patients indicates that fluorine is a mutagenic agent which can cause DNA and chromosomal damage."* [96]

Meng (1995) *"Our study here provided evidence that the air pollutants at the phosphate fertilizer factory, of which HF and SiF4 are the main chemicals, could induce SCEs in human blood lymphocytes in vivo. These results imply that even if the concentration of the chemical pollutants in the air is low (e.g.F: 0.50 – 0.80 mg/m3), it may cause damage to genetic material at the chromosomal level, although the general health of the workers in the phosphate fertilizer factory was found to be satisfactory."* [97]

Chromosome Aberrations: Sheth (1994)*"A number of investigators have utilized the SCE*

[95] Meng Z, Zhang B. (1997). Chromosomal aberrations and micronuclei in lymphocytes of workers at a phosphate fertilizer factory.Mutation Research393: 283-288.

[96] Wu DQ, Wu Y. (1995). Micronucleus and Sister Chromatid Exchange Frequency in Endemic Fluorosis. Fluoride28(3):125-127.

[97] Meng Z, et al. (1995). Sister-chromatid exchanges in lymphocytes of workers at a phosphate fertilizer factory. Mutation Research 334(2):243-6.

(Sister Chromatid Exchange) test to study the genotoxicity of fluoride. In the present study, human populations directly exposed to fluoride in drinking water in endemic regions of North Gujarat were investigated to evaluate the possible effect of fluoride on SCE. To the best of our knowledge this is the first report on genotoxic effects following long-term fluoride intake in an endemic area in India…The results of the present investigation suggest that in fluoride-affected persons exposed to 1.95 – 2.2 ppm fluoride in drinking water chromosomal alterations as indicated by SCE frequency and chromosome aberrations were higher than in normal persons exposed to 0.6 – 1.0 ppm drinking water fluoride." [98]

DNA Damage and Fluorosis: Li (1991)"*With peripheral blood lymphocyte culture, a study of SCE and micronuclei test was done in 24 patients with fluorosis and same number of normal people as control. The results obtained showed that in the patient group the mean value of SCE per cell and the frequency of micronuclei were 10.24±1.67 and 1.42‰ ,respectively, while in the control only 7.62 ± 0.80 and 0.33‰, respectively, were found. And both of the two respective parameters, statistically, were in significant difference. These findings suggested that excess fluorine would cause increases of SCE frequency and micronuclear number in lymphocyte and make DNA damaged."* [99]

SCE Rate Induced: Velazquez-Guadarrama (2005): *"The results concerning the SCE rate*
induced by sodium fluoride are shown in Table 1. Although no significant increase was observed with the two low doses tested (from 2 to 4 mg/kg), a significant SCE increase was found with the three highest doses. The cumulative frequency of these data reveals about 70% of cells with four SCE in the group

[98] Sheth FJ, et al. (1994). Sister chromatid exchanges: A study in fluorotic individuals of North Gujurat.Fluoride27: 215-219.

[99] Li J, et al. (1991). The influence of high-fluorine on DNA stability in the human body. Chinese Journal of Endemiology.[Article in Chinese]

treated with the high dose, a value which is twice the level of the negative control." [100]

Chromosome Damage: Mohamed (1982)*"Cytological studies on bone marrow cell chromosomes and spermatocytes showed that 1-200 ppm F (as sodium fluoride) was able to induce chromosomal changes in a dose-dependent manner. The frequency of the induced chromosomal damage was significantly higher in each treatment than in the controls. The observed abnormalities included translocations, dicentrics, ring chromosomes, and bridges plus fragments, or fragments by themselves. There was a significant correlation between the amount of fluoride in the body ash and the frequency of the chromosomal abnormalities."* [101]

Chromosomal aberrations: Gileva (1975)*"Cryolite concentrations of 3 mg/m3 as well as a mixture of 0.5 mg/m3 of cryolite and 0.35 mg/m3 of hydrogen fluoride increases 3 1/2 to 4 1/2 times (over controls) the percentage of cells with chromosomal aberrations in the bone marrow of rats. The data indicate the need for further study of the mutagenic features of fluoride compounds in relation to their potential for harmful impact on the mechanism of inheritance in humans."* [102]

Mutagen: Voroshilin (1975) *"The mutagenic effect of hydrogen fluoride in concentration 1.0 mg/ m-3 was studied in rats and mice. Prolonged inhalation of this compound increased the frequency of cells with chromosome abnormalities in the bone marrow of albino rats. The mutagenic effect was higher in older animals."* [103]

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[100] Velazquez-Guadarrama N, Madrigal-Bujaidar E, Molina D, Chamorro G. (2005). Genotoxic evaluation of sodium fluoride and sodium perborate in mouse bone marrow cells. Bulletin of Environmental Contamination and Toxicology 74(3):566-72.

[101] Mohamed AH, Chandler ME. (1982). Cytological effects of sodium fluoride on mice. Fluoride 15(3):110-18.

[102] Gileva EA, et al. (1975). The mutagenic activity of inorganic fluorine compounds. Fluoride 8(1):47-50. [Originally published in Russian; condensed from Gig. Sanit., 37(1):9-12, Jan. 1972.]

[103] Voroshilin SI, et al. (1975). Mutagenic effect of hydrogen fluoride on animals. Tsitol Genet. 9(1): 42-44.

Acceleration of tumor tissue growth: Taylor (1965) *"In 54 tests involving 991 mice bearing transplanted tumors and 58 tests including 1817 tumor-bearing eggs, data were obtained which indicated a statistically significant acceleration of tumor tissue growth in association with comparatively low levels of NaF."* [104]

NTP 1990: Dose-Dependent increase in Osteosarcoma: NTP (1990) In 1977, the U.S. Congress requested that animal studies regarding the potential of a fluoride/cancer connection. NTP and published the study in 1990.

The main finding of NTP's 1990 study was a dose-dependent increase in osteosarcoma (bone cancer) among the fluoride-treated male rats. However, despite the fact that 1) the cancer occurred in the target organ (bone) for fluoride accumulation, that 2) the increase in bone cancer was statistically-significant, that 3) the doses of fluoride were low for an animal cancer study, and that 4) NTP acknowledged it is "biologically plausible" that fluoride could induce bone cancer, the NTP ruled that the study only provided "equivocal evidence" that fluoride was the cause of the cancer.

According to a report in Chemical & Engineering News: *"A number of government officials who asked not to be identified also have told C&EN that they have concerns about the conclusions of the NTP study. They, too, believe that fluoride should have been placed in the "some evidence" category, in part because osteosarcoma is a very rare form of cancer in rodents."*

In addition to increased bone cancer, the NTP study also found increases in rare liver cancers, oral cavity cancers and thyroid cancers among the fluoride-treated rats. NTP ruled, however, that the cancers were not related to the fluoride treatment despite reaching "statistical significance" in some of NTP's analyses.

[104] Taylor A, Taylor NC. (1965). Effect of sodium fluoride on tumor growth. Proceedings of the Society for Experimental Biology and Medicine 119:252-255.

THE DOSE OF FLUORIDE USED BY NTP 2006:

"the level of fluoride the low- and mid-dose animals had in their drinking water was within an order of magnitude of what humans are exposed to when drinking water containing the EPA-established maximum level of 4 ppm fluoride. This is almost unheard of in animal bioassays. Usually, animal exposure is four to six orders of magnitude more than what humans receive." [105]

"it is important to note that the dose range is not, as is sometimes the case, orders of magnitude higher than that encountered in human population, nor is the body burden expressed as concentrations in bone orders of magnitude higher than that found in human populations also ingesting fluoride." [106]

"the difference between the animal study and the human exposures is not nearly as great as typical with synthetic chemicals." [107]

"I think it's important to realize that even though the water concentrations were higher than what we see, or what humans are exposed to, the bone concentrations were not." [108]

"a small number of osteosarcomas occurred in mid- and high-dose male rats. These neoplasms occurred with a significant dose response trend, but at arate wtihin the upper range of incidences previously seen in control male rats in NTP studies. Three of the tumors arose in the vertebra, a site not commonly associated with chemically induced osteosarcomas. Bone is known to accumulate fluoride, and fluoride has been shown to be genotoxic to some mammalian cells in culture. No osteosarcomas were seen in female rats, and several osteosarcomas seen in mice occurred with an incidence that did not suggest a relationship with sodium fluoride exposure.Taken together, the current

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[105] Hileman B. (1990). Fluoride bioassay study under scrutiny. Chemical & Engineering News September 17.

[106] Silbergeld E. (1990). Peer Review of Draft Technical Report of Long-Term Toxicology and Carcinogenesis Studies and Toxicity Study, Sodium Fluoride; Research Triangle Park, North Carolina, Thursday, April 26, 1990. **p. 62-63.**

[107] Gold IBID **p. 71**.

[108] Zeise L. IBID . **p. 79.**

findings are inconclusive, but are weakly supportive of an association between sodium fluoride administration and the occurrence of osteosarcomas in male rats." [90]

20 Large City Comparison: Burk 1977, head of cytochemistry section of the USA [91] National Cancer Institute, reported year-by-year average observed cancer death rates of ten large central cities of the United States, which served as the control group and remained un-fluoridated from 1940 through 1968. These were compared for the years 1940 through 1968 with the year-by-year average observed cancer death rates of ten large central cities of the United States which served as the experimental group and remained unfluoridated from 1940 through 1951, but fluoridated between 1952 and 1956, and remained fluoridated through 1968 and thereafter.92 The experiment came to an end in 1968 because fluoridation was introduced in the control cities step-by-step from and after 1969. The necessary data are available for all years except for 1951 and 1952. Seven million in ten control cities and eleven million in ten experimental cities over about thirty years. Cancer rates in the fluoridated cities (CDRo(+F) clearly increased faster compared to the non fluoridated cities at a rate of 31.3 excess cancer deaths per 100,000 persons.

	1940	1950	1950	1970
CDRo(+F)	154.2	181.8	186.3	222.6
CDRo(- F)	153.5	181.3	l83.6	188.8

USPHS responded in defense of their policy that Burk had not adjusted for age, race or sex. PHS was suspicious the subject cities had all aged faster. However, Burk had adjusted for demographic variables and he testified to the fact to Congress and to the courts of law. In response Arthur Upton provided the "Upton Statement" in a 17 page

[90] National Toxicology Program [NTP] (1990). Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3f1Mice. Technical report Series No. 393. NIH Publ. No 91-2848. National Institute of Environmental Health Sciences, Research Triangle Park, N.C. **p. 71-73.**

[91] .most important versions of the epidemiological data here in question, including reference to related laboratory studies, and conventional adjustments for age, race, and sex, are the following: Dean Burk & John Yiamouyiannis, *Fluoridation and Cancer: Age Dependence of Cancer Mortality Related to Artificial Fluoridation*, 10 FLUORIDE 123 (1977) [hereinafter Burk & Yiamouyiannis];
Dean Burk and J. R. Graham, *Lord Jauncey and Justice Flaherty: Opposing Views of the Fluoridation-Cancer Link*, 17 FLUORIDE 63
(1984) [hereinafter Burk & Graham]; Pierre Morin et al., *Les fluorures versus le cancer et les maladies congentales: l'image globale*,
GOURVERNEMENT DU QUEBEC, MINISTERE DES AFFAIRES SOCIALES (The 1984); Pierre Morin et al., *Fluorides, Water Fluoridation,*
Cancer, and Genetic Diseases, 12 SCI. & PUB. POLY 36 (1985); Rudolf Ziegelbecker, *Zur Frage eines Zusammenhanges zwischen*
Trinkwasserfluordierung, Krebs, und Leberzirrhose, 218 GWF WASSER/ABWASSER 111 (1987); Dean Burk et al., *A Current Restatement and Continuing Reappraisal Concerning Demographic Variables in American Time-Trend Studies on Water Fluoridation and Human Cancer*, 61 PROC. PA. ACAD. OF SCI. 138 (1988) [hereinafter Burk, Graham, & Morin].

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.*See* Burk & Yiamouyiannis, *supra* note 108, at 104; Burk, Graham, & Morin, *supra* note 108, at 138.

document. Upton set for an adjustment in weighted averages, suggesting cancer [109]mortality actually grew 1% faster in the unfluoridated cities.

1950	1970	Change
CDRo/CDRe (+F)	1.23	1.24 +.0l
CDRo/CDRe (-F)	1.15	1.l7 +.02

Cities	1940	1950	1960	1970
CDRo (+F)	154.2	181.8	186.3	222.6
CDRe (+F)	128.1	146.9	146.9	174.7
CDRo/CDRe (+F)	1.204	1.238	1.268	1.274
CDRo-CDRe (+F)	26.1	34.9	39.4	47.9

Burk and Yiamouyiannis demonstrated Upton's [110] flaw. Upton had simply used 1950 with 1970 and failed to also consider data reported in-between those two points, and before and after the two points.

CDRo (-F)	153 5	181 3	183 6	188 8

[109] *National Cancer Program (Part 2), Hearings Before the Subcomm. of the Comm. on Government Operations*, 95th Cong. 471 (1977) [hereinafter *National Cancer Program*].

[110] Dr. John Yiamouyiannis executed an adjustment of the basic data, using weighted averages and US-1950 as the standard population, exactly as stipulated in the Upton Statement. He adjusted only for the years after 1950, deriving CDRo values for 1950 and 1970, by linear regression analysis of the CDRo data for 1950 and 1953-1969, and showed an association in terms of CDRo/CDRe = +.042, and in terms of CDRo-CDRe = 12.4 cancer deaths per 100,00 persons exposed within after fifteen to twenty years after the introduction of fluoridation in the experimental cities. *See National Cancer Program*, *supra* note 109, at 64-65. The main objection to this technique came from Dr. David Newell of the Royal Statistical Society in defense of the Upton Statement. He claimed that, because populations between census years and thus denominators in intercensal CDRs must be estimated by linear interpolation, they are not reliable data, and therefore not suitable for linear regression analysis. *See* Aitkenhead v. Borough of West View, No. GD-4585, Trial Transcript, May 8, 1978, at 72, 72A, 73-76 (Allegheny Court of Common Pleas, Pa). This criticism was exploded by none other than Dr. Guy Newell, Deputy Director of the NCI, who supervised preparation of the Upton Statement and introduced it before Congress. Later speaking as a professor of epidemiology at the University of Texas, he stated emphatically that use of linear interpolation to derive denominators in intercensal CDRs is accepted procedurein modern applied epidemiology, and, therefore, perfectly reliable. *See* Safe Water Found. of Texas v. City of Houston, No. 80-52271, Trial Transcript, Jan. 26, 1982, at 1648-54 (151st Jud. Dist., Tex.). The correctness of undertaking a linear regression analysis of intercensal CDRs in which the denominators were estimated by linear interpolation was further confirmed by Dr. Hubert Arnold, professor of statistics at the University of California, Davis. *See National Cancer Program, supra* note 109, at 580. The propriety and necessity of such use of interpolated data, based on fundamental principles of inductive logic, is discussed in Burk & Graham, *supra* note 108, at 68-69, and Burk, Graham, & Morin, *supra* note 108, at 143-44.

CDRe (-F)	140 3	155 5	155 5	166 0
CDRo/CDRe (-F)	1 094	1 166	1 181	1 137
CDRo-CDRe (-F)	13 2	25 8	28 1	22 8

The change in CDRo/CDRe = [(1.274-1.137) – (1.268-1.181)] + [(1.204-1.094) – (1.238-1.166)] = +.088. This coefficient means that, relative to what might be expected in light of the demographic structure of the two populations here in question, adjusted cancer mortality grew about 9% faster in the fluoridated cities.

In terms of CDRo-CDRe, fluoridation is associated with [(47.9-22.8) – (39.4-28.1)] + [(26.1-13.2) – (34.9-25.8)] = 17.6 excess cancer deaths per 100,000 persons exposed after 15-20 years.

Burk and Yiamouyiannis reported 17.6 additional cancer deaths per 100,000. Apparently Black males have a higher cancer rate than White males. Returning to Burk's data and correcting for race might show a further increase.

Crnosija et al, (2019)[111] "We found no evidence of an association between community water fluoridation category and secondary bone cancer from 2008 to 2010 at the county level in New York State."

Although we know fluoride exposure causes cancer, there is much we don't know. How much fluoride causes each type of cancer? What chemicals have synergistic effects with fluoride in contributing or causing cancer? What age has the greatest risk for each cancer?

Based on cancer research, fluoridation must be considered a presumed a contributing carcinogen.

[111] Crnosija N, Choi M, Meliker JR. Fluoridation and county-level secondary bone cancer among cancer patients 18 years or older in New York State. Environ Geochem Health. 2019 Apr;41(2):761-768. doi: 10.1007/s10653-018-0170-4. Epub 2018 Aug 14. PMID: 30109528.

SPECIFIC CANCERS

A. **BONE CANCER**:

PHS 2015 notes about 100 unique comments regarding fluoride as a carcinogen. Of the many references provided to PHS 2015, they include nine references and dismiss carcinogenicity. Osteosarcoma is the singular cancer listed. PHS 2015 references:

1. PHS 2015 lists Bassin 2006 as reporting an association between [112]fluoride and osteosarcoma; although PHS 2015 does not go into specifics. The Bassin 2006 reported significant osteosarcoma rates for boys during growth spirts. The study was well done, going to each house and confirming the house had fluoridated water during the study period and was consumed. The study has not been refuted. The Bassin study is the only study to ever carefully consider the age-specific risk of fluoride exposure on cancer. When all ages are included, the evidence is concealed.

CHESTER DOUGLASS HISTORY:

DOUGLASS REPORTS NO ASSOCIATION: A team of Harvard scientists, led by
Dr. Chester Douglass, publish the preliminary findings of a large case-control analysis of fluoride and osteosarcoma (McGuire et al 1995). In the preliminary analysis the authors **report no association** between fluoride and osteosarcoma.

DOUGLASS REPORTS ELEVATED RISK: To the NIH, Chester Douglass

[112] Bassin EB et al, Age-specific fluoride exposure in drinking water and osteosarcoma (United States). Cancer Causes Control 2006;17:421-8

reports “all” of his analyses which assumed bottled water contains no fluoride found that fluoridated drinking water (>0.7 ppm) is associated with elevated, but not statistically significant, rates of osteosarcoma (because he compared two cancers). Douglass later expresses concern about the ramifications to water fluoridation from reporting that fluoridation is associated with an elevated, even if not statistically significant, rate of bone cancer:

“Because of the importance of the question at hand, we think the policy implications of reporting that the relative risk maybe higher than 1.5 would have consequences for fluoridation health policies.”

DOUGLASS REPORTS NO RISK: In 1995, 1998 & 2002 Douglass states that the study shows fluoridation has either no effect, or a slightly protective effect, on osteosarcoma rates.

DOUGLASS KNOWS THERE IS RISK: However, Douglass’s signature is on Bassin’s 2001 thesis using Douglass’s data which found a statistically significant increase in osteosarcomas.

DOUGLASS REPORTS NO RISK: In 2004, the National Research Council (NRC) begins a review of the safety of currently allowable levels of fluoride in drinking water. Douglass submits a summary of his fluoride/osteosarcoma study to the NRC, claiming no significant association between fluoridation and osteosarcoma. Douglass even cites Bassin’s study as one of 2 supporting references for this summary of no fluoride osteosarcoma association. Douglass fails to report that Bassin found a statistically significant, 5-to-7-fold risk of osteosarcoma among boys drinking fluoridated water a decade prior to their diagnosis of cancer.

Bassin et al published some of her thesis data in 2006. She reports that boys drinking fluoridated water during the ages of 6 to 8 have a five-fold increased risk of developing osteosarcoma during their teenage years:

“We observed that for males diagnosed before the age of 20 years, fluoride level in drinking water during growth was associated with an increased risk of osteosarcoma, demonstrating a peak in the odds ratios from 6 to 8 years of age.

All of our models were remarkably robust in showing this effect, which coincides with the mid-childhood growth spurt.For females, no clear association between fluoride in drinking water during growth and osteosarcoma emerged." [113]

The Bassin study is consistent with other studies. The fluoride carcinoma risk appears age and cell cycle dependent.

DOUGLASS ADMITS SOME ASSOCIATION: Douglass publishes a letter in the same issue in which he publicly discloses for the first time that he had found some associations between fluoride exposure and osteosarcoma in the (retrospective) dataset that Bassin analyzed.

DOUGLASS CAUTIONS AND PROMISE: Douglass states that he was unable to replicate these findings in a new (prospective) dataset, and thus cautions readers from making any conclusions based on Bassin's findings. Douglass notes, however, that he has yet to conduct an age-specific analysis on the prospective data. He notes though that he is planning on doing so. To quote:

"A parallel analysis of age-specific exposure to fluoride,especially during growth periods, is also being pursued byour study team in the second set of cases of our study.Accordingly, readers are cautioned not to generalize andover-interpret the results of the Bassin et al. paper and toawait the publications from the full study, before makingconclusions, and especially before influencing any relatedpolicy decisions." [114]

Note: As of April, 2015 Douglas, to our knowledge, has not published the agespecific analysis on the prospective data.

COMPLAINT AGAINST DOUGLASS: The Environmental Working Group filed a complaint of scientific misconduct with the National Institute of Health which

[113] Bassin EB, et al. 2006. Age-specific fluoride exposure in drinking water and osteosarcoma (United States). Cancer Causes & Control 17(4):421-8. May.)

[114] Douglass CW, and Joshipura K. 2006. Caution needed in fluoride and osteosarcoma study. Cancer Causes & Control 17(4):481-82. May.

launched an investigation run by Harvard University; however, EWG is reported to have not been contacted.

NO INTENT TO MISREPRESENT: Harvard issued a short, one page press release announcing that Douglass did not "intentionally misrepresent" the research. Well, the evidence was misrepresented.

DOUGLASS FAILS TO CORRECT HIS MISREPRESENTATIONS: Although Douglass was able to convince Harvard he did not "intentionally misrepresent" the evidence, the Board of Health must not miss the fact Harvard implied that he did misrepresent the evidence.

Kim/Douglass (2011) compares two cancers: Nineteen years after receiving his grant from the NIH to study a possible fluoride osteosarcoma connection, Chester Douglass publishes his first paper. Douglass failed, as promised in his 2006 [115]letter, to provide age-specific analysis. Instead, the Kim/Douglass study compares two cancers.

Although the paper concludes that there is no statistical significant difference in fluoride concentrations between the two cancers, a few flaws are noted here.

a. Kim/Douglass failed to address the title and stated purpose of their study and thus intentionally misled readers.

Kim/Douglas title is "Relation Between Bone Fluoride and Osteosarcoma." *"The purpose of this study was to evaluate whether fluoride levels in bone are associated with the occurrence of osteosarcoma."* [99]

Both title and purpose compare fluoride and osteosarcoma. The question in the title and purpose is crisp, clean and precise: "whether fluoride increases in osteosarcoma cases?" One would think after allegations of misrepresentation, Douglass would attempt to be "squeaky clear." Douglass again misrepresents

[115] Kim et al, Relation Between Bone Fluoride and Osteosarcoma, Fluoride 45(2)1422-150 April-June 2012. Abstract at http:// www.fluorideresearch.org/452/files/FJ2012_v45_n2_p142-150_sfs.pdf. And article at Kim FM, Hayes C, Williams PL, Whitford GM, Joshipura KJ, Hoover RN, Douglass CW, National Osteosarcoma Etiology Group, J Dent Res. 2011 Oct;90(10):1171-6. [99] IBID Introduction

his stated title and stated purpose of the study by comparing two cancers rather than healthy bone fluoride concentrations with osteosarcoma bone fluoride concentratons.

"In this study, cases were all recruited from academic referral centers for bone cancer and thus were not a random sample of osteosarcoma patients. Controls were also bone cancer patients recruited from these same centers. . ."

In other words, two different "cancers" were compared. The question of whether there is a *"Relation Between Bone Fluoride and Osteosarcoma"* as stated in the title, was not evaluated and misrepresented.

Although, the PHS 2015, p 7, appropriately gave more weight to actual measured bone fluoride concentrations than estimates of exposure, the PHS 2015 committee apparently failed to understand the "controls" were also cancer cases.

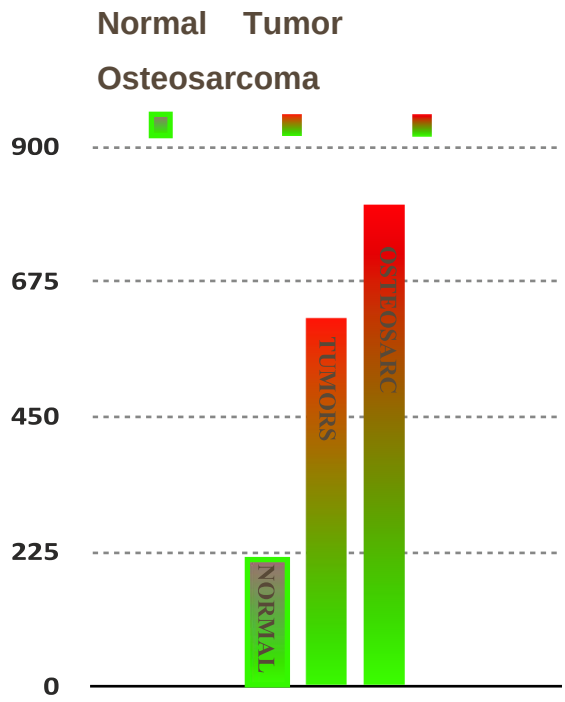
PHS 2015 falsely claims,*"The study (Kim/Douglass) assessed fluoride exposure using actual bone fluoride concentration —a more accurate and objective measure than previous estimates based on reported fluoride concentrations in drinking water at locations in the reported residence history. The later study (Kim/Douglass) showed no significant association between bone fluoride levels and osteosarcoma risk.*"

We provide here an example of what Kim/Douglass should have included in his study and the PHS 2015 committee assumed Kim/Douglass presented.

Suzuki's[116] normal 19 year olds at 202 ppm bone fluoride are graphed with Kim/Douglass 17 yr old tumor cases at 611.0 ppm and osteosarcoma cases at

[116] We use Suzukis normal,for low fluoride exposure normals. Bone fluoride samples with 1 ppm fluoride in the water results in about 400 ppm bone fluoride concentration and is not a low dose normal.

804 ppm bone fluoride concentrations[117][118]



Suzuki's 19 yr old normals vs Kim's 17 yr old cases

[117] Douglasss tumor-adjacent bone and Iliac crest fluoride concentrations had higher Iliac fluoride concentrations (median 558.0 vs

[118] .5) we can reasonably compare Douglasss Illiac cases with Suzukis normal Illium, 212. Douglass found, *There was no significant difference in the median fluoride concentration in bone between the matched osteosarcoma case and tumor control pairs (N = 32) (median = 804 vs. 714 mg F/kg of bone ash, p = 0.63) (Fig., c)*

Compare the ppm fluoride bone concentration F bone concentration

Suzuki 1979 Normal 19 year old = 212 ppm

Richards 1994 Normal 20 year old 1 ppm F water = 463 ppm

Douglass osteosarcoma “matched cases” 17 year olds = 804 ppm
Douglass tumor “matched controls” 41 year olds = 714 ppm

Douglas all “controls (41 year old average) = 754 ppm

Douglass all “cases”(17 year old average) = 611 ppm

Without question, Douglass misrepresented the evidence to claim lack of statistical significance by comparing two cancers rather than health bone of similar ages with fluoride concentration in osteosarcoma bone.

Bone fluoride concentrations are significantly higher in tumor cases and osteosarcoma cases than bone fluoride concentrations in normal patients.

We submit the Richards “Normal” 20 year-olds with 1 ppm fluoride in the water is not an appropriate “control.” Artificial fluoridation is not a “normal” control to evaluate fluoridation. Suzuki’s “normal” is a more appropriate control because it is closer in age with the subjects and lower fluoride exposure.

In other words, osteosarcoma patients have four times the fluoride concentration of normal patients. Douglass knew that and cooked the evidence to protect fluoride, for which he received millions as editor of a toothpaste magazine.

Kim Douglass data is evidence fluoride is carcinogenic.

2. Kim/Douglass’s study was much smaller and weaker than Bassin’s: It had only 21 control subjects under age 30, a fifth the size of Bassin’s sample, and incapable of detecting the difference between two types of bone tumors. Even Kim/ Douglass admitted this serious limitation. Again, the PHS 2005 claim of no significant association between fluoride bone concentration and cancer is significantly flawed.

3. The Kim/Douglass controls were much older than the cases: Controls were median = 41 years and cases median = 18 yrs. Kim/Douglass references Eble et al 1992 who reported 22 ppm increase with each year of life,

Suzuki[119] found dry ash fluoride ilium for those under 19 years of age was 212 ppm[120] ash weight (M&F) and for 40-49 year olds averaged about 870 ppm ash weight, approximately a 400% increase in fluoride in 20 to 30 years (See Suzuki Table 2 and 3, average M&F)

Kim/Douglass using 41 year-olds for controls and <18 yr olds for cases should have resulted in a 400 ppm to 600 ppm higher bone fluoride concentration for the controls when adjusting for age alone.

Since fluoride builds up in bone with age, it is obvious that Kim/Douglas's attempt to compare mean age 41-year-old cohorts with mean age 18-year-old cohorts would have little chance of demonstrating significance. The fact that Douglass did not find higher bone fluoride levels in 18-year-old osteosarcoma cancer patients than 41-yearold non-osteosarcoma tumor cancer patients is significant evidence of a fluoride cancer connection. Although the authors claimed to have "adjusted for age" the adjustment of 1.32 is clearly not adequate and biased.

The PHS 2015 committee failed to consider Kim/Douglas statement, *"For example, if risk is related to exposures at a specific time in life, rather than total accumulated dose, this metric would not be optimal."* Human and animal studies found osteosarcoma age dependent and those studies failing to consider age or race have generally failed to find a connection.

4. Actual tumor bone fluoride concentration was not measured: *"Given that bone at the tumor site was destroyed as a result of the tumor, tumor-adjacent bone was analyzed for fluoride content."* Limitations of harvesting bone required an assumption to be made that adjacent bone of the cohort had the same fluoride concentration. This

[119] Suzuki, Y, The Normal Levels of Fluorine in Bone Tissue of Japanese Subjects, Tohoku J. exp. Med., 1979, 129, 327-336.

[120] The two more recent studies referenced by Douglass reported nearly double the fluoride concentration as normal,reflecting increased fluoride exposure.

assumption could also be significant. The proliferation of cells in cancer and tumors are generally more rapid than normal tissue. A more rapid bone growth would attract more calcium and fluoride, perhaps "pulling" or accepting the fluoride from adjacent bone which is turning over. The 15% difference in median F/kg of bone ash between osteosarcoma and tumor control pairs was deemed non-significant. The authors note, *"Also, it is possible that fluoride concentrations in bone may be influenced by the disease, or that concentrations in tumor tissue are not representative of pre-disease levels."*

5. Only 25% of cases had matched controls.

7. Conflict of Interest: The data was supervised in part by Chester Douglass who works for GlaxoSmithKline, Colgate- Palmolive, Dentsply, Quintile, Delta Dental Plans, and USPHS. All of these have strong profit motives for proving fluoride exposure is safe. The study was funded by the NIEHS, NIH grant 5R01ES06000 and NIDCR NIH grant T32DE07151and the non-confidential raw data should be available to NIEHS for review and public evaluation.

Douglass was given good tax payer money to publish reasonable research and he promised to provide age-specific data which he has not done. NTP should have considered probable bias with someone heavily invested with fluoride product manufacturers, prior to awarding him money. NTP must take legal action to gain access to the data for their review.

Thiessen's Review of Kim et al. (2011), (Referenced in PHS 2015 as evidence of safety).

"The paper by Kim et al. (2011) is part of the Harvard osteosarcoma study. The paper describes a comparison of bone fluoride levels in cases of osteosarcoma and a set of controls. The authors report no significant difference in bone fluoride levels between cases and controls and no significant association between bone fluoride levels and osteosarcoma risk.

“To give some context it is important to know that an earlier part of the Harvard osteosarcoma study, namely the work of Bassin et al. (2006; based on a 2001 dissertation by Bassin 2001), reported an association between age-specific fluoride exposure and risk of osteosarcoma, with the highest risks for childhood exposure for young males. Bassin's study involved 103 cases under the age of 20 (median age, 13.7) and 215 matched controls (median age, 14.5; matching based on age, gender, and distance from the hospital) from the orthopedics departments of the same hospitals. Cases were diagnosed between November 1989 and November 1992. Bassin estimated fluoride exposure from drinking water and fluoride supplements or rinses for each participant, for each year of life, based on residential histories. Bassin et al. describe the limitations of their study and point out that additional studies with larger numbers of osteosarcoma patients, with incidence under age 20, that examine age-specific and sex-specific associations are required to confirm or refute the findings of the current study.

“The NRC report (NRC 2006, pp. 329-330) was published shortly before the Bassin et al. paper appeared, but included an analysis of Bassin's dissertation (2001), which reported essentially the same findings. The NRC also reported a personal communication from C. Douglass of the Harvard School of Dental Medicine, describing a second study involving 189 cases and 289 controls. This study was said to include residence history, detailed interviews about water consumption, and fluoride assays of bone specimens and toenails of all subjects. The NRC committee was told that the preliminary results indicated no statistically significant association with fluoride intakes and that the results were expected to be reported in the summer of 2006. The NRC report describes some concerns about possible bias (in either direction) in the selection of controls and the expectation that the study could have limited statistical power to detect a small increase in osteosarcoma risk due to fluoride exposure.

“When Bassin's work was published (Bassin et al. 2006), the same issue of the journal contained a letter to the editor by Douglass and Joshipura (2006), both of whom were coauthors on an earlier paper describing Bassin's exposure analysis (Bassin et al. 2004). This letter mentioned that preliminary findings from the second set of cases did

not appear to replicate the earlier work (Bassin's study) and indicated that their findings, which were "currently being prepared for publication," did not suggest an overall association between fluoride and osteosarcoma. It also indicated that both a fluoride intake history and a bone specimen were being obtained for each participant, and that their preliminary analysis indicated that the fluoride content of the bone was not associated with excess risk of osteosarcoma. However, this letter provided no data and therefore constitutes no more than an opinion.

"The paper by Kim et al. (2011) was submitted to the Journal of Dental Research in January 2011 and published electronically in late July 2011. No mention is made of why it took 5 years from the time Douglass and Joshipura indicated that their findings were "currently being prepared for publication." Nor is it obvious why the paper was published in a dental journal, when it does not deal directly with anything related to dentistry. Other recent papers that include some of the same coauthors (specifically, C. Douglass and R.N. Hoover) have been published in cancer research journals, (e.g., Savage et al. 2007; Mirabello et al. 2011a,b,c), as was Bassin's work (Bassin et al. 2006).

"Kim et al. (2011) describe a study involving 137 cases (37 ages 0-14, 72 ages 15-29, 13 ages 30- 44, and 15 ages 45 and older) and 51 controls, with cases diagnosed between 1993 and 2000.

"Although there is mention of "orthopedic" controls (patients with benign tumors or non-neoplastic conditions), only "tumor" controls were in fact used. The selection of cases and controls was affected in part by the need to obtain bone specimens. The cases had a median age of 17.6 years, the controls, 41.3 years. Kim et al. report no significant difference in the median fluoride concentration in bone between matched osteosarcoma case and tumor control in 32 pairs where age matching was possible. In an unmatched analysis of all cases and controls, the median bone fluoride concentration was significantly higher in controls than in cases. The authors conclude that their study "did not demonstrate an association between fluoride levels in bone and osteosarcoma."

"The use of an individual measure of fluoride exposure (bone fluoride concentration) is important to note. However, as the authors themselves point out, "if risk is related to

exposures at a specific time in life, rather than total accumulated dose, this metric would not be optimal" (Kim et al. 2011). Bone fluoride concentration is a measure of cumulative fluoride exposure to the time of diagnosis and surgery. Given a "lag time" of at least 5 years between initiation and diagnosis of most cancer types, the bone fluoride concentration at time of diagnosis can be affected by fluoride exposures that occurred after the cancer was initiated. Most importantly, a bone fluoride concentration at time of diagnosis says nothing about fluoride exposure at specific ages, so it does not address the key finding of Bassin et al. (2006).

"The osteosarcoma cases analyzed by Kim et al. (2011) included 28 individuals aged 30 or older. The actual number of patients under 20 years old is not given, but was said to be too few to provide sufficient statistical power. Thus the cases analyzed by Kim et al. are not fully comparable to the cases analyzed by Bassin et al. While osteosarcoma obviously occurs in adults, the majority of cases occur in children and young adults (Sergi and Zwerschke 2008; Mirabello et al. 2011a,b,c; Savage et al. 2007); Kim et al. (2011) themselves indicate that osteosarcoma is more prevalent in individuals less than 20 years old. Kim et al. have not explained their justification for including older individuals, other than to have large enough numbers to do their statistical analyses. The possibility that different mechanisms are involved in pediatric and geriatric osteosarcoma has not been addressed.

"As mentioned, the controls were all patients with malignant bone tumors other than osteosarcoma, apparently because bone samples were more readily available for tumor controls than for other controls (Kim et al. 2011). Kim et al. point out that if "fluoride levels were related to bone cancer in general, the current study design would be unable to detect this. There is no published evidence of such an association." There also is no published evidence clearly demonstrating a lack of such an association. The one small finding that has been published (as part of an appendix to a Public Health Service report) was an excess of Ewing's sarcoma in fluoridated counties as opposed to nonfluoridated counties (Hoover 1991). This was explained as an artifact of the analysis. However, given the distinct lack of adequate analyses of fluoride exposure and

other types of bone cancer, the use by Kim et al. (2011) of tumor controls alone obviously has to be regarded with caution.

"Bassin et al. (2006) limited their analysis to 103 cases diagnosed before the age of 20 (median age 13.7) and used 215 orthopedic controls (median age 14.5). Kim et al. (2011) used a much broader range of ages among cases, together with a relatively small set of controls very different in age from the cases and who were themselves bone cancer patients. While there were apparently limitations in selecting controls who could provide bone samples, nevertheless, the result is that the analysis by Bassin et al. had a much better set of controls than did the analysis of Kim et al.

"Kim et al. (2011) report a higher median fluoride concentration of controls compared with cases, which they attribute to the older ages of the controls than the cases. Comparison of the distributions of bone fluoride concentrations between cases and controls (Figure, part D) indicates that the ranges are not greatly different. Given that the median age of the controls is more than twice the median age of the cases (41.3 vs. 17.6), the obvious conclusion is not a lack of association between fluoride exposure and osteosarcoma, but considerably higher average exposure (by a factor of 2) in cases and controls, in order to reach similar bone fluoride concentrations. Kim's 2007 dissertation, on which the 2011 paper is based, reports estimates of "median cumulative lifetime water fluoride" of 14.4 ppm year for the cases and 16.5 ppm year for the controls. These cumulative exposures together with the median ages of the two groups again indicate higher average fluoride exposure among cases than controls, by a factor of 2. Rather than refuting the work of Bassin et al., these findings by Kim et al. support an association between fluoride exposure and osteosarcoma.

"In order to obtain the estimates of median cumulative lifetime water fluoride, Kim had to develop the exposure histories for the individual cases and controls. In addition, her dissertation indicates that the exposure histories were available for the orthopedic (noncancer) controls. Douglass and Joshipura (2006) indicated that exposure histories were being obtained. Any meaningful comparison of Kim's findings with those of Bassin

et al. (2011) will require use of the individual exposure histories to look at exposures at various ages, as opposed to just the comparison of bone fluoride concentrations.

"As an incidental note, the bone fluoride concentrations reported by Kim et al. (2011, Figure) for both osteosarcoma cases and tumor controls, extend into the range reported for skeletal fluorosis (NRC 2006).

Also of note is that Kim et al. (2011) found that a history of broken bones was a significant predictor of osteosarcoma risk. An increased risk of bone fracture has been associated with fluoride exposure in a variety of studies (e.g., NRC 2006; Alarcón-Herrera et al. 2001; Danielson et al. 1992)."[121]

Thiessen's Review of Comber et al. (2011) (Comber et al was cited by the PHS 2015 recommendation as evidence fluoride is not carcinogenic and safe.)

"Comber et al. (2011) compare osteosarcoma rates in nonfluoridated Northern Ireland and in partially fluoridated Republic of Ireland, with the latter data divided between fluoridated and nonfluoridated areas. They report no significant differences in either age-specific or age- standardized incidence rates of osteosarcoma between fluoridated and nonfluoridated areas.

"Comber et al. also describe several limitations of their study, including uncertainty about fluoridation status of particular areas (the possibility of misclassification), the possibility that the place of residence at the time of diagnosis may not be an accurate proxy for lifetime exposure to fluoridated water, and the lack of an accurate measure of total fluoride exposure. Perhaps the most important limitation pointed out by Comber et al. is the relative rarity of the cancer and the correspondingly wide confidence intervals of the relative risk estimates. They estimate that the risk for a fluoridated population would need to be at least 1.7 times that of the nonfluoridated population (a 70% increase) for a statistically significant effect to be detected. In other

[121] Thiessen IBID Pages 12-14.

words, fluoride could cause a 50-60% increase in risk of osteosarcoma, and this study would not be able to detect it.

"With respect to using the place of residence at the time of diagnosis as a proxy for lifetime exposure to fluoridated water, Comber et al. point out that if fluoride exposure at a specific age is critical to osteosarcoma development (citing Bassin et al. 2006), use of the fluoride estimation at the time of diagnosis is less valuable. In other words, their analysis cannot evaluate the importance of age-specific exposure.

"With respect to the lack of an accurate measure of total fluoride exposure, the authors mention that at least one-third of fluoride intake is estimated to come from sources other than drinking water, citing tea, fish, and toothpaste as examples. The authors do not discuss the possibility that variability in total fluoride intake within the Irish populations could overwhelm differences between populations in fluoride intakes from drinking water alone.

"In summary, the paper by Comber et al. does not demonstrate an absence of a relationship between fluoride exposure and osteosarcoma, simply that any effect of fluoridated water (as opposed to total fluoride intake) is not large enough to detect by the methods employed."[122]

Review of Levy (2012)

Levy 2012. As evidence of fluoride's lack of carcinogenicity, PHS 2015 cites at 77, Levy 2012.

The Levy 2012 study concludes that water fluoridation in the U.S. is not associated with an increased risk of osteosarcoma. Levy 2012 use a notably crude measurement for determining fluoride exposure, the National Cancer Institute's SEER data, average fluoridation rate of the child's STATE of residence at the time of diagnosis rather than exposure a decade earlier.

[122] Thiessen IBID p. 12.

By contrast, when the NCI conducted its analysis of the SEER data in 1990 (in which NCI found elevated rates of osteosarcoma among young males in fluoridated areas), the NCI considered the fluoridation status on the COUNTY level — a smaller unit which is less prone to classification error. A study without significance is not proof of safety. The Levy study thus sheds little light on fluoride's possible relationship to osteosarcoma.

Blakey et al (2014) [123]

"The study objective was to examine whether increased risk of primary bone cancer was associated with living in areas with higher concentrations of fluoride in drinking water."

This is an ecological study where cases were obtained from cancer registries and fluoride levels in drinking water from regional companies, Drinking Water Inspectorate, and Scottish Water. The record does not show total fluoride exposure, supplements, blood, bone, urine or any other fluoride concentration measurement, nor whether the cohorts were actually drinking the water or swallowing toothpaste. *"Other sources of fluoride are not taken into consideration."*

In contrast with Bassin's 2006 study, cases with Blakey 2014 were divided into three age groups, 0-14, 15-29 and 30-49 years of age at diagnosis. Bassin's study used each year of life and contacted each water source to ensure the address while growing up actually received fluoride in the water (10% reporting error) and the subject lived in that location. Bassin found ingestion of fluoridated water during 6-8 years of age increased cancer several years later. By including all ages 0-14 in one group and 15-29 in another group, Blakey would have "watered down the evidence" and not account for the high risk growth spurts reported by Bassin. Blakey assumes fluoride consumption was consistent throughout the study time-frame.

[123] Blakey, K, Feltbower, R et al, Is fluoride a risk factor for bone cancer? Small area analysis of osteosarcoma and Ewing sarcoma diagnosed among 0-49-year-olds in Great Britain, 1980-2005. Int J Epidemiol. 2014 Feb; 43(1): 224-234.

Blakey 2014 reported, *"The monitoring data suggests that levels in some AF areas were much lower than 1 ppm. Indeed, 33% of AF WSZs were below 0.7 ppm. . . and 61% of AF SAUs had such a level. This suggest that 35% of populations residing in AF areas were being supplied with AF water dosed below the optimal level."*

Blakely 2014 states, *"Furthermore, although the overall results contradict those from Bassin's study, the use of total accumulated fluoride dose rather than a specific time in life course prevents any direct comparisons being made."*

Osteosarcoma is a rare cancer (Blakely 2.64/million) and unless a study is carefully controlled, the data can be easily diluted, negating significance.

Blakely's Table 1 is produced here for the purpose of understanding the importance of age. In this study, an increase in osteosarcoma is evident during 15-29 years of age and over 49 years of age. Studies must include age and measured fluoride serum, urine, and bone concentrations. Perhaps the rate of bone turnover is reduced during middle age. Fluoride accumulates with time and seniors have higher bone fluoride concentrations perhaps triggering risk.

Age-group (years)	Number of osteosarcoma cases			Number of Ewing sarcoma cases		
	Males	Females	Total	Males	Females	Total
0-14	406	411	817	356	303	659
15-29	821	494	1315	516	284	800
30-49	266	168	434	116	75	191
0-49	1493	1073	2566	988	662	1650

Gelberg et al (1994)

The PHS 2015 failed to consider Gelberg KH. (1994) reporting, *"When fluoride exposure*

increases, the following bone responses generally occur: 1) an increase in the number of osteoblasts, 2) an increase in the rate of bone formation, 3) an increase in the serum activity of alkaline phosphatase, and 4) an inhibition of osteoblastic acid phosphatase… The increase in osteoblast proliferation and activity may increase the probability that these cells will undergo malignant transformation."[124]

The case-control study by Gelberg, published first as a PhD dissertation (Gelberg 1994) and then later in two peer-reviewed journals (Gelberg 1995, 1997), may represent the most substantive study on fluoride/osteosarcoma previous to Bassin's 2001 analysis.

While Gelberg has errors, such as stating cases were females when they were males, and reversing cases and controls in the "Total Fluoride" and "Toothpaste" categories in Tables 2 and 3, primary concerns with Gelberg's work relates to the methods used to analyze her data.

Gelberg uses data from NY Cancer Registry and state rather than county fluoridation rates. Gelberg, like Hoover 1991,[125] never analyzes her data with subjects divided into a simple two-category model: exposed versus unexposed, but rather quartiles.

However, for males the lower "quartile" group shows a borderline statistically significant increased risk OR of 2.8 (95%CI 1.0-8.1). For females the OR is even higher and statistically significant at 10.5 (95%CI 1.2-91). For both males and females in the higher "quartiles" of exposure, the ORs are no longer significant, but the risk for osteosarcoma generally stays above 1.0. If, instead of breaking the data into "quartiles", it had been broken into just "exposed" and "unexposed", it is quite possible the exposed group would have a significantly elevated risk for osteosarcoma compared to the unexposed group.

In looking for other possible risk factors for osteosarcoma, Gelberg (1994) found that a history of exposure to dental x-rays was significantly related to the development of

[124] Gelberg KH. (1994). Case-control study of osteosarcoma. Doctoral Thesis, Yale University. p. 13.
[125] Hoover R.N., Devesa S.S., Cantor K.P., Lubin J.H., Fraumeni J.F. (1991). *Time trends for bone and joint cancers and osteosarcomas in the Surveillance, Epidemiology and End Results (SEER) Program. National Cancer Institute*. National Cancer Institute. In: Review of Fluoride: Benefits and Risks Report of the Ad Hoc Committee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs US Public Health Service.

osteosarcoma (OR 4.0; 95%CI 1.3-12) . Dental x-rays were, in fact, one of the few variables Gelberg examined that had an effect reaching statistical significance.

However, increased dental x-rays would indicate possibly more frequent dental visits which indicate more frequent topical applications of fluoride (22,300 ppm fluoride) in the dental office. The efficacy of fluoride varnish is mixed, and risks have not been studied.

Bassin 2006; Cohn 1992; Hoover 1991 are consistent with the National Toxicology Program's (NTP) cancer bioassay which raised concerns that fluoride-treated male rats had a dose-dependent increase in osteosarcoma. (Bucher 1991). Although a number of studies including PHS 2015 citations have failed to detect an association between fluoride and osteosarcoma, none of these studies have measured the risk of fluoride at specific windows in time, which is the critical question with respect to fluoride and osteosarcoma.

A report by the National Academy of Sciences (NAS), titled "Drinking Water and Health", expresses concern about a possible connection between water fluoridation and osteosarcoma in young males:

"There was an observation in the Kingston-Newburgh (Ast et al, 1956) study that was considered spurious and has never been followed up. There was a 13.5% incidence of cortical defects in bone in the fluoridated community but only 7.5% in the non-fluoridated community… Caffey (1955) noted that the age, sex, and anatomical distribution of these bone defects are `strikingly' similar to that of osteogenic sarcoma. While progression of cortical defects to malignancies has not been observed clinically,it would be important to have direct evidence that osteogenic sarcoma rates in males under 30 have not increased with fluoridation."(NAS 1977)

b. Concerns with 1990 NTP Review of Fluoride

Despite criticism, the NTP maintains their assessment of "equivocal evidence." In 1991, NTP scientists publish a paper which concludes:

"The current findings are weakly supportive of an association between sodium fluoride administration and the occurrence of osteosarcomas in male rats, but are not conclusive…[I]n view of the widespread exposure of the population to fluorides from a

variety of sources it would appear prudent to re-examine previous animal and human epidemiologic studies, and perform further studies as needed to evaluate more fully any possible association between exposure to fluorides and the occurrence of osteosarcomas of bone."[126]

NTP 1990 review comments on page 10, include:

1. "Dr. Ashby, the second principal reviewer, agreed with the conclusions. However, he considered the definition for equivocal evidence of carcinogenic activity to be insufficiently precise for male rates. . . ." He suggested: "Taken together the current findings are inconclusive, but are weakly supportive of an association between sodium fluoride administration and the occurrence of osteosarcomas in male rats."

2. Dr. Silbergeld, "pointed out that the doses used were not orders of magnitude above human exposure levels. She supported further research on genotoxicity and on mechanisms of sex differences seen."

3. Dr. Gold noted that this was an unusual study in that there was not a zero control group."

4. "There was discussion by Dr. McKnight with Dr. J. Haseman, NIEHS, as to why data from paired (age-matched) controls were not used in primary data tables.

5. Dr. Zeise "reiterated the need expressed by other Panel members for designing another study with higher top doses. Dr. Zeise noted that the fluoride concentrations in high-dose rats were within the range observed in humans and the differences in pharmacokinetics and deposition of fluoride in bone between humans and animals should be studied."

6. Dr. Yiamouyiannis said, "a dose-dependent relationship between fluoride and the number of male rats with oral squamous cell tumors and a dose-dependent relationship between oral squamous cell metaplasia In tumors in female rats

[126] Bucher JR, et al. (1991). Results and conclusions of the National Toxicology Programs rodent carcinogenicity studies with sodium fluoride. International Journal of Cancer 48(5):733-7. July 9.

along with the increased incidence of osteosarcomas in male rats supported a finding of clear evidence of carcinogenic activity of fluoride in rats."

7. Those representing dentists and industry objected to the conclusions.

When fluoride damages DNA, is the damaged DNA make the offspring more susceptible to cancer? With the current research, objection to the NTP study should also be made to the lack of a "life-time" exposure from preconception with parents, throughout life of the offspring. Starting the rats and mice at 5 and 4 weeks of age in the NTP study, did not demonstrate the effects of the fluoride on sperm, egg, fetus, and during a major growth period of their early lives.

Downgrading by NTP of non-bone tumors (liver, oral, and thyroid) found with increased incidence among the fluoride-treated animals is controversial.

Concerns with NTP study: The journal Chemical & Engineering News reports:

"A number of other government officials who asked not to be identified also have told C&EN that they have concerns about the conclusions of the NTP study. They, too, believe that fluoride should have been placed in the "some evidence" category, in part because osteosarcoma is a very rare form of cancer in rodents."

Cancer diagnosis upheld: Battelle's diagnosis of hepatocholangiocarcinoma was upheld by the scientist (Dr. Melvin Reuber) who first identified hepatocholangiocarcinoma as a distinct cancer. As noted by EPA toxicologist Dr. William Marcus:

"Melvin Reuber, M.D., a board certified pathologist and former consultant to EPA and part time EPA employee, reviewed some of [the] pathology slides and the Batelle report. . . . [Reuber] first published the work that identified hepatochangiocarcinoma as a

pathologic entity. . . . Dr. Reuber reviewed the pathology slides and stated that these lesions are indeed hepatocholangiocarcinoma."[127]

Despite Reuber's concurrence, the NTP ultimately downgraded the hepatocholangiocarcinoma finding. The NTP did so through a two-step process. First, NTP's "Quality Assurance" pathogist reclassified them as hepatoblastomas (another form of liver cancer). Then, while conducting their statistical analysis, NTP reclassified the hepatoblastomas as hepatocarcinomas – a more common form of tumor. Because there was no significant increase in hepatocarcinomas among the fluoride-treated animals, the NTP concluded that there was no effect.

The NTP has issued the following statements about this analysis:

"During the pathology review procedures several of the tumors diagnosed originally as hepatocholangiocarcinomas were considered more apppropriately callled hepatoblastomas."[128]

"The study pathologist (Battelle) diagnosed hepatocholangiocarcinomas in one special control female, one low dose male, one low dose female, one medium dose male, three high dose males, and three high dose females. The QA (Quality Assurance) pathologist confirmed the presence of these tumors but felt that most of them were more appropriately diagnosed as hepatoblastomas."[129]

"The incidences of liver neoplasms in all groups of dosed and control male and female mice were higher than incidences previously seen in NTP studies, but did not appear related to chemical treatment. Several hepatoblastomas and hepatocholangiocarcinomas were diagnosed in male and female mice. Hepatoblastoma and hepatocholangiocarcinoma of mice are phenotypic variants of hepatocellular

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[127] Marcus W. (1990). Memorandum from Dr. William Marcus,to Alan B. Hais, Acting Director Criteria & Standards Division Office of Drinking Water, US EPA. May 1, 1990.

[128] Bucher J. (1990). Testimony at Board of Scientific Counselors, National Toxicology Program; Peer Review of Draft Technical Report of Long-Term Toxicology and Carcinogenesis Studies and Toxicity Study, Sodium Fluoride; Research Triangle Park, North Carolina, Thursday, April 26, 1990.

[129] Hamilton BF. (1989). Carcinogenesis bioassay of sodium fluoride with dosed water in B6C3F1 mice: Quality Assessment Narrative. Experimental Pathology Laboratories, Inc. p. 26-27.

carcinoma with characteristic cell types and morphologic patterns. The hepatoblastomas contained a cell population which resembled embryonal liver cells as well as neoplastic cells characteristic of a typical hepatocellular carcinoma, whereas the hepatocholangiocarcinomas exhibited both hepatocyte and biliary differentiation. As phenotypic variants of hepatocellular carcinoma, the incidences of these neoplasms were combined with the other hepatocellular neoplasms for analysis. The appearance of these phenotypic variants in dosed animals is unusual, and the biologic significance, if any, is unknown."[130]

Summary of NTP 1990 study by LANCET:

"The original study was directed from 1985 to 1987 by Dr John D. Toft II, manager of the pathology section at Battelle Memorial Institute in Columbus, Ohio. The Battelle study's principal finding was the occurrence of an extremely rare liver cancer, hepatocholangiocarcinoma, in male and female mice. In 1989, the NTP asked Experimental Pathology Laboratories, of Sterling, Virginia, to review Battelle's data. At this point, the liver cancer finding, along with a diagnosis of metaplastic and precancerous cells in the mouths of rats, was downgraded.

The only effect of fluoride that was left after these reclassifications and still another review by a board of pathologists and others was osteosarcoma. Dr Marcus believes the Battelle diagnosis of liver cancers was sound and should have been included in the NTP report. This, he says, would change "the (NTP) equivocal finding… to at least some evidence or clear evidence of carcinogenicity".

NTP's failure to emphasize another finding also figured in Dr Marcus' critique. Three out of four in-vitro tests, he says, proved fluoride to be mutagenic, "supporting the conclusion that fluoride is a probable human carcinogen". A careful reader can find this information in the text of the report, but the authors make no mention of these data in their conclusions."[131]

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[130] Bucher JR, et al. (1991). Results and conclusions of the National Toxicology Programs rodent carcinogenicity studies with sodium fluoride. International Journal of Cancer 48: 733-737.

[131] Sibbison JB. (1990). USA: More About Fluoride. The Lancet 336(8717): 737. Sept 22.

Summary of NTP 1990 study by C&E News:

"The final report for the study was prepared by the NTP staff, but the testing itself was done by Battelle Columbus Laboratories under contract to NTP. A report prepared by Battelle was audited by a quality assurance contractor, and a separate group of pathologists reviewed the studies. In the process, a number of positive findings in the original Battelle report were downgraded. Slides first diagnosed as showing a rare form of liver cancer called hepatochlolangiocarcinoma were later said to indicate hepatoblastoma, another type of rare malignant lesion, and finally to show the far more common cancer hepatocarcinoma. These hepatocarcinomas were combined with the other hepatocarcinomas found in both treated and control animals, Marcus said. In addition, dose-dependent oral lesions noted in the Battelle report were downgraded from dysplasia and metaplasia to degeneration. Some other liver carcinomas were eventually reclassified as nonmalignant lesions. Because of what he calls systematic downgrading of the slides, Marcus has written a memo to the director of the criteria and standards division in the office of drinking water asking that EPA assemble an independent board of pathologists to review the slides again.[132]

Summary of NTP 1990 by Yiamouyiannis:

"In 1977, Congress instructed the U.S. Public Health Service to conduct animal studies to determine whether or not fluoride causes cancer. As a result, the National Toxicology Program retained the Battelle Memorial Institute in Columbus, Ohio to perform two studies, one on mice, and another on rats.

Doctor John T. Toft, II, manager of the Pathology Section at Battelle, was placed in charge of the NTP mouse study. On October 28, 1988, after a year of analyzing these results, Doctor Toft completed the pathology narrative and final report.

[132] Hileman B. (1990). Fluoride bioassay study under scrutiny. Chemical & Engineering News September 17

The most significant finding was the occurrence of an extremely rare form of liver cancer, hepatocholangiocarcinoma in fluoride-treated male and female rats — mice, excuse me.

Among male mice, no such cancers were observed among 79 in the control group. At 11 parts per million, the lowest dose used, one was observed among 50 male mice; and 45 parts per million, one was observed among 51 male mice and at seventy-nine parts per million three were observed among 80 male mice.

Using historical controls and doing a binomial analysis of this, the odds of these results occurring by chance are less than one in two million. Normally, we consider it significant one in twenty; this is one in two million.

Making these findings even more convincing are the results with female mice. In the control group, no hepatocholangiocarcinomas were observed among eighty. At 11 parts per million, one was observed among 52. At 45 (ppm), none were observed among 50. And at 79 parts per million, three were observed among 80 female mice — female mice.

Based on these findings, and these findings alone, there was clear evidence of the carcinogenic activity of the fluoride in mice receiving 11, 45, or 79 parts per million in drinking water for two years or less."[133]

PHS confirms risk: The Public Health Service and NCI in 1991 report that the incidence of osteosarcoma throughout the U.S. has increased at a greater rate among young males in fluoridated areas vs. unfluoridated areas. The NCI, however, dismisses this result because of an inability to demonstrate a linear-dose relationship between the duration of fluoridation and the increased osteosarcoma incidence in fluoridated areas:

"In summary,analysis of incidence data from the SEER program has revealed some age- and sexspecificincreases over time for bone and joint cancers, and for osteosarcomas, which are more prominent in fluoridated than in non-fluoridated areas.

[133] Yiamouyiannis J. (1990). Testimony before Board of Scientific Counselors, National Toxicology Program; Peer Review of Draft Technical Report of Long-Term Toxicology and Carcinogenesis Studies and Toxicity Study, Sodium Fluoride; Research Triangle Park, North Carolina, Thursday, April 26, 1990.

However, on further analysis these increases are unrelated to the timing of fluoridation, and thus are not linked to the fluoridation of water supplies." (Hoover 1991) Proof of harm is required rather than proof of safety.

Calabrese[134] 1993 was requested by the East Bay Municipal Utility District to conduct an independent appraisal of the 1990 NTP report. He found the NTP's choice of the word "equivocal" to be confusing, inappropriate and not consistent with what most people would call equivocal, for the following reasons:

1. Its own definition of equivocal is in disagreement with the generally accepted definition of equivocal.

2. The findings with the male rat clearly exceeded marginal increases and are biologically plausible given the capacity for fluoride to both concentrate and be biologically active in bone.

3. The statistical analysis for trend effects is stronger than pair-wise comparisons since it uses all available data not just data from two comparison groups, yet this point is never acknowledged.

4. The basic reality is that humans can be exposed in critical target tissues to as much fluoride as the high dose rats while consuming water at the EPA maximum contaminant level of 4 mg/liter.

Procter and Gamble:

Procter & Gamble, releases the findings of its own rat study of fluoride and cancer they conducted between 1981-1983. While Procter and Gamble's study finds several bone tumors in the fluoride-treated animals (versus none in the controls), the results do not achieve statistical significance and Proctor & Gamble's scientists dismiss them as random. According to the published report:

[134] Calabrese, EJ, Lee, JR, Evaluation of the National Toxicology Program (NTP) Cancer Bioassay on Sodium Fluoride, Fluoride 26 (1) 1993 Accessed 4/25/15 http://www.fluorideresearch.org/261/files/FJ1993_v26_n1_p001-078.pdf

"All bone neoplasms were considered to be incidental and spontaneous and not related to fluoride treatment, because of their low incidence and random distribution"[135]

In 1991, the FDA publishes a review of Procter & Gamble's rat study. The FDA identifies two additional osteosarcomas in the fluoride-treated rats which were not identified in Procter & Gamble's published report. The FDA states:

"The adequacy of the gross examination at necropsy was questioned based upon the rat tumors that were not identified by the contract (Procter & Gamble) laboratory" (FDA 1991).

The FDA notes that the incidence of bone tumors in the Procter & Gamble study still do not achieve statistical significance. The FDA thereby concurs with Procter & Gamble that the bone tumors are incidental.

Contributes to Osteomas: Maurer 1993, the FDA also reviews Procter & Gamble's mouse study. Among both sexes of the fluoride-treated mice, there is a significant, dosedependent increase in osteomas, although no osteosarcomas. The occurrence of the osteomas is believed to be related to the presence of a virus in the mice; however, the FDA finds:

"Active virus was found in the osteomas but not in animals that did not have osteomas. It is clear, nonetheless, that if [the virus] had a role it was only in the presence of fluoride."

Known Osteosarcoma Association: Cohn 1992. The New Jersey Department of Health conducts a study of osteosarcoma occurrence in Central New Jersey, "An Epidemiologic Report on Drinking Water and Fluoridation." The study finds a statistically significant relationship between fluoridation and osteosarcoma among males less than 20 years old:

"Recently, a national study of drinking water fluoridation at the country level found a significant association with osteosarcoma incidence among males under 20 years of

[135] Maurer JK, et al. 1990. Two-year carcinogenicity study of sodium fluoride in rats. Journal of the National Cancer Institute 82(13): 1118-26. July 4.

age (Hoover et al., 1991). However, the meaning of the association was questioned by the authors because of the absence of a linear trend of association with the duration of time for which the water supplies were fluoridated… As a follow-up to the study by Hoover et al., a small study of similar design was initiated by the New Jersey Department of Health to compare drinking water fluoridation at the municipal level with the municipal residence of osteosarcoma cases at the time of diagnosis…The study observed an association between fluoridation of water and osteosarcomas among males under 20 years of age in seven Central New Jersey counties."

Known Carcinogenic: Lee[136] 1993 Reported 6.9 times higher osteosarcoma incidence for males aged 10-19 years old when comparing fluoridated and non-fluoridated seven counties in the central New Jersey area.

Known Carcinogenic: Yiamouyiannis, 1993, analyzes the National Cancer Institute's data in addition to two other databases containing fluoride exposure/ osteosarcoma information. Like NCI's investigators (Hoover 1991), Yiamouyiannis finds osteosarcoma rates to be higher among young males under 20 in fluoridated versus unfluoridated areas. To quote:

"Recent studies showing substantial increases in the incidence of bone cancer and osteosarcoma in males (but not females) exposed to fluoride gave us the unique opportunity of using females as a control group to determine whether there is a link between fluoridation and bone cancer in males. Using three different data bases, we found that

1) *the bone cancer incidence rate was as much as 0.95 cases a year per 100,000 population higher in males under age 20 living in fluoridated areas;*

2) *the osteosarcoma incidence rate was 0.85 new cases a year per 100,000 population higher in males under age 20 living in fluoridated areas; and*

[136] Lee JR Fluoridation and Bone Cancer, Fluoride, Vol.26. No.2 1993 Accessed 4/25/2015 http://www.fluorideresearch.org/262/files/FJ1993_v26_n2_p079-164.pdf

3) *for males of all ages, the bone cancer death rate and bone cancer incidence rate was as much as 0.23 and 0.44 cases higher per 100,000 population, respectively, in fluoridated areas.These findings indicate that fluoridation is linked to an increase in bone cancer and deaths from bone cancer in human populations among males under age 20 and that this increase in bone cancer is probably all due to an increase in osteosarcoma caused by fluoride."*

Genotoxic Mihashi 1996 report fluoride isgenotoxicto rat bone. The authors note that the fluoride-induced genotoxicity in bone reinforce the biologic plausibility of a fluorideosteosarcoma connection. The authors used the same type of rat (F344/N) used in NTP's cancer bioassay.

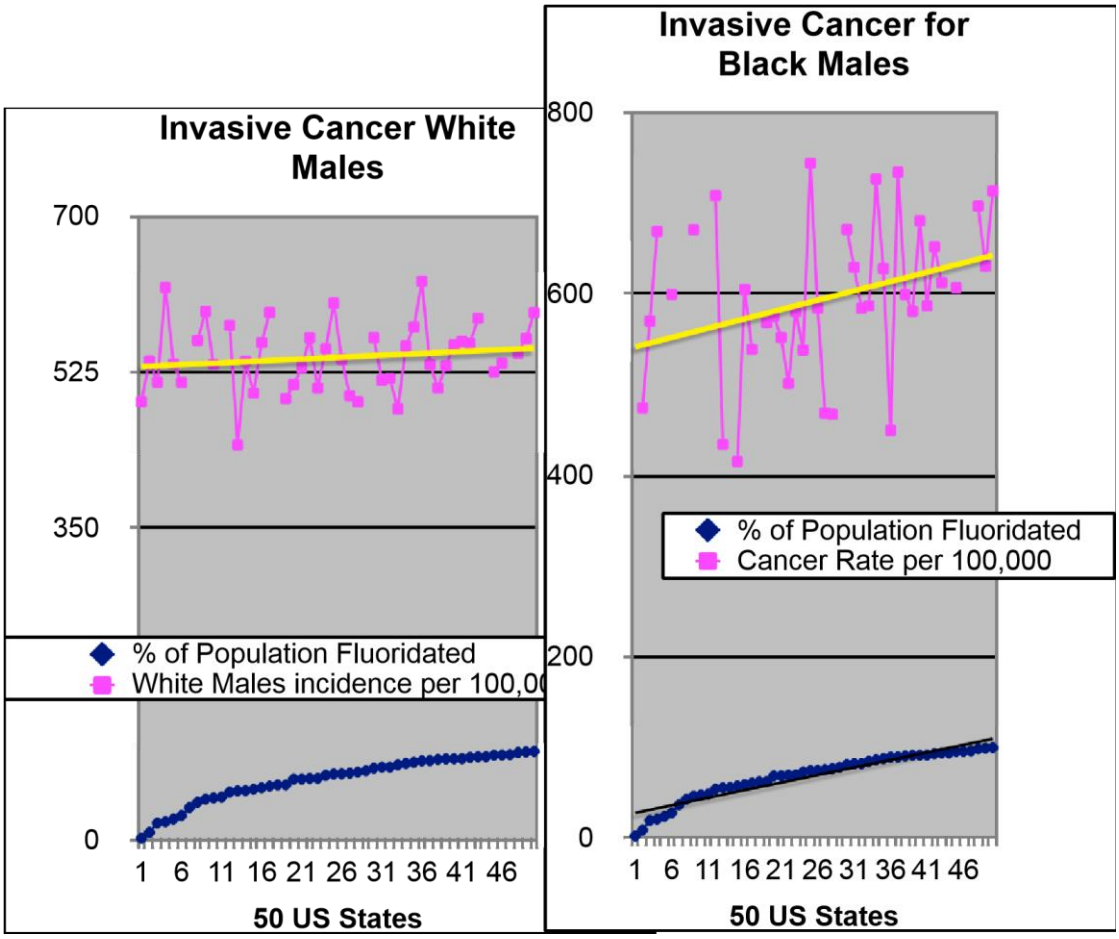
"Because the origin of osteosarcoma is considered to be osteoblastic/osteogenic cells,the ability of sodium fluoride to induce chromosome aberrations in these cells provides a mechanistic basis for the occurrence of osteosarcomas observed in sodium fluoride treated animals in the NTP study.Ingested fluoride is accumulated in bone, suggesting that osteoblastic/osteogenic cells in the bone microenvironment can be exposed to high levels of fluoride during bone formation.Our data and the NTP findings provide evidence that bone can be an organ for NaF carcinogenesis."[137]

B. BRAIN CANCER RATES

Ranking the 50 states on the percentage of whole population fluoridated,[138] the trend of increased cancer continues as graphed below, although Blacks appear to take the most significant hit. It is strange almost no studies look specifically at race and the fluoride cancer connection.

[137] (Mihashi M, Tsutsui T. (1996). Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. Mutation Research 368(1):7-13. May.)

[138] http://apps.nccd.cdc.gov/nohss/FluoridationV.asp pubs.usgs.gov/circ/2004/circ1268/htdocs/table05.html and http://pubs.usgs.gov/circ/2004/circ1268/htdocs/table05.html CDC for cancer data. Fluoridation data is used to determine the percentage of the whole population fluoridated in each state for graphs below.

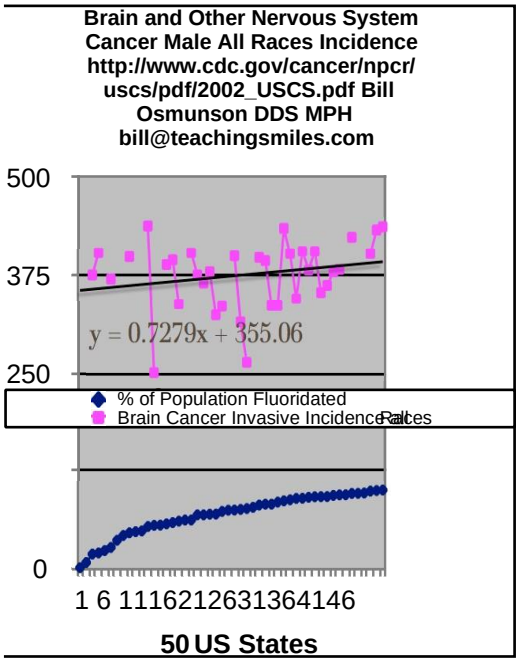


A similar comparison for Black women shows less increase. Perhaps fluoride affects the male chromosome more than female?

Considering that fluoride exposure has increased significantly in all states, an increase in White male cancer of perhaps 8%-10% and Black male cancer rates of perhaps 13%-15% is reasonably consistent with Burk's 17%.

Comparing states based on water fluoridation does not account for other sources of fluoride, age, diagnostic and treatment centers, toothpaste ingestion, whether a person is actually drinking the water and other confounding effects. The PHS 2015 suggests water fluoridation currently represents perhaps 14% of total fluoride exposure and comparing a 30% fluoridated state with an 80% fluoridated state would represent even less of a difference.

When we rank the 50 USA states on the percentage of the whole population fluoridated, a slight increase in brain cancer is found for males.[139] (Females did not show an increase)



Moolenburgh[140] 1994 "Tiel was fluoridated until late in 1973. After those twenty years the High Court of the Netherlands came to the conclusion that fluoridation of the water 125 supplies had been illegal all that time, and Tiel stopped adding fluoride to the drinking water.

Van den Berg wanted to know if differences in health had occurred between Tiel and Culemborg (not fluoridated) 20 years after the measure was stopped. She chose the people between 40 and 60 years of age, as these people had drunk fluoridated water from their birth onwards for twenty years. Of course only those people were taken into consideration who had lived in the two cities the whole of their lives (as happens frequently in the Netherlands). There was a surprising 40 and 46% response to the 14,200 enquiry forms that were sent out.

[139] Data for these graphs was obtained from the CDC fFact sheets on fluoridation and then corrected for whole populationof each state on public water. As of 4/25/15 this link was good http://apps.nccd.cdc.gov/nohss/FluoridationV.asp www.cdc.gov/cancer/npcr/uscs/pdf/2002_USCS.pdf 2002 cancer statistics still current as of 4/25/15 http://pubs.usgs.gov/circ/2004/circ1268/htdocs/table05.html Current 4/25/15 used to determine percentage of population on public water

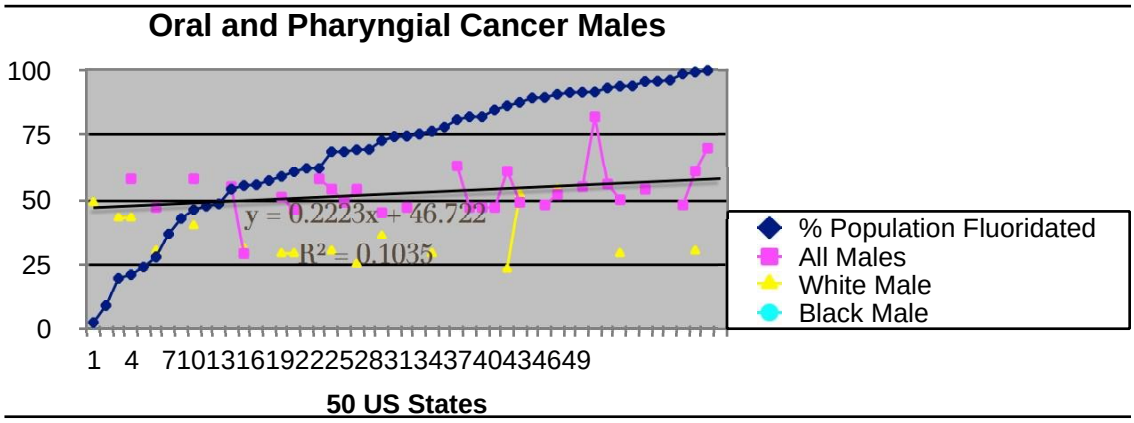
[140] Moolenburgh, H. MORE NEWS FROM TIEL AND CULEMBORG, Fluoride Vol. 28 No.2 119-122 1995 Letters to the Editor 119 Accessed 4/25/15 http://www.fluorideresearch.org/282/files/FJ1995_v28_n2_p119-122.pdf

Here are a couple results:

Brain and Nervous Diseases:		Fluoridated	Non-fluoridated
Women 51-55 years,	N=146	Tiel 18.6%	0% Culemborg 7.0%
Cancer:			
Women 56-60 years,	N= 109	Tiel 11.10%	Culemborg 3.10%

A more than tripling of cancer for women due to water fluoridation seems extreme based on other studies. The small sample might be a factor along with other confounding factors. However, the trend is consistent with a fluoride/cancer connection.

C. ORAL CANCER: Plotting the percentage of the whole population and oral cancer in the population at large for the 43 reporting states, we again see an increase trend, the higher the percentage of fluoridation, the higher rate of oral cancer. When consideration is given to the high fluoride concentrations in fluoridated toothpaste and fluoride varnish, the modest concentration of fluoride in water would seem insignificant. However, the fluoride in water is systemic and represents an additional chronic dosage.



Dentists frequently have office policies to give everyone additional fluoride without diagnosis, regardless of whether the patient has dental fluorosis, the science, FDA approval, total exposure, or any considerations other than the dental insurance

company pays. “Never want to put a rational thought in the way of a lucrative procedure.”

NTP (1990) *“A second potential target site for sodium fluoride when given in drinking water is the upper digestive tract and oral cavity. Squamous cell neoplasms of the oral mucosa (tongue, palate, or gingiva) occurred with marginally increased incidences in dosed males and female rats over the rates in controls. The increased incidences of these neoplasms were not statistically significant when compared with the incidences in concurrent controls; however, the incidences in the high-dose groups were significantly higher than the incidences observed in historical control animals (0.7% male rats; 0.6% female rats).*

“As with lesions of the bone, a direct comparison with the historical rates for oral cavity neoplasms is not completely accurate because of the increased attention given to the oral cavity and teeth in the sodium fluoride studies compared to previous NTP studies. Rates for oral cavity neoplasms similar to those observed in high-dose male and female rats in the sodium fluoride studies (4%) have been observed twice for males and once for females in the historical control database of 42 dosed feed or water studies. Neoplasms of the oral cavity were observed in control male and female rats in the current studies; one was observed in an age-matched control male rat and one occurred in a control female rat in the main study.

“*An argument could be made for combining the male and female rat studies for analysis of oral cavity neoplasms because a marginal increase occurred in both groups. An analysis for significance of the combined P values for the logistic regression trend tests for males and female rats resulted in a nonsignificant P value of 0.065.*

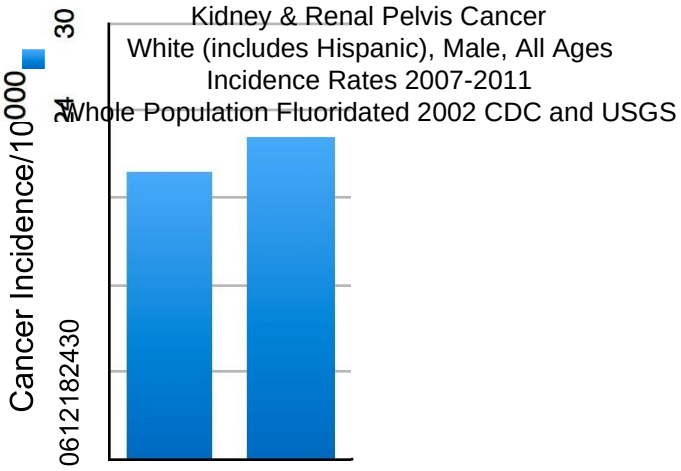
“In contrast to osteosarcomas, for which there are no recognized benign or preneoplastic counterparts (Litvinov and Soloviev, 1973), squamous cell hyperplasias of the oral cavity are considered preneoplastic precursor lesions of squammous cell neoplasms of the oral cavity (Brown and Hardisty, 1990). Squamous cell hyperplasia occurred in no more than one animal in any of the dosed or control groups in the current studies. Thus, based on the absence of statistical significance versus the concurrent

controls, the occurrence of these tumors in control animals, and the lack of a dose-related increase in non-neoplastic precursor lesions, it is concluded that there is insufficient evidence to relate tumors of the oral cavity with administration of sodium fluoride to male or female rats. Glattre and Wiese (1979) reported an association between a decrease in human mortality due to oral cavity neoplasia and increasing fluoride content in water over the range of 0 to 0.5 ppm."[141]

Research animals were not given fluoride varnish, fluoride toothpaste, fluoride medical and dental products and these other sources need to be included in research on a possible connection between oral cancer and fluoride.

[141] National Toxicology Program [NTP] (1990). Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats andB6C3f1 Mice. Technical report Series No. 393. NIH Publ. No 91-2848. National Institute of Environmental Health Sciences, Research Triangle Park, N.C. **p. 73-74.**

D. KIDNEY, RENAL PELVIS AND LUNG CANCER.



Comparing the 10 least fluoridated states with the 10 most fluoridated states, Kidney and Renal Pelvis Cancer we do find an increased cancer rate of cancer, graphed here. CDC reporting for race is not complete, yet.

Grandjean[142] 2004 reported on an extended followup on cancer morbidity for 422 male workers exposed for at least six months at a cryolite mill in Copenhagen. Over 90% of the workers have since died. 10 Least 10 Most The authors conclude that "fluoride should Fluoridated States be considered a possible cause of bladder cancer and a **contributory cause of primary lung cancer.**"

E. LIVER CANCERS:

Hepatic Neoplasm: Toft (1988) *"CONCLUSION:The feeding of sodium fluoride to B6C3F1 mice in their drinking water for 104 weeks at the stated doses resulted in the formation of an infrequently encountered hepatic neoplasm which, for purposes of this study, was diagnosed as hepatocholangiocarcinoma."*[143]

[142] Grandjean P, Olsen JH, EXTENDED FOLLOW-UP OF CANCER INCIDENCE IN FLUORIDE-EXPOSED WORKERS, Fluoride 2004;37(3):231238 Abstracts 231 http://www.fluorideresearch.org/373/files/FJ2004_v37_n3_p231-238.pdf

[143] J.D. Toft, II, D.V.M., M.S., Manager, Pathology Section, Battelle Columbus Laboratories. Final Report to National Toxicology Program, October 28, 1988.

Anamika (2012) *"From the present findings conclusion can be drawn that sodium fluoride can induce damage to the nucleic acids and protein content in mice liver, which can be effectively reversed by black tea infusion."*[144]

Yiamouyiannis comments on the NTP rat and mouse studies of the '80's. *"The most significant finding was the occurrence of an extremely rare form of liver cancer, heptocholangiocarcinoma in fluoride-treated male and female mice. . . . Using historical controls and doing a binomial analysis of this, the odds of these results occurring by chance are less than one in two million. Normally, we consider it significant one in twenty; this is one in two million."*

F.THYROID CANCERS:

NTP (1990) *"Follicular cell neoplasms of the thyroid gland appeared with a marginally increased incidence in high-dose male rats compared with controls.This increase is not statistically significant compared with controls unless control animals from both interim groups (27 and 66 weeks) and the agematched controls are pooled with the main study control group. If this is done, the logistic regression P value for the trend is 0.027.Thyroid follicular cell neoplasms typically occur with an incidence of 1.2% in historical control animals. Incidences of 6% have previously been observed in untreated control groups for gavage studies.The incidence of these neoplasms in the high-dose groups was 5/90 (5.5%;includes 10 animals from the 66-week interim sacrifice, one of which had a thyroid follicular cell carcinoma). Three of these tumors were adenomas. The incidence of carcinomas did no differ across the dosed groups and the incidence of follicular cell hyperplasia was not increased. No increase in the incidence of these*

[144] Anamika JHA, Komal S, RAMTEJ JV, Effects of Sodium Fluoride on DNA, RNA and Protein Contents in Liver of Mice and Its Amelioration by *Camellia Sinensis, Acta Poloniae Pharmaceutica* - Drug Research, Vol. 69 No. 3 pp. 551-555, 2012

tumors occurred in female rats. Based on these considerations, follicular cell neoplasms of the thyroid are not considered related to sodium fluoride administion."[145]

UTERINE CANCER: Tohyama (1996)[146] "The Okinawa Islands located in the southern-most part of Japan were under U.S. administration from 1945 to 1972. During that time, fluoride was added to the drinking water supplies in most regions. The relationship between fluoride concentration in drinking water and uterine cancer mortality rate was studied in 20 municipalities of Okinawa and the data were analyzed using correlation and multivariate statistics. The main findings were as follows. (1) A significant positive correlation was found between fluoride concentration in drinking water and uterine cancer mortality in 20 municipalities ($r = 0.626$, $p < 0.005$). (2) Even after adjusting for the potential confounding variables, such as tap water diffusion rate, primary industry population ratio, income gap, stillbirth rate, divorce rate, this association was considerably significant. (3) Furthermore, the time trends in the uterine cancer mortality rate appear to be related to changes in water fluoridation practices.

[145] National Toxicology Program [NTP] (1990). Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3f1 Mice. Technical report Series No. 393. NIH Publ. No 91-2848. National Institute of Environmental Health Sciences, Research Triangle Park, N.C. **p. 74.**

[146] Tohyama E. Relationship between fluoride concentration in drinking water and mortality rate from uterine cancer in Okinawa prefecture, Japan. J Epidemiol. 1996 Dec;6(4):184-91. doi: 10.2188/jea.6.184. Erratum in: J Epidemiol 1997 Sep;7(3):184. PMID: 9002384.

XI. ENDOCRINE SYSTEM HARM

NATIONAL RESEARCH COUNCIL 2006 "FLUORIDE IN DRINKING WATER: A SCIENTIFIC REVIEW OF EPA'S STANDARDS"

THYROID, PARATHYROID, PANCREAS, PINEAL, ADRENAL, GONADS, ENTEROENDOCRINE, PARAGANGLIA, PITUITARY, AND PLACENTA

NRC (2006) REPORT ON THE ENDOCRINE SYSTEM

FLUORIDE, IODINE AND GOITER.

SUMMARY: Fluoride is an endocrine disruptor.

Maximum fluoride intake goal <0.001 mg/kg/day (Based on Mother's Milk)

Hundreds of research articles have reported adverse effects of excess fluoride exposure including but not limited to arthritis, bone, tooth, brain, cancer, cardiovascular, diabetes, thyroid, parathyroid, pancreas, pineal, adrenal, gonads, enteroendocrine, paraganglia, pituitary, placenta, endocrine, GI, kidney, and reproductive harm.

Historically in Germany, physicians treated ADHD with sodium fluoride. The advice was to keep increasing the dose of fluoride until effective. Most ADHD medications contain fluoride. Manufacturers are careful to reduce the free fluoride from their medications and an estimate of only an average of 5% of the fluoride in the medications is retained.

Fluoride has effects throughout the body. Fluoride should be evaluated at the biochemical, cellular, and organ levels as well as synergistic toxic effects with a margin of safety for race, age, nutritional deficiencies, ill health of those most vulnerable, total exposure and unknowns. To protect the public, we must use a margin of safety from the lowest observed adverse effect and a factor of 100. We do a disservice to humanity and science when we compartmentalize evidence without

bringing the weight from all effects to the table for evaluation and judgment. In the end, judgment is required from a "global" perspective for all, not just the mean.

This nomination is for OHAT to evaluate fluoride as an endocrine disrupting toxicant and is supported by the NRC (2006) report to the EPA which labeled fluoride an "endocrine disruptor,"[147] as well as numerous studies,[148] reviews, and reasonable judgment.

The NRC (2006)[149] review members were tasked to determine "with absolute certainty" that research had demonstrated adverse effects---one member remembers the term, "bet the farm certainty". Such a high degree of certainty is not supported by Congress who requires the EPA to determine contaminate levels to be *"set at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety."* The committee unanimously "bet the farm" that fluoride is an endocrine disruptor.

The endocrine system includes all of the glands of the body and the hormones produced by those glands, such as anterior and posterior pituitary, thyroid, parathyroid, adrenal, gonads, islets of pancreas, pineal, enteroendocrine, paraganglia and placenta. The glands are controlled directly by stimulation from the nervous system as well as by chemical receptors in the blood and hormones produced by interaction with other glands. By regulating the functions of organs in the body, these glands help to maintain the body's homeostasis, such as cellular metabolism, reproduction, sexual development, sugar and mineral homeostasis, heart rate, and digestion. Research has only begun to glimpse into fluoride's effects on these systems; however, we have enough evidence to confidently state fluoride is

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[147] National Academies of Sciences, Engineering and Medicine 500 Fifth St. N.w. Washington, DC, 20001. Page 266 "Fluoride in Drinking Water: A Scientific Review of EPA's Standards."

[148] Such as Malin A, Till C, Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association. Environmental Health (2015) 14:17 and
Peckham et al, (2015) Centre for Health Services Studies, University of Kent, Canterbury, Kent, UK. J. Epidemiology Community Health do:10.1136/jech-2014-204971

[149] "Fluoride in Drinking Water: A Scientific Review of EPA's Standards."
http://www.nap.edu/catalog/11571/fluoride-in-drinking-water-a-scientific-review-of-epas-standards

an endocrine toxicant, a disruptor. Current research supports the NRC (2006) conclusion and provides greater evidence to establish a least observable effect with margin of safety. The question is no longer whether fluoride is safe, the question is "like lead, is any dosage of fluoride is safe for everyone?"

This nomination should not be taken in isolation without also reviewing the studies in our nomination on cancer and neurotoxicity previously submitted. The endocrine system is closely connected to the neurological system such as through neurosecretors which release neurotransmitters into the blood through extracellular fluids. We may consider three major classes of molecules that function as hormones in vertebrates: 1. water soluble peptide hormones such as epinephrine, 2. lipid soluble/fluid hormones with receptor on the nucleus of target cells which turns on transcription quickly such as testosterone, 3. local regulators/paracrine signaling which convey messages between neighboring cells such as cytokines (immune response). Numerous hormones such as ADH, FSH, LH, ACTH, growth hormones, pituitary hormones, pancreatic hormones, insulin IGF, hypo- and hyperthyroidism, insulin (diabetes), glucagon, adrenal glands, need to be considered individually, synergistically, and as they effect the entire human body. We must not leave the public at risk, waiting for the patients (public) to provide absolute proof of harm, such as prospective randomized controlled trials of lower IQ, before governments stop mass medication of fluoride without consent for a nonlethal and noncontagious disease prevented with good hygiene and diet.

We have a null probability of fluoride being safe for everyone at EPA's MCL, especially when in combination with synergistic toxicants, compromised endocrine systems, or various ages and stages of life and at concentrations greater than mother's milk which in most samples has no detectible fluoride (mean 0.004 ppm or about 0.001 mg/Kg/day) and the longest running fluoride research project known. Until we have robust research proving the level of fluoride in mother's milk is deficient, incomplete, or defective; mother's milk should be the normative model against which all other infant formulas should be compared, **<0.001 mg/Kg/day.** Most infants (80%-90%) receive some or all formula usually reconstituted with public

water resulting in about 175 to 250 times more fluoride than mother's milk, mean of 0.004 ppm. (most samples not detectible)

Therefore, the evidence of mother's milk may not fit into a formula, rubric or matrix but the weight of evidence should be used for common sense judgment. Judgment, keeping in mind the insufficient evidence of benefit, lack of individual informed consent and weight of all evidence of risks for each individual, not just the mean or 90th percentile. Fluoride is an endocrine disruptor and should be treated as a toxicant like lead.

Mechanism of action

Fluorine enters the body by ingestion, respiration and skin absorption. Exposed tissues are utilized by HF in neutralization reactions leaving the fluoride ion free to pass further into the body. The fluoride anion reacts with HCl in the stomach to form HF. HF is then absorbed by the GI tract and passes into the liver via the portal vein. Elemental F is one of the strongest oxidizers currently known. The anion is immune to the body's first line of defense of biotransformation, phase 1 metabolic reactions, which are generally oxidative reactions in the liver. HF passes into the blood stream and to all tissues. Calcium in all tissues reacts with HF to form an insoluble salt, calcium fluoride. Calcium fluoride is cleared by the body, leaching out some calcium which would be part of the bones, teeth, pineal gland, nerves, etc. The process results in increased density and brittleness, compressive strength of bones and teeth, with decreased tinsel strength.

"Normal" serum concentrations are vague. In part, because there is no "optimal" serum fluoride concentration, and no "optimal" tooth fluoride concentration. Teeth with and without dental caries have the same range of fluoride concentrations. The CDC suggests, *"Normal serum fluoride levels are <20 mcg/L (**0.02 ppm**) but varies substantially. . . ."*[150] We will see below, 0.02 ppm serum fluoride is not protective. Researchers have reported various serum fluoride concentrations in studies for their

[150] http://www.bt.cdc.gov/agent/sulfurylfluoride/casedef.asp

"controls." It is not unusual for studies which report harm to have controls assuming "normal" with fluoride serum concentrations higher than 0.02 ppm.

Taves ('66)	normal <0.013 ppm	
Sowers	controls 0.05 ppm (4th quartile)	
Sandhu	controls 0.042 ppm and tumors at	0.072 ppm (Xiang 0.064 ppm)
Zang	controls 0.04 ppm and 8 IQ loss	0.08 ppm
Rathe	controls 0.025 ppm and stones at	0.12 ppm
Hossney Mother's Milk	0.000 most samples - none detected	

If controls had been <0.02 ppm, greater significance might have been reported.

Keep in mind, birth control has efficacy at parts per billion. We report fluoride here in parts per million.

Ben Goldacre suggests,[151] "Medicine shouldn't be about authority, and the most important question anyone can ask on any claim is simple: 'how do you know?'" Fluoridation of public water is a web of guesses, assumptions and beliefs. Healthcare is littered with the use of treatments that are based on habit, firmly held beliefs and policy rather than evidence. Several medical treatments and research studies were started in the 40's and 50's which lacked scientific rigor evaluating risks, such as artificial fluoridation, thalidomide, and the US Public Health Service Tuskegee experiments on syphilis,[152] Vioxx, Avandia, Herceptin, diethylstilbestrol, are further recent examples.

Another bias is the "natural" ebb and flow of diseases and natural resolution of disease. Dentists seldom see dental caries resolve on their own. If we see caries, we treat. Dentists tend to approach prevention with the same arbitrary mind set. However, prevention and good health are frustratingly less in our control and arbitrary than dental

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151 http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0050892/pdf/TOC.pdf "Testing Treatments Better Research For Better Healthcare, 2nd Ed. Imogen Evans et al. 2011.

152 http://www.tuskegee.edu/about_us/centers_of_excellence/bioethics_center/about_the_usphs_syphilis_study.aspx

treatment, and less lucrative. Comparing developed countries finds caries have been reduced the same amount regardless of fluoridation. Fair tests, prospective RCT studies of efficacy need to be done rather than assumptions. OHAT must not assume fluoride ingestion mitigates dental caries. RCT studies are possible.

> "Our many errors show that the practice of causal inference. . . remains an art. Although to assist us, we have acquired analytic techniques, statistical methods and conventions, and logical criteria, ultimately the conclusions we reach are a matter of judgement."[153]

The NRC (2006) review of fluoride in water used a "weight of evidence" approach. Without any prospective RCT studies, a "weight of evidence" approach is reasonable.

Patients of healthcare should be participants rather than recipients. Doctors and public health professionals are in error when they attempt to dispense health through chemistry under police powers. Professionals are more effective for good overall health when they dispense information for collaboration in better health. "Education, not Fluoridation."

The assumption of ingested fluoride's efficacy has biased public health policy and scientific evaluation. We have misled ourselves and need fair tests of the evidence. Studies funded by those with vested interests are four times more likely to have a positive result. Many desire miracle cures. The marketing claim of fluoride "preventing" caries is just marketing. If ingested fluoride has any benefit, the term mitigating, rather than "preventing" would be more appropriate.

"Absence of evidence is not evidence of absence or evidence of safety."

CDC: "Ingestion of fluoride is not likely to reduce tooth decay."[154]

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[153] Susser M. *Causal thinking in the health sciences,* Oxford: Oxford University Press, 1983. As quoted in "Testing Treatments Better Research For Better Healthcare, 2nd Ed.

[154] (1999). Achievements in Public Health, 1900-1999: Fluoridation of Drinking Water to Prevent Dental Caries. MMWR, 48(41); 933-940, October 22

CDC: ". . . fluoride prevents dental caries predominately after eruption of the tooth into the mouth, and its actions primarily are topical for both adults and children…"[155]

"**Systemic Fluoride has theoretical benefit while the enamel is developing, up to age 6-8.**"[156]

The CDC and NRC appear at odds on potential benefit. Not a surprise because benefit is so hard to detect, if there is a benefit.

It makes no sense to medicate everyone with artificially fluoridated water to theoretically benefit about 10% of the population while 41% of children have dental fluorosis, a biomarker of excess fluoride exposure, for a non contagious almost never lethal disease, without patient consent.

Dental caries is not the result of inadequate fluoride ingestion and no physiologic process requires fluoride. For those wishing to ingest fluoride, other sources of fluoride ingestion (such as toothpaste) are available.

Vandenberg et al. (2012)[157] included sodium fluoride in a list of endocrine disrupting chemicals (EDCs) with low-dose effects. They noted the EDC action of sodium fluoride as: "Inhibits insulin secretion, PTH, TH." The Vanderberg et al. paper was cited in a larger report, Science of Endocrine Disrupting Chemicals – 2012, co-published in January 2013 by the United Nations Environment Programme and the World Health Organization – see page 13

[155] IBID

[156] NRC 2006 & HHS HTSDR 2003 p 9

[157] Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. Endocrine Reviews. First published ahead of print March 14, 2012 as doi:10.1210/er.2011-1050

The NRC (2006) report, in part, is included in sections here. Their review, although historic, is still the most definitive on the relationship between fluoride and the endocrine system. This section is quoted directly from the NRC (2006) report, starting page 214.

"OTHER ENDOCRINE ORGANS

> "The effects of fluoride exposure have been examined for several other endocrine organs, including the adrenals, the pancreas, and the pituitary (for details, see Appendix E, Tables E-16 and E-17). Effects observed in animals include changes in organ weight, morphological changes in tissues, increased mitotic activity, decreased concentrations of pituitary hormones, depressed glucose utilization, elevated serum glucose, and elevated insulin-like growth factor-1 (IGF-1). Effects reported in humans include "endocrine disturbances," impaired glucose tolerance, and elevated concentrations of pituitary hormones. Studies of the effects of fluoride on glucose metabolism and in diabetic animals are discussed below; information on other effects is extremely limited.

"Animal Studies (Diabetic Animals)

> "Two studies have examined the effects of fluoride exposure in diabetic rats. In the first study, Dunipace et al. (1996) compared male Zucker fatty diabetic rats and Zucker age-matched controls given drinking water with fluoride at 5, 15, or 50 mg/L. [These fluoride intakes were considered to be equivalent to intakes by humans of 1, 3, and 10 mg/L (Dunipace et al. 1996).] For the physiological, biochemical, and genetic variables that were monitored, no "measurable adverse effects" were noted. Statistically significant differences with respect to fluoride intake (as opposed to differences between normal and diabetic animals) were observed only for diabetic rats with fluoride at 50 mg/L. No endocrinological parameters (e.g., PTH) were measured. Dunipace et al. (1996) reported that fluoride intake, excretion, and balance were generally similar in this study and in a previous study with Sprague-Dawley rats but that there were "strain-specific differences in fluoride sensitivity"; these differences were not defined or explained. The Zucker fatty diabetic rat is considered to be an animal model for human Type II (noninsulin-dependent)

diabetes mellitus, although the diabetic rats in this study did not experience renal insufficiency, and the study was terminated before an age that might be more comparable to ages associated with late-onset diabetes and diabetic complications in humans. The authors concluded that the diabetic rats “were not at increased risk of fluorosis,” even though femoral fluoride concentrations (2,700-9,500 µg/g in ash for diabetic rats given fluoride at 15 or 50 mg/L versus 2,500-3,600 in normal rats given fluoride at 50 mg/L) were in the range associated with fluorosis in humans and exceeded concentrations of bone fluoride associated with decreased bone strength in rabbits (6,500-8,000 ppm in ash; Turner et al. 1997); no basis for their conclusion was given.

“In the second study, Boros et al. (1998) compared the effects of fluoride at 10 mg/L in drinking water for 3 weeks on young female rats (Charles River, Wistar), either normal (nondiabetic) or with streptozotocin-induced, untreated diabetes. An additional group of normal rats was given an amount of fluoride in drinking water corresponding to the fluoride intake by the diabetic rats (up to about 3 mg/day per rat). Both feed and water consumption increased significantly in the diabetic rats (with and without fluoridated water); water consumption was significantly higher in the diabetic rats on fluoridated water than in those on nonfluoridated water. Fasting blood glucose concentrations were increased significantly in both diabetic groups, but more so in the group on fluoridated water. Fluoride treatment of nondiabetic animals did not cause any significant alteration in blood glucose concentrations. Plasma fluoride was higher, and bone fluoride was lower, in diabetic than in nondiabetic animals given the same amount of fluoride, indicating lower deposition of fluoride into bone and lower renal clearance of fluoride in the diabetic animals. The increased kidney weight found in diabetic animals on nonfluoridated water was not seen in the fluoride-treated diabetic animals. Additional biochemical and hormonal parameters were not measured.

“In contrast to the Zucker fatty diabetic rats in the study by Dunipace et al. (1996), the streptozotocin-induced diabetic rats in this study (Boros et al., 1998) provide an animal model considered representative of Type I (insulin-dependent) diabetes

mellitus in humans. In these rats, the general severity of the diabetes (blood glucose concentrations, kidney function, weight loss) was worse in animals given fluoride at 10 mg/L in their drinking water. In both types of diabetic rats, fluoride intake was very high because of the several-fold increase in water consumption, and corresponding plasma, soft tissue, and bone fluoride concentrations were elevated accordingly. Thus, any health effects related to plasma or bone fluoride concentrations, for example, would be expected to occur in animals or humans with uncontrolled (or inadequately controlled) diabetes at lower fluoride concentrations in drinking water than for nondiabetics, because of the elevated water intakes. In addition, the results reported by Boros et al. (1998) suggested that, for some situations (e.g., diabetes in which kidney function is compromised), the severity of the diabetes could be increased with increasing fluoride exposure.

“Animal Studies (Normal Animals)

“Turner et al. (1997) reported a 17% increase in serum glucose in female rabbits given fluoride in drinking water at 100 mg/L for 6 months. IGF-1 was also significantly increased (40%) in these rabbits, but other regulators of serum glucose, such as insulin, were not measured. The authors suggested that IGF-1 concentrations might have changed in response to changes in serum glucose concentrations. Dunipace et al. (1995, 1998) found no significant differences with chronic fluoride treatment in mean blood glucose concentrations in rats; specific data by treatment group were not reported, and parameters such as insulin and IGF-1 were not measured.

“Suketa et al. (1985) and Grucka-Mamczar et al. (2005) have reported increases in blood glucose concentrations following intraperitoneal injections of NaF; Suketa et al. (1985) attributed these increases to fluoride stimulation of adrenal function. Rigalli et al. (1990, 1992, 1995), in experiments with rats, reported decreases in insulin, increases in plasma glucose, and disturbance of glucose tolerance associated with increased plasma fluoride concentrations. The effect of high plasma fluoride (0.1-0.3 mg/L) appeared to be transient, and the decreased response to a glucose challenge

occurred only when fluoride was administered before (as opposed to together with or immediately after) the glucose administration (Rigalli et al. 1990). In chronic exposures, effects on glucose metabolism occurred when plasma fluoride concentrations exceeded 0.1 mg/L (5 µmol/L) (Rigalli et al. 1992, 1995). The in vivo effect appeared to be one of inhibition of insulin secretion rather than one of insulin-receptor interaction (Rigalli et al. 1990). Insulin secretion (both basal and glucose-stimulated) by isolated islets of Langerhans in vitro was also inhibited as a function of fluoride concentrations (Rigalli et al. 1990, 1995). Rigalli et al. (1990) pointed out that recommended plasma fluoride concentrations for treatment of osteoporosis are similar to those shown to affect insulin secretion.

"Human Studies

"Jackson et al. (1994) reported no differences in mean fasting blood glucose concentrations between osteoporosis patients treated with fluoride and untreated controls, although 3 of 25 treated individuals had values outside the normal range (versus 1 of 38 controls). No significant differences were found between groups of older adults with different fluoride concentrations in drinking water in studies in China (Li et al. 1995; subjects described as "healthy" adults) and the United States (Jackson et al. 1997), and all mean values were within normal ranges. [In the study by Jackson et al. (1997), samples were nonfasting; in the study by Li et al. (1995), it is not clear whether samples were fasting or nonfasting.] Glucose tolerance tests were not conducted in these studies.

"Trivedi et al. (1993) reported impaired glucose tolerance in 40% of young adults with endemic fluorosis, with fasting serum glucose concentrations related to serum fluoride concentrations; the impaired glucose tolerance was reversed after 6 months of drinking water with "acceptable" fluoride concentrations (<1 mg/L). It is not clear whether individuals with elevated serum fluoride and impaired glucose tolerance had the highest fluoride intakes of the group with endemic fluorosis or a greater susceptibility than the others to the effects of fluoride. For all 25 endemic fluorosis patients examined, a significant positive correlation between serum fluoride and

fasting serum immunoreactive insulin (IRI) was observed, along with a significant negative correlation between serum fluoride and fasting glucose/insulin ratio (Trivedi et al. 1993).

"The finding of increased IRI contrasts with findings of decreased insulin in humans after exposure to fluoride (Rigalli et al. 1990; de la Sota et al. 1997) and inhibition of insulin secretion by rats, both in vivo and in vitro (Rigalli et al. 1990, 1995). However, the assay for IRI used by Trivedi et al. (1993) could not distinguish between insulin and proinsulin, and the authors suggested that the observed increases in both IRI and serum glucose indicate either biologically inactive insulin—perhaps elevated proinsulin—or insulin resistance. Inhibition of one of the prohormone convertases (the enzymes that convert proinsulin to insulin) would result in both elevated proinsulin secretion and increased blood glucose concentrations and would be consistent with the decreased insulin secretion reported by Rigalli et al. (1990, 1995) and de la Sota et al. (1997). Although Turner et al. (1997) suggested fluoride inhibition of insulin-receptor activity as a mechanism for increased blood glucose concentrations, Rigalli et al. (1990) found no difference in response to exogenous insulin in fluoride-treated versus control rats, consistent with no interference of fluoride with the insulin-receptor interaction.

"Discussion (Other Endocrine Function)

"More than one mechanism for diabetes or impaired glucose tolerance exists in humans, and a variety of responses to fluoride are in keeping with variability among strains of experimental animals and among the human population. The conclusion from the available studies is that sufficient fluoride exposure appears to bring about increases in blood glucose or impaired glucose tolerance in some individuals and to increase the severity of some types of diabetes. In general, impaired glucose metabolism appears to be associated with serum or plasma fluoride concentrations of about 0.1 mg/L or greater in both animals and humans (Rigalli et al. 1990, 1995; Trivedi et al. 1993; de al Sota et al. 1997). In addition, diabetic individuals will often have higher than normal water intake, and consequently, will have higher than

normal fluoride intake for a given concentration of fluoride in drinking water. An estimated 16-20 million people in the U.S. have diabetes mellitus (Brownlee et al. 2002; Buse et al. 2002; American Diabetes Association 2004; Chapter 2); therefore, any role of fluoride exposure in the development of impaired glucose metabolism or diabetes is potentially significant.

“SUMMARY

“The major endocrine effects of fluoride exposures reported in humans include elevated TSH with altered concentrations of T3 and T4, increased calcitonin activity, increased PTH activity, secondary hyperparathyroidism, impaired glucose tolerance, and possible effects on timing of sexual maturity; similar effects have been reported in experimental animals. These effects are summarized in Tables 8-1 and 8-2, together with the approximate intakes or physiological fluoride concentrations that have been typically associated with them thus far. Table 8-2 shows that several of the effects are associated with average or typical fluoride intakes of 0.05-0.1 mg/kg/day (0.03 with iodine deficiency), others with intakes of 0.15 mg/kg/day or higher. A comparison with Chapter 2 (Tables 2-13, 2-14, and 2-15) will show that the 0.03-0.1 mg/kg/day range will be reached by persons with average exposures at fluoride concentrations of 1-4 mg/L in drinking water, especially the children. The highest intakes (> 0.1 mg/kg/d) will be reached by some individuals with high water intakes at 1 mg/L and by many or most individuals with high water intakes at 4 mg/L, as well as by young children with average exposures at 2 or 4 mg/L.

“Most of the studies cited in this chapter were designed to ascertain whether certain effects occurred (or in cases of skeletal fluorosis, to see what endocrine disturbances might be associated), not to determine the lowest exposures at which they do occur or could occur. Estimates of exposure listed in these tables and in Appendix E are, in most cases, estimates of average values for groups based on assumptions about body weight and water intake. Thus, individual responses could occur at lower or higher exposures than those listed. Although the comparisons are incomplete, similar effects are seen in humans at much lower fluoride intakes (or

lower water fluoride concentrations) than in rats or mice, but at similar fluoride concentrations in blood and urine. This is in keeping with the different pharmacokinetic behavior of fluoride in rodents and in man (Chapter 3) and with the variability in intake, especially for humans."

THYROID, PARATHYROID, PANCREAS, PINEAL, ADRENAL, GONADS, ENTEROENDOCRINE, PARAGANGLIA, ANTERIOR AND POSTERIOR PITUITARY, AND PLACENTA.

NRC (2006) "In summary, evidence of several types indicates that fluoride affects normal endocrine function or response; the effects of the fluoride-induced changes vary in degree and kind in different individuals. **Fluoride is therefore an endocrine disruptor** in the broad sense of altering normal endocrine function or response. The mechanisms of action remain to be worked out and appear to include both direct and indirect mechanisms, for example, direct stimulation or inhibition of hormone secretion by interference with second messenger function, indirect stimulation or inhibition of hormone secretion by effects on things such as calcium balance, and inhibition of peripheral enzymes that are necessary for activation of the normal hormone." (page 266). (National Research Council, 2006) (Emphasis supplied)

A. THYROID GLAND:

Metabolic active cells in the body require hormones produced by the thyroid gland, triiodothyronine (T3) and thyroxine (T4). Health consequences arise when the thyroid produces too much, or too little, of these hormones.

At relatively low doses fluoride is effective at reducing thyroid function in the hyperthyroid patients. Research confirms that (1) fluoride can exacerbate the anti-thyroid effects of iodine deficiency, (2) can cause goiter in some individuals, and (3) can

alter thyroid hormone levels in a manner consistent with a general thyroid suppressant. Until the 1950s, doctors in Europe and South America prescribed fluoride for hyperthyroidism. (Merck Index 1968). Fluoride therapy did reduce thyroid activity in the treated patients. (McClaren 1969; Galletti 1958; May 1937). Clinical indications suggested 2 to 5 mg of sodium fluoride per day over several months was effective, (Galletti & Joyet 1958). Note: a person drinking 3 liters of fluoridated water at 0.7 ppm with NO other fluoride source, would receive a clinical dosage to reduce thyroid activity. A comparable proposed EPA safe dosage RfD of 0.08 mg/kg/day would exceed clinically used dosages. (0.08 mg/kg X 50 kg = 4 mg. For a 100 kg person, 0.08 mg/kg X 100 kg = 8 mg fluoride). Some ADD medications still contain fluoride.

Alterations in thyroid hormones, including reduced T3 and increased TSH, in populations exposed to elevated levels of fluoride in the workplace or in the water have been reported. (NRC 2006; Susheela 2005; Mikhailets 1996; Yao 1996; Bachinskii 1985; Yu 1985).

In **clinical hypothyroidism,** the thyroid gland fails to produce sufficient quantities of the hormones triiodothyronine (T3) and thyroxine (T4). Reduced T3 and T4 can contribute to fatigue, muscle/joint pain, depression, weight gain, menstrual disturbances, impaired fertility, impaired memory, and inability to concentrate. When T3 and T4 levels begin to fall, the pituitary gland responds by increasing production of “Thyroid Stimulating Hormone” (TSH) as a means of getting the thyroid to produce more T3 and T4.

In **subclinical hypothyroidism,** TSH levels decrease but T3 and T4 hormones are in a normal range. Subclinical hypothyroidism in pregnant women results in reduced IQ in offspring, (Klein 2001; Haddow 1999), and a recent study in the Journal of the American Medical Association found that adults with subclinical hypothyroidism had a significantly higher rate of coronary heart disease. (Rodondi 2010).

Dental fluorosis is a poor indicator of fluoride’s effect on they thyroid gland.

Thyroid Hormone Levels Based on Severity of Dental Fluorosis (Hosur 2012).

In 2006, the NRC report on fluoride for the EPA suggested studies investigating fluoride's impact on thyroid hormone levels have produced divergent findings, but are consistent with fluoride having an anti-thyroid effect under certain circumstances. Singh (2014 see Human Thyroid below) may in part explain the "divergent findings" because dental fluorosis is a poor indication of TSH levels (see Table 3 below). **77% with dental fluorosis and 67% without dental fluorosis had derangement in thyroid hormone levels.** Both groups had abnormal serum fluoride levels and delayed eruption. **Even Group 2 drinking 0.02 ppm-0.77 ppm fluoride in water had 50% of children with abnormal serum fluoride levels.** Note: USPHS new recommendation of 0.7 ppm, represents a 14% reduction of fluoride exposure and is not enough.

Table 3

Derangement in Thyroid hormone (FT_3, FT_4, TSH) levels and serum fluoride levels in children of different groups

Group	No. of cases with Derangement in Thyroid hormone (FT_3, FT_4, TSH) level	No. of children with abnormal serum fluoride level	No. of children with delayed eruption
Group1A (n = 30)	23 (77%)	29 (97%)	17 (57%)
Group1B (n = 30)	20 (67%)	30 (100%)	15 (50%)
Group 2 (n = 10)	1 (10%)	5 (50%)	0 (0%)

The most common thyroid effect associated with fluoride exposure appears to be an increase in TSH levels, with or without a corresponding effect on T3 or T4. (Susheela 2005). One of the most recent studies, for example, found a trend towards higher TSH in children based on the severity of their dental fluorosis, but without a significant effect on either T3 or T4. (Hosur 2012, see figure below). These and other findings indicate that fluoride can contribute to a subclinical, if not clinical, hypothyroid condition. It

remains difficult to predict the toxic dose, however, as it appears to depend, in part, on the nutritional and health status of the individual, particularly the adequacy of iodine intake. (NRC 2006).

NRC (2006) page 218. "Thyroid Function

> "Fluoride exposure in humans is associated with elevated TSH concentrations, increased goiter prevalence, and altered T4 and T3 concentrations; similar effects on T4 and T3 are reported in experimental animals, but TSH has not been measured in most studies. In animals, effects on thyroid function have been reported at fluoride doses of 3-6 mg/kg/day (some effects at 0.4-0.6 mg/kg/day) when iodine intake was adequate (Table 8-1); effects on thyroid function were more severe or occurred at lower doses when iodine intake was inadequate. In humans, effects on thyroid function were associated with fluoride exposures of 0.05-0.13 mg/kg/day when iodine intake was adequate and 0.01-0.03 mg/kg/day when iodine intake was inadequate (Table 8-2).
>
> "Several sets of results are consistent with inhibition of deiodinase activity, but other mechanisms of action are also possible, and more than one might be operative in a given situation. In many cases, mean hormone concentrations for groups are within normal limits, but individuals may have clinically important situations. In particular, the inverse correlation between asymptomatic hypothyroidism in pregnant mothers and the IQ of the offspring (Klein et al. 2001) is a cause for concern. The recent decline in iodine intake in the United States (CDC 2002d; Larsen et al. 2002) could contribute to increased toxicity of fluoride for some individuals."

TABLE 8-1 Summary of Major Observed Endocrine Effects of Fluoride in Experimental Animals, with Typical Associated Intakes and Physiological Fluoride Concentrations

End Point	Fluoride Intake, mg/kg/day	Fluoride in Serum or Plasma, mg/L	Fluoride in Urine, mg/L	Fluoride in Bone, ppm in ash	Key References
Altered thyroid function (altered T4 and T3 concentrations)	3-6 (lower with iodine deficiency)	NA[a]	≥ 6 (possibly ≥ 2-3)	≥2,400	Stolc and Podoba 1960; Bobek et al. 1976; Hillman et al. 1979; Guan et al. 1988; Zhao et al. 1998; Cinar and Selcuk 2004
Altered calcitonin activity	2	NA	NA	3,200-3,500[b]	Rantanen et al. 1972
Altered melatonin production; altered timing of sexual maturity	3.7	NA	NA	2,800	Luke 1997
Inhibited parathyroid function	5.4	NA	NA	NA	Rosenquist et al. 1983
Increased serum glucose; increased severity of diabetes	7-10.5	0.1-0.7[c,d]	NA	>1,000	Rigalli et al. 1990, 1992, 1995; Turner et al. 1997; Boros et al. 1998
Increased parathyroid hormone concentrations, secondary hyperparathyroidism	9-10	≥ 0.2[c]	NA	2,700-3,200	Faccini and Care 1965; Chavassieux et al. 1991

[a]Not available.
[b]ppm.
[c]Serum.
[d]Plasma.

NRC (2006) Tables 8-1 and 8-2 are reproduced here.

The NRC (2006) listed several limitations of the endocrine studies. More current research has included some of these limitations. One of the limitations is the interdependence of endocrine systems. The NRC (2006) p 223. “In addition, the different endocrine organs do not function entirely separately: thyroid effects (especially elevated TSH) may be associated with parathyroid effects (Stoffer et al. 1982; Paloyan Walker et al. 1997), and glucose metabolism may be affected by thyroid or parathyroid status (e.g., McCarty and Thomas 2003; Procopio and Borretta 2003; Cettour-Rose et al. 2005). Adverse effects in individuals might occur when hormone concentrations are still in the normal ranges for a population but are low or high for that individual (Brucker-Davis et al. 2001; Belchetz and Hammond 2003). Some investigators suggest that

endocrine-disrupting chemicals could be associated with nonmonotonic dose- response curves (e.g., U-shaped or inverted-U-shaped curves resulting from the superimposition of multiple dose-response curves) and that a threshold for effects cannot be assumed

TABLE 8-2 Summary of Major Observed Endocrine Effects of Fluoride in Humans, with Typical Associated Intakes and Physiological Fluoride Concentrations

End Point	Fluoride Intake, mg/kg/day[a]	Fluoride in Serum or Plasma, mg/L	Fluoride in Urine, mg/L	Key References
Altered thyroid function (altered T4 and/or T3 concentrations)	0.05-0.1 (0.03 with iodine deficiency)	≥0.25[a]	2.4	Bachinskii et al. 1985; Lin et al. 1991; Yang et al. 1994; Michael et al. 1996; Susheela et al. 2005
Elevated TSH concentrations	0.05-0.1 (0.03 with iodine deficiency)	≥0.25[a]	≥2	Bachinskii et al. 1985; Lin et al. 1991; Yang et al. 1994; Susheela et al. 2005
Elevated calcitonin concentrations	0.06-0.87	0.11-0.26[b]	2.2-18.5 mg/day	Teotia et al. 1978
Goiter prevalence ≥ 20%	0.07-0.13 (≥ 0.01 with iodine deficiency)	NA[c]	NA	Day and Powell-Jackson 1972; Desai et al. 1993; Jooste et al. 1999
Impaired glucose tolerance in some individuals	0.07-0.4	0.08[a] 0.1-0.3[b]	2-8	Rigalli et al. 1990, 1995; Trivedi et al. 1993; de la Sota 1997
Increased parathyroid hormone concentrations, secondary hyperparathyroidism, in some individuals	0.15-0.87	0.14-0.45[b]	3-18.5 mg/day	Juncos and Donadio 1972; Teotia and Teotia 1973; Larsen et al. 1978; Teotia et al. 1978; Duursma et al. 1987; Dandona et al. 1988; Stamp et al. 1988, 1990; Pettifor et al. 1989; Srivastava et al. 1989; Dure-Smith et al. 1996; Gupta et al. 2001

[a]Serum.
[b]Plasma.
[c]Not available.

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(Bigsby et al. 1999; Brucker-Davis et al. 2001)."

Peckham (2015) "We found that higher levels of fluoride in drinking water provide a useful contribution for predicting prevalence of hypothyroidism. We found that practices located in the West Midlands (a wholly fluoridated area) are nearly twice as likely to report high hypothyroidism prevalence in comparison to Greater Manchester (non-fluoridated area)."

Zhang (2015)[158] (Note: although this study focused on decrease in IQ with fluoride, thyroid hormone levels were also measured.) ". . . The children's IQ, fluoride

[158] Zhang S, Zhang X, Liu H, Qu W, Guan Z, Zeng Q, Jiang C, Gao H, Zhang C, Lei R, Xia T, Wang Z, Yang L, Chen Y, Wu X, Cui Y, Yu L, Wang A. Modifying effect of COMT gene polymorphism and a predictive role for

contents in drinking water (W-F), serum (S-F), and urine (U-F); serum thyroid hormone levels, COMT Val158Met polymorphism, and plasma proteomic profiling were determined. . . . In conclusion, fluoride exposure was adversely associated with children's intelligence, whereas the COMT polymorphism may increase the susceptibility to the deficits in IQ due to fluoride exposure. Moreover, the proteomic analysis can provide certain basis for identifying the early biological markers of fluorosis among children."

A critical study to consider is Singh (2014) which raised serious concerns that **dental fluorosis is a poor indication of excess total fluoride exposure.** Both those with and without dental fluorosis had thyroid derangement and high serum fluoride concentrations.

Singh (2014)[159] "The study was undertaken to determine serum/urinary fluoride status and comparison of free T4, free T3 and thyroid stimulating hormone levels of 8 to 15 years old children with and without dental fluorosis living in an endemic and non-endemic fluorosis area. . . A significant relationship of water fluoride to urine and serum fluoride concentration was seen. The serum fluoride concentration also had significant relationship with thyroid hormone (FT3/FT4) and TSH concentrations. The testing of drinking water and body fluids for fluoride content, along with FT3, FT4, and TSH in children with dental fluorosis is desirable for recognizing underlying thyroid derangements and its impact on fluorosis. . . . Conclusion: The results of this study question the validity of the fluoridation of drinking water, milk, fruit juices, and salt by public health authorities and also the step taken to prevent ill effects of excess fluorine and iodine deficiencies in endemic fluorosis areas. The children with dental fluorosis living in endemic fluorosis areas may not have a frank thyroid disease due to excessive fluorine consumption but they do show thyroid disease leading to many health effect hence they require special care and attention."

proteomics analysis in children's intelligence in endemic fluorosis area in Tianjin, China. Toxicol Sci. 2015 Apr;144(2):238-45. doi: 10.1093/toxsci/kfu311. Epub 2015 Jan 1.

[159] Singh N[1], Verma KG[2], Verma P[3], Sidhu GK[4], Sachdeva S[3]. A comparative study of fluoride ingestion levels, serum thyroid hormone & TSH level derangements, dental fluorosis status among school children from endemic and non-endemic fluorosis areas. Springerplus. 2014 Jan 3;3:7. doi: 10.1186/2193-1801-3-7. eCollection 2014.

Table 1

Levels of fluoride naturally ingested from drinking water and body fluids in different sample groups

Parameters	Group 1A	Group 1B	Group 2	Total
Water fluoride (WF)	1.6–5.1 ppm	1.6–5.5 ppm	0.98–1 ppm	0.98–5.5 ppm
Urine fluoride (UF)	0.24–8.9 ppm	0.4–7.79 ppm	0.19–1.01 ppm	0.24–8.9 ppm
Serum fluoride (SF)	0.02–0. 77 ppm	0.03–0.75 ppm	0.02–0.09 ppm	0.02–0.77 ppm

And further, Singh (2014), “Group 1 included 60 male and female school children, which were equally divided into two subgroups: Group 1A (children with dental fluorosis) and Group 1B (children without dental fluorosis). Group 2 included 10 children from Sardarpura colony of Udaipur city, a non endemic area, which was taken as a control for the study samples.”

Tables 1, 2, 3, and 6 of Singh (2014) are reproduced here.

Table 1: Comparing fluoride Group 1 A (dental fluorosis) and 1B (no fluorosis), with control Group 2 is consistent with other studies when urine and serum fluoride concentrations are compared with water fluoride concentrations, provided significant other sources such as fluoridated toothpastes are not in use.

NOTE: The absence of dental fluorosis does not indicate lower or safe fluoride urine or serum concentrations.

NOTE: All three groups had some individuals with low serum and urine fluoride concentrations. The significant difference is those with high serum and urine fluoride concentrations.

And remember, endemic fluoride is usually CaF which is estimated at 800 times less toxic than NaF or HSF used for artificial fluoridation.

Table 2

Levels of thyroid hormones in all sample groups

Parameters	Group 1A	Group 1B	Group 2	Total
Free T 3 (FT 3)	1.1–4.39 pg/ml	1.2–4.57 pg/ml	1.90–4.13 pg/ml	1.1–4.57 pg/ml
Free T 4 (FT 4)	0.94–1.98 ng/dL	0.8–1.7 ng/dL	0.87–1.67 ng/dL	0.8–1.98 ng/dL
TSH	1.41–8.46 µIU/m	1.92–10.99 µIU/m	0.96–3.54 µIU/m	0.96–10.99 µIU/m

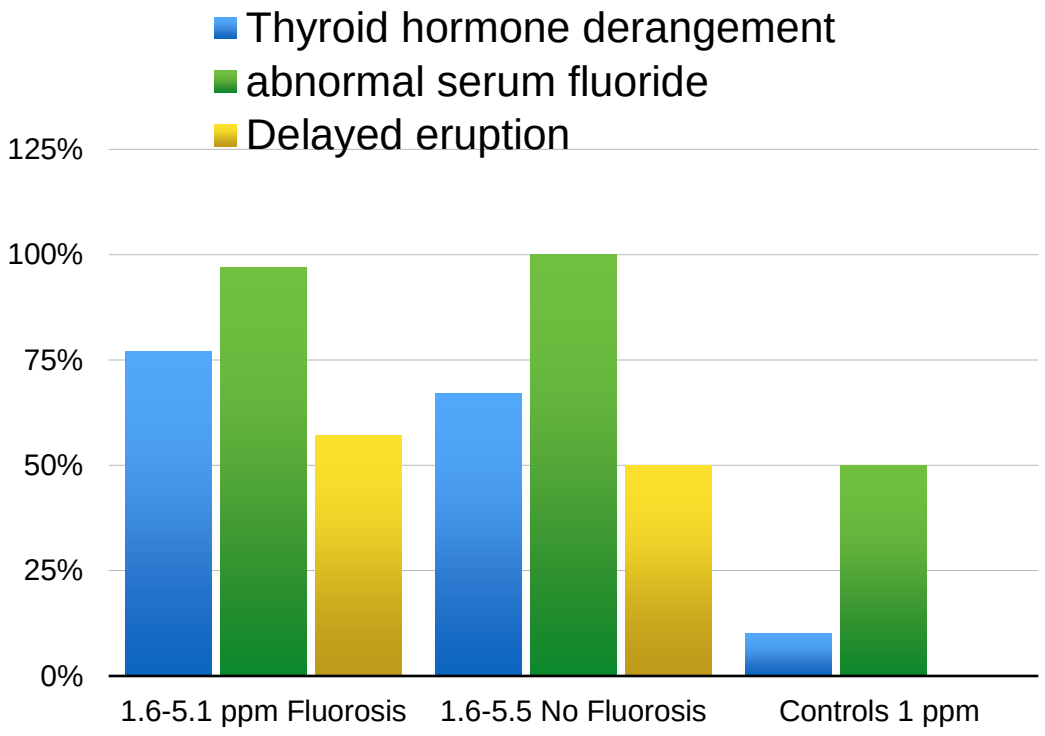
Table 6

Correlation analysis between fluoride content in body fluids and their effect FT3, FT4, TSH within Group 1

Parameters	Spearman rho analysis	FT_3	FT_4	TSH	WF	UF	SF
FT_3	'r'	1	-0.169	-0.252	-0.711	-0.388	-0.400
	p-value	-	0.196	0.052*	0.000**	0.002**	0.002**
FT_4	'r'	-0.169	1	-0.079	0.196	0.119	0.119
	p-value	0.196	-	0.547	0.134	0.365	0.366
TSH	'r'	-0.252	-0.079	1	0.151	0.079	0.552
	p-value	0.052*	0.547	-	0.250	0.550	0.000**
WF	'r'	-0.711	0.196	0.151	1	0.690	0.529
	p-value	0.000**	0.134	0.250	-	0.000**	0.000**
UF	'r'	-0.388	0.119	0.079	0.690	1	0.525
	p-value	0.002**	0.365	0.550	0.000**	-	0.000**
SF	'r'	-0.400	0.119	0.552	0.529	0.525	1
	p-value	0.002**	0.366	0.000**	0.000**	0.000**	-

*Correlation is significant at 0.05 levels (2 tailed), **Correlation is highly significant below 0.01 levels correlation coefficient(r).

Table 3 should be carefully considered and we graphed their Table 3 below. **Even with fluoride serum levels between 0.02 ppm and 0.09 ppm (1 ppm fluoride in water), 10% had derangement of the thyroid.** Remember, endemic fluoride is not as toxic as sodium fluoride or HFS, and second, rural villagers often use less fluoride toothpaste, dental and medical products or fluoride pesticides.



The CDC's recommendation of normal fluoride serum concentrations <0.02 ppm may not be protective and provides no margin of safety. A 0.7 ppm artificial fluoridation will

Table 3

Derangement in Thyroid hormone (FT_3, FT_4, TSH) levels and serum fluoride levels in children of different groups

Group	No. of cases with Derangement in Thyroid hormone (FT_3, FT_4, TSH) level	No. of children with abnormal serum fluoride level	No. of children with delayed eruption
Group1A (n = 30)	23 (77%)	29 (97%)	17 (57%)
Group1B (n = 30)	20 (67%)	30 (100%)	15 (50%)
Group 2 (n = 10)	1 (10%)	5 (50%)	0 (0%)

not reduce serum fluoride concentrations to within CDC recommendations.

Liu (2014)[160] "In many regions, excessive fluoride and excessive iodide coexist in groundwater, which may lead to biphasic hazards to human thyroid. To explore fluoride-induced thyroid cytotoxicity and the mechanism underlying the effects of excessive iodide on fluoride-induced cytotoxicity, a thyroid cell line (Nthy-ori 3-1) was exposed to excessive fluoride and/or excessive iodide. Cell viability, lactate dehydrogenase (LDH) leakage, reactive oxygen species (ROS) formation, apoptosis, and the expression levels of inositol-requiring enzyme 1 (IRE1) pathway-related molecules were detected. Fluoride and/or iodide decreased cell viability and increased LDH leakage and apoptosis. ROS, the expression levels of glucose-regulated protein 78 (GRP78), IRE1, C/EBP homologous protein (CHOP), and spliced X-box-binding protein-1 (sXBP-1) were enhanced by fluoride or the combination of the two elements. Collectively, excessive fluoride and excessive iodide have detrimental influences on human thyroid cells. Furthermore, an antagonistic interaction between fluoride and excessive iodide exists, and cytotoxicity may be related to IRE1 pathway-induced apoptosis."

[160] Liu H, Zeng Q, Cui Y, Yu L, Zhao L, Hou C, Zhang S, Zhang L, Fu G, Liu Y, Jiang C, Chen X, Wang A. The effects and underlying mechanism of excessive iodide on excessive fluoride-induced thyroid cytotoxicity. Environ Toxicol Pharmacol. 2014 Jul;38(1):332-40. doi: 10.1016/j.etap.2014.06.008. Epub 2014 Jun 27.

Kutlucan (2013)[161] "AIM: To compare the urine iodine, fluoride, and to measure thyroid volumes in 10-15-year-old children using ultrasonography, a gold standard in evaluating thyroid volume. . . . After puberty, echobody index in subjects with fluorosis was markedly high. Based on our results, we thought that fluorosis increases thyroid volume in children with fluorosis after puberty."

TSH is considered a "'precise and specific barometer' of thyroid status in most situations" (NRC 2006) The relationship between fluoride and elevated TSH has been found even where T3 and T4 levels remain normal, suggesting that fluoride could contribute to subclinical hypothyroidism, which is a condition of "mild thyroid failure" marked by increased TSH and normal T3/T4.

Subclinical hypothyroidism is now considered a "clinically important disorder that has adverse clinical consequences." (Gencer 2012). Several studies have found that subclinical hypothyroidism in pregnant woman was a risk factor for reduced IQ in the offspring. (Klein 2001; Haddow 1999). Although most of the more than 40 human studies evaluating fluoride and IQ did not measure TSH, those that did so reported that children with high fluoride exposures had elevated TSH levels. (Wang 2001; Yao 1996; Lin 1991). Lin reported that elevated TSH correlated with reduced IQ. TSH levels could be one of the contributing factors towards the reduced IQ reported in the studies to date.

In 2010, a study in the Journal of the American Medical Association found that adults with subclinical hypothyroidism had a significantly higher incidence of, and mortality from, coronary heart disease. (Rodondi 2010). Whether this could help explain the relationship between elevated fluoride and cardiovascular disease remains to be determined. As reported below, one recent study (Karademir 2011) did find a relationship between fluoride exposure, thyroid levels, and cardiovascular indices, although TSH levels were not found to be elevated.

[161] Kutlucan A[1], Kale Koroglu B, Numan Tamer M, Aydin Y, Baltaci D, Akdogan M, Ozturk M, Vural H, Ermis F. The investigation of effects of fluorosis on thyroid volume in school-age children. Med Glas (Zenica). 2013 Feb;10(1):93-8.

Banjo (2013) "The study investigated the role of Spirulina platensis in reversing sodium fluoride-induced thyroid, neurodevelopment and oxidative alterations in offspring of pregnant rats. . . . Fluoride-induced alterations in thyroid hormones, behaviour and increased oxidative stress. Spirulina augmented the displacement of fluoride, facilitated antioxidant formation, improved behaviour and protected Purkinje cells. Supplementing Spirulina during pregnancy could reduce the risk of fluoride toxicity in offspring."[162]

Karademir (2011)[163] "In this study we examined the deleterious effect of fluorosis on cardiovascular system including detailed ECG with dispersion analysis, echocardiography, and HRV with Holter analysis in children. We found statistically significant low T4 levels, hypocalcemia and hyponatremia, increased QT and QTc interval in children with dental fluorosis. Our results show that fluorosis might increase risk of arrhythmia indirectly, due to its hypocalcemic, hypernatremic, and hypothyroidism effects."

Ba (2009)[164] "The concentration of serum TSH of children from high fluoride and iodine area and high iodine area was higher than that of children from high fluoride area and control area. Conclusion: High fluoride and iodine increase the prevalence of goiter. High iodine increases the concentration of FT4. Fluoride can increase the concentration of FT4 under high iodine condition."

Ruiz-Pagan (2006)[165] "This study was designed to evaluate adverse health effects in adolescents from chronic exposure to various water fluoride concentrations in three

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[162] Banji D et al (2013) Investigation on the role of Spirulina platensis in ameliorating behavioural changes, thyroid dysfunction and oxidative stress in offspring of pregnant rats exposed to fluoride. 2013 Sep 1;140(1-2):321-31. doi: 10.1016/j.foodchem.2013.02.076. Epub 2013 Feb 28.

[163] Karademir S, et al. (2011). Effects of fluorosis on QT dispersion, heart rate variability and echocardiographic parameters in children. Anadolu Kardiyol Derg 11(2):150-55.

[164] Ba Y, et al. (2009). Effect of different fluoride and iodine concentration in drinking water on children's dental fluorosis and thyroid function. Chinese Journal of Public Health 25(8):942-43.

[165] Ruiz-Payan A. (2006). Chronic effects of fluoride on growth, blood chemistry and thyroid hormones in adolescents residing in three communities in Northern Mexico. *ETD Collection for*

communities located in Northern Mexico: Ciudad Juarez, Samalayuca, and Villa Ahumada. In these communities the fluoride concentration in water averages 0.3, 1.0, and 5.3 mg/L, respectively. The residents of Villa Ahumada have been exposed to excessive levels of fluoride in drinking water since their birth. . . . In Villa Ahumada, a significant inverse relationship was found between urine fluoride levels and stature; this association suggests that fluoride exposure may affect the teeth but also the growth of adolescents. Serum samples of these individuals showed elevated levels of alkaline phosphatase (ALP), potassium, magnesium, calcium, and phosphate, and decreased levels of thyroid hormone T3 and uric acid. These findings show that chronic exposure to high levels of fluoride have a definitive impact on the prevalence and severity of dental fluorosis, decreased stature, and decreased [] thyroid hormone secretion."

Susheela (2005)[166] "Although it has long been suggested that dental fluorosis is associated with IDD and thyroid dysfunction,7-9,14 this study, to our knowledge, is the first to investigate dental fluorosis in relation to TSH and the thyroid hormones FT4 and FT3, the latter now confirmed to be the biologically active thyroid hormone. As evident from the data in Table 5, deviations in thyroid hormone levels in the 49 affected children of the sample group fall into five distinct categories, which are discussed below. It is also evident that even in some of the children in the two control groups consuming "safe" water (<1.0 ppm F–), fluoride levels in their blood and urine are above current upper limits, indicating other sources of fluoride ingestion, such as from foods and beverages, dental products, drugs, air, or salt. In those children disturbances in thyroid hormone ratios are observed as well. . . . Some of the conclusions and recommendations we draw from this study are:

• Children with dental fluorosis living in endemic fluorosis areas and IDD (iodine deficiency disorder) may have thyroid derangements that require special care and attention.

University of Texas, El Paso. Paper AAI3214004.
http://digitalcommons.utep.edu/dissertations/AAI3214004

[166] AK Susheela, M Bhatnagar, K.Vig, NK Mondald, EXCESS FLUORIDE INGESTION AND THYROID HORMONE DERANGEMENTS IN CHILDREN LIVING IN DELHI, INDIA. Fluoride 2005;38(2):151–161 Research report 151

• The primary cause of IDD may not always be iodine deficiency, but it might be induced by fluoride poisoning.
• Testing of drinking water and body fluids for fluoride content, along with FT3, FT4, and TSH—even in children without dental fluorosis—is desirable for recognizing thyroid derangements.
• Prevention and control of fluorosis and IDD require an integrated approach for diagnosis and patient management, contrary to prevailing practices.
• The results of this study question the validity of the fluoridation of drinking water, milk, fruit juices, and salt by public authorities."

Social (2005)[167] "In the current investigation 46.9% of the children in the [high fluoride] group have elevated TSH and normal FT4 and FT3 levels, while a similar derangement is also observed in 18.2% of the children in [the lower fluoride group]. This is our first category and is usually the first indication of thyroid dysfunction, termed sub-clinical hypothyroidism."

Cigar (2005)[168] "In this study, the serum levels of thyroxine (T4), triiodothyronine (T3), and protein-bound iodine (PBI) in the control cows were in the normal range of healthy cows, but they were significantly lower ($p<0.05$) in the fluorotic cows. These findings are consistent with the results of research with sheep, calves, cattle, and rats. . . . On the other hand, Choubisa reported that none of a group of fluorotic domestic animals exhibited any apparent evidence of hypothyroidism, stunted growth, [or] low milk production . . . . In our view, the reason for decreased levels of T4, T3, and PBI in our cows with chronic fluorosis might be due to: 1) inhibition of the absorption of the iodine and some amino acids (e.g., tyrosine) in the gastrointestinal tract, 2) insufficient synthesis and secretion of thyroglobulin and oxidized iodides from the thyroid glands, 3) low levels of bioavailable iodine in the

[167] Susheela AK, et al. (2005). Excess fluoride ingestion and thyroid hormone derangements in children living in New Delhi, India. Fluoride 38(2):98-108.
[168] Cinar A, Selcuk M. (2005). Effects of chronic fluorosis on thyroxine, triiodothyronine, and protein-bound iodine in cows. Fluoride 38(1):65-68.

Tendurek Mountain region."

"Wang (2001)[169] In conclusion, high iodine and high fluorine in the drinking water have, to some extent, effects on children's intelligence and thyroid function."[170]Wang (2001) "TSH value was obviously higher than the control point, indicating that, under high iodine and high fluorine condition, T3 and T4 secreted by the thyroid are in the normal range, while TSH value secreted by the pituitary clearly increased. This is probably because high iodine and high fluorine suppress the synthesis and secretion of the thyroid peroxidase and thyroid hormones . . . . The body accelerates the Hypothalamic TSH secretion by negative feedback regulation, thus increasing the secretion of TSH, stimulating the composition of T3 and T4 of the thyroid. As a result, the TSH in the peripheral blood circulation is high while T3 and T4 are not clearly reduced."

Liu (2001) "Objective: To investigate the effects of fluoride on thyroid structure in chicks.. . . Conclusions Fluoride can seriously damage thyroid structure . During the earlier stage, fluoride can induce thyroid atrophia, however, during the later stage, it can induce thyroid enlargement which is nodular and colloid goiter."[171]

Wan (1999)[172] [Objective: To study the significant test of diagnosing endemic fluorosis. Methods Twenty one routine and biochemical marks of blood and urine from 600 cases of the patients with different degree endemic fluorosis were determined and analysed. Results . . . The average of T3 and T4 were lower than the reference value, particularly in those with moderate and severe stages of the disease. Conclusions The RBC, Hb, serum calcium,phosphorus, AKP, urinary calcium,

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169 Wang X, et al. (2001). Effects of high iodine and high fluorine on children's intelligence and thyroid function. *Chinese Journal of Endemiology* 20(4):288-90.

170 Wang X, et al. (2001). Effects of high iodine and high fluorine on children's intelligence and thyroid function. Chinese Journal of Endemiology 20(4):288-90.

171 Liu GY, et al. (2001). Effects of fluoride on thyroid structure in chicks. Chinese Journal of Endemiology.

172 Wan G, et al. (2001). Determination and analysis on multimark of test of patients with endemic fluorosis. Chinese Journal of Endemiology 20(2):137-39.

globulin, T3 and T4 were signifiant diagnostic indicators of endemic fluorosis.]

Xiaoli (1999)[173] [In a group of 8-12 year old children living in an endemic fluorosis area in China, TSH levels were significantly elevated, while T4 levels were significantly decreased and T3 levels significantly increased.]

Yao (1996)[174] "The TSH level is a sensitive index which both reflects the state of the body's thyroid function, and screens the level of iodine (lack thereof) in a population. TSH is also a sensitive indicator in terms of making timely discoveries of people suffering from poor thyroid function or below-average intelligence. The results from this test show that TSH values of children with dental fluorosis from the two endemic areas is at a remarkably higher level than those from the non-endemic area. Children from the endemic areas were also found to have a lower level of intelligence than the non-endemic group. The heavier the level/concentration of fluoride found in the region, the more significant the difference in the results."

Mikhail's (1996)[175] "Conclusions: 1. Abnormalities in the thyroid function characterized by a decreased iodine absorption function of the thyroid, a low level T3 syndrome, and a slight increase of the TSH level are observed in cases of chronic fluorine intoxication in the industrial workers. 2. The observed changes progressed with the increase of the time of exposure to fluorides and a more advanced disease stage. 3. The highest frequency of occurrence of the low level T3 syndrome was observed in workers with chronic fluoride intoxication including TPP (toxic liver damage). 4. The lowered iodine absorption function of the thyroid and/or the low level T3 syndrome can serve as diagnostic signs of chronic fluorine intoxication. 5. The decrease in the T3 level most probably occurs due to the disrupted conversion of T4 to T3 at the cell-target level. The disruption of conversion may be caused by fluorine affecting the

[173] Xiaoli L, et al. (1999). The detection of children's T3, T4 and TSH contents in endemic fluorosis areas. Endemic Disease Bulletin 14(1):16-17.
[174] Yao Y, et. al. (1996). Analysis on TSH and intelligence level of children with dental Fluorosis in a high fluoride area. Literature and Information on Preventive Medicine 2(1):26-27
[175] Mikhailets ND, et al. (1996). Functional state of thyroid under extended exposure to fluorides. Probl Endokrinol 42:6-9.

enzyme system of deiodination as well as the toxic liver damage it causes."

Shufen (1996)[176] "The levels of serum T3, T4 and TSH were analyzed in children with fluoride-aluminum combined toxicosis in the Shuicheng area of Guizhou as compared with the children without fluoride-aluminum combined toxicosis. The results showed that serum T4 content decreased in the children with fluoride aluminum combined toxicosis (103.9±15.9 nmol/L vs 150.67±16.5 nmol/L, p 0 01), but no obvious differences of serum T3 and TSH were found among total three groups. It suggests that the disorder of the thyroid function should be considered when treating the children with fluoride aluminum combined toxicosis."

Michael (1996)[177] "While levels of thyroid stimulating hormone (TSH) and triiodothyronine (T3) did not vary, a significant increase in the thyroxine (T4) levels suggested alteration in thyroid function."

Yang (1994)[178] "An excess of fluoride and a lack of iodine in the same environment has been shown to have a marked effect on child intellectual development, causing a more significant intellectual deficit than lack of iodine alone. In our study the study group of children from the high fluoride-high iodine village area had an average IQ of 76.67±7.75, which was somewhat lower than the control (IQ 81.67 ±11.9), although the difference is not statistically significant (P > 0.05). However, as seen in Table 2, the percentage of children in the low range (16.67%) is higher in the endemic group than in the control group (10.0%), suggesting that a high iodine-high fluoride environment also has a definite negative influence on child intellectual ability."

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[176] Shufen J, et al. (1996). The change of thyroid functlon from children with fluoride aluminum combined toxicosis in Shuicheng area of Guizhou. Journal of Guiyang Medical College.

[177] Michael M, et al. (1996). Investigations of soft tissue function in fluorotic individuals of North Gujurat. Fluoride 29(2):63-71.

[178] Yang Y, et al. (1994). The effects of high levels of fluoride and iodine on intellectual ability and the metabolism of fluoride and iodine. Chinese Journal of Epidemiology 15(4):296-98 (republished in Fluoride 2008; 41:336-339).

Xu (1994)[179] “The number of children whose level of intelligence is lower is significantly increased in regions of high fluoride/iodine, regions of high fluoride only, regions of high fluoride/low iodine, against their respective comparative groups.”

Lin (1991)[180] “Area A (high fluoride, low iodine) differed from area B (normal fluoride, low iodine) by having lower mean IQ, higher TSH, slightly higher 1311 uptake, and higher urinary iodine. . . . The significant ditferences in IQ among these regions suggests that fluoride can exacerbate central nervous lesions and somatic developmental disturbance caused by iodine deficiency. . . . [W]e found that 69% of the children with mental retardation had elevated TSH levels. IQ and TSH were negatively correlated. Many investigators regard an elevated TSH in the presence of normal T4 and T3 levels as evidence for hypothyroidism that is subclinical but that can still affect the development of brain and cerebral function to some degree.”

Liu (1988)[181] “Endemic fluorosis is a systemic disease. We investigated the serum free fluoride, thyroid hormones and TSH concentrations in 37 cases. Significantly lowered serum T4 . . . and increased TSH were found in patients. Patients’serum T3 concentrations were not significantly different from the controls. Significant negative correlations were found between serum free fluoride concentrations and T3 concentrations or T3/T4 ratios. We propose that fluoride intoxication might decrease thyroid function and suggest the method to prevent and treat this condition.”

Bachinskii (1985)[182] “The ingestion of drinking water with high concentrations of fluoride (122 +/- 5 micromoles per liter) leads, in healthy people, to stress of the functional status of the pituitary-thyroid system, as evidenced by a reduction in the

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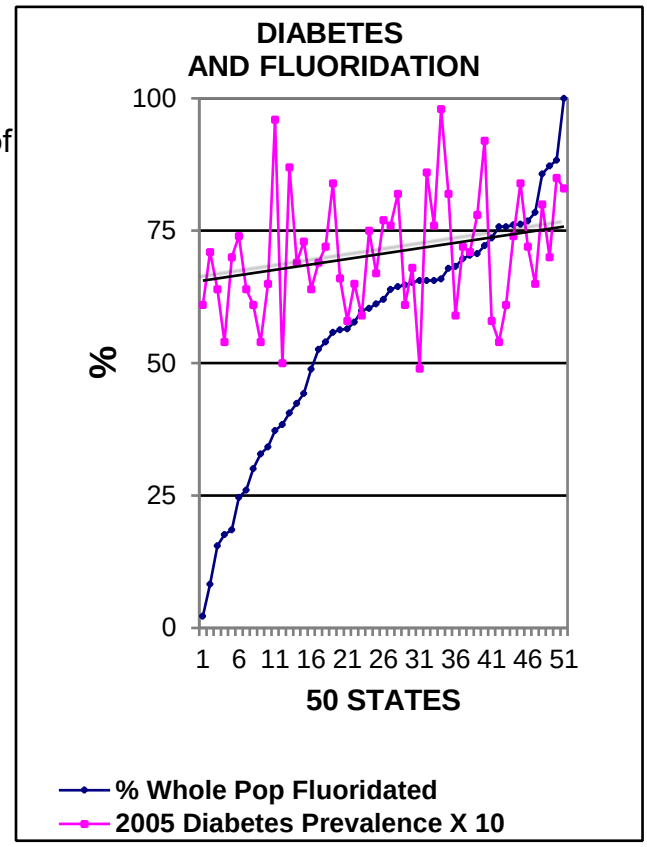
[179] Xu Y, et al. (1994). The effect of fluorine on the level of intelligence in children. *Endemic Disease Bulletin* 9(2):83-84.

[180] Lin F; et al (1991). The relationship of a low-iodine and high-fluoride environment to subclinical cretinism in Xinjiang. *Endemic Disease Bulletin* 6(2):62-67 (republished in *Iodine Deficiency Disorder Newsletter* Vol. 7(3):24-25).

[181] Liu Z, et al. (1988). An investigation on the serum thyroid hormones and fluoride concentrations in patients with endemic fluorosis. Chinese Journal of Endemiology 7(4):216-18. [Article in Chinese with English summary]

[182] Bachinskii PP et al. 1985. Action of the body fluorine of healthy persons and thyroidopathy patients on the function of hypophyseal-thyroid the system. Probl Endokrinol (Mosk) 31(6):25-9. [Article in Russian, translated into English]

concentration of T3, an increase in the production (by the hypothalamus) of TSH in the serum, and a more avid uptake of I131 by the thyroid tissue. This permits us to classify the excessive accumulation of fluorine in the body as a risk factor providing a basis for the development of thyroid dysfunction."



Yu (1985)[183] "A study on the serum T4, T3 and TSH levels was performed in 27 patients with chronic skeletal fluorosis and the data obtained were compared with those of 20 health persons. The results showed that serum T4 in the patients was lower than in the controls and TSH was higher, while serum T3 showed no significant difference. There was no goiter found in the patients. These data indicate that fluorine may reduce serum T4 by interfering [with] thyroid function.The increase of TSH secretion is the consequence stimulated by a feedback mechanism but no proliferation and enlargement of the thyroid gland resulted . . . ."

[183] Yu Y. (1985). Study on serum T4, T3, and TSH levels in patients with chronic skeletal fluorosis. Chinese Journal of Endemiology 4(3):242-43.

Graphing the 50 US states ranked on the percentage of the whole population fluoridated and plotting their respective rate of diabetes (X10)[184] provides this graph, perhaps a 10% increase in diabetes. Remember, fluoridated water represents only about half of fluoride exposure.

Treatment

ANIMAL TREATMENT Sarkar (2014) Resveratrol (3,4,5-trihydroxystilbene), a polyphenol and well-known natural antioxidant has been evaluated for its protective effect against fluoride-induced metabolic dysfunctions in rat thyroid gland. . .Resveratrol supplementation in fluoride-exposed animals appreciably prevented metabolic toxicity caused by fluoride and restored both functional status and ultra-structural organization of the thyroid gland towards normalcy. This study first establishes the therapeutic efficacy of resveratrol as a natural antioxidant in thyroprotection against toxic insult caused by fluoride."[185]

[184] Note: In order to view the data on one graph, the percentage of fluoridated in each state is correct but the percentage of diabetes is increased by 10 fold. In other words, 75 is actually 7.5% for diabetes and 75% for fluoridation. Source of data: http://apps.nccd.cdc.gov/nohss/FluoridationV.asp
http://www.unitedhealthfoundation.com/shr2005/components/obesity.html
http://pubs.usgs.gov/circ/2004/circ1268/htdocs/table05.html

[185] Sarkar C[1], Pal S. Ameliorative effect of resveratrol against fluoride-induced alteration of thyroid function in male wistar rats. Biol Trace Elem Res. 2014 Dec;162(1-3):278-87. doi: 10.1007/s12011-014-0108-3. Epub 2014 Aug 28.

B. PARATHYROID GLAND

Wang (2015)[186] "Parathyroid hormone (PTH), PTH-related peptide (PTHrP), and calcium-sensing receptor (CaSR) play important roles in maintaining calcium homeostasis. Here, we study the effect of fluoride on expression of PTH, PTHrP, and CaSR both in vitro and in vivo. MC3T3-E1 cells and Sprague-Dawley rats were treated with different concentrations of fluoride. Then, the free calcium ion concentration in cell culture supernatant and serum were measured by biochemical analyzer. The expression of PTH, PTHrP, and CaSR was analyzed by qRT-PCR and Western blot. We found that the low dose of fluoride increased ionized calcium (i[Ca(2+)]) and the high dose of fluoride decreased i[Ca(2+)] in cell culture supernatant. The low dose of fluoride inhibited the PTH and PTHrP expression in MC3T3-E1 cells. The high dose of fluoride improved the PTHrP expression in MC3T3-E1 cells. Interestingly, we found that NaF decreased serum i[Ca(2+)] in rats. Fluoride increased CaSR expression at both messenger RNA (mRNA) and protein levels in MC3T3-E1 cells and rats. The expression of PTHrP protein was inhibited by fluoride in rats fed regular diet and was increased by fluoride in rats fed low-calcium diet. Fluoride also increased the expression of PTH, NF-kappaB ligand (RANKL), and osteoprotegerin (OPG) in rats. The ratio of RANKL/OPG in rats fed low-calcium food in presence or absence of fluoride was significantly increased. These results indicated that fluoride might be able to affect calcium homeostasis by regulating PTH, PTHrP, and CaSR."

Shashi (2013)[187] **Abstract:** The present study assessed the effect of fluoride on parathyroid function in 860 patients (mean age 32.50±10.50) affected with skeletal fluorosis, selected randomly from endemic fluorotic areas of district Bathinda, Punjab, India. The fluoride content in water sources was found to vary from 0.68-

[186]Wang Y1, Duan XQ, Zhao ZT, Zhang XY, Wang H, Liu DW, Li GS, Jing L., Fluoride Affects Calcium Homeostasis by Regulating Parathyroid Hormone, PTH-Related Peptide, and Calcium-Sensing Receptor Expression. Biol Trace Elem Res. 2015 Jun;165(2):159-66. doi: 10.1007/s12011-015-0245-3. Epub 2015 Feb 3.

[187]*A Shashi and Swati Singla.* **Parathyroid Function in Osteofluorosis,** World Journal of Medical Sciences 8 (1): 67-73, 2013 ISSN 1817-3055 © IDOSI Publications, 2013**,** DOI: 10.5829/idosi.wjms.2013.8.1.72168 http://www.idosi.org/wjms/8(1)13/11.pdf

15.78 mg/L in study areas. Hence, the study areas were categorized as five different groups Control (0.68- 1.00 mg/L), A-I (1.01-4.00 mg/L), A-II (4.01-8.00 mg/L), A-III (8.01-12.00 mg/L) and A-IV (12.01-16.00 mg/L). An age and sex matched group of 140 control subjects without skeletal fluorosis were also included. The functional activity of the parathyroid was measured by radio immuno assay of parathyroid hormone (PTH). The biochemical estimations were made for serum and urinary fluoride, serum calcium, phosphorus, calcitonin and alkaline phosphatase (ALKP). The results revealed that level of serum and urinary fluoride was significantly ($p<0.001$) higher in fluorotic patients in comparison to control. The serum PTH, calcitonin and activity of ALKP was significantly ($P<0.001$) elevated in fluorotic patients. Significant ($P<0.05$) hypocalcaemia was observed in study group A-I and A-II and elevation in group A-IV. However, the alterations in calcium level in group A-III was statistically non significant. Hyperphosphatemia ($P<0.001$) was also observed in patients of fluorosis. Pearson's bivariate correlation showed positive correlation between water F vs serum F ($r= 0.98$, $P<0.001$), serum F vs PTH ($r= 0.97$, $P<0.007$), serum F vs calcitonin ($r=0.80$, $P<0.01$) and serum F vs ALKP ($r=0.93$, $P<0.02$). Negative correlation was noted between serum and urinary concentration of fluoride. When the serum fluoride concentration was increased the corresponding urinary fluoride excretion declined along with the advancing age. It may be concluded that high fluoride ingestion has a definite relation with increased calcitonin concentration, which may be the major cause of hypocalcemia in fluorotic patients, which may further leads to the increased parathyroid function i.e raised PTH levels in the serum to maintain serum calcium levels and may have a role in toxic manifestations of clinical and skeletal fluorosis."

Puranik (2013)[188] "Objective: This study investigated fluoride's effects on iPTH secretion and its underlying mechanism. . . . Conclusion: Fluoride modulates iPTH secretion in vitro and in vivo. However, Fluoride's action on the parathyroid gland is

[188] *Puranik, Chaitanya Prakash*, Ph.D., **Effect of Fluoride on Parathyroid Hormone Secretion,** Dissertation. **THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL**, 2013, 129 pages; 3606754

not mediated through CASR. While fluoride's effects, in vitro, were equivalent between the two mouse strains, early strain-dependent effect on iPTH secretion was observed in vivo. Difference in fluoride-mediated gene expression in C3H and B6 suggests an underlying difference in physiologic handling of fluoride by the two strains."

Peng (2013)[189] "Chronic exposure to combined fluoride and arsenic continues to be a major public health problem worldwide, affecting thousands of people. In recent years, more and more researchers began to focus on the interaction between the fluorine and the arsenic. In this study, the selected investigation site was located in China. The study group was selected from people living in fluoride-arsenic polluted areas due to burning coal. The total number of participants was 196; including the fluoride-arsenic anomaly group (130) and the fluoride-arsenic normal group (63). By observing the changes in gene and protein expression of PTH/PKA/AP1 signaling pathway, the results show that fluoride can increase the expression levels of PTH, PKA, and AP1, but arsenic can only affect the expression of AP1; fluoride and arsenic have an interaction on the expression of AP1. Further study found that fluoride and arsenic can affect the mRNA expression level of c-fos gene (AP1 family members), and have an interaction on the expression of c-fos, but not c-jun. The results indicate that PTH/PKA/AP1 signaling pathway may play an important role in bone toxicity of fluoride. Arsenic can affect the expression of c-fos, thereby affecting the expression of transcription factor AP1, indirectly involved in fluoride-induced bone toxicity."

Gutowska (2013)[190] "Chronic long-term exposure to high levels of fluoride leads to fluorosis, manifested by skeletal fluorosis and damage to internal organs, including kidneys, liver, parathyroid glands, and brain. Excess fluoride can also cause DNA

[189]Zeng QB1, Xu YY1, Yu X2, Yang J2, Hong F3, Zhang AH1. Arsenic may be involved in fluoride-induced bone toxicity through PTH/PKA/AP1 signaling pathway. Environ Toxicol Pharmacol. 2014 Jan;37(1):228-33. doi: 10.1016/j.etap.2013.11.027. Epub 2013 Dec 7.

[190] Gutowska I1, Baranowska-Bosiacka I, Siwiec E, Szczuko M, Kolasa A, Kondarewicz A, Rybicka M, Dunaj-Stanczyk M, Wiernicki I, Chlubek D, Stachowska E. Lead enhances fluoride influence on apoptosis processes in liver cell line HepG2. Toxicol Ind Health. 2013 Nov 5. [Epub ahead of print]

damage, trigger apoptosis, and change cell cycle. The effect of fluoride may be exacerbated by lead (Pb), a potent inhibitor of many enzymes and a factor causing apoptosis, still present in the environment in excessive amounts. Therefore, in this study, we investigated the effects of sodium fluoride (NaF) and/or lead acetate (PbAc) on development of apoptosis, cell vitality, and proliferation in the liver cell line HepG2. We examined hepatocytes from the liver cell line HepG2, incubated for 48 h with NaF, PbAc, and their mixture (NaF + PbAc), and used for measuring apoptosis, index of proliferation, and vitality of cells. Incubation of the hepatocytes with NaF or PbAc increased apoptosis, more when fluoride and Pb were used simultaneously. Vitality of the cells depended on the compound used and its concentration. Proliferation slightly increased and then decreased in a high fluoride environment; it decreased significantly after addition of Pb in a dose-dependent manner. When used together, fluoride inhibited the decreasing effect of Pb on cell proliferation."

Wen (2012)[191] The aim of this study was to explore the association of parathyroid hormone (PTH) gene Bst BI polymorphism, calciotropic hormone levels, and dental fluorosis of children. A case-control study was conducted in two counties (Kaifeng and Tongxu) in Henan Province, China in 2005-2006. Two hundred and twenty-five children were recruited and divided into three groups including dental fluorosis group (DFG), non-dental fluorosis group (NDFG) from high fluoride areas, and control group (CG). Urine fluoride content was determined using fluoride ion selective electrode; PTH Bst BI were genotyped using PCR-RFLP; osteocalcin (OC) and calcitonin (CT) levels in serum were detected using radioimmunoassay. Genotype distributions were BB 85.3% (58/68), Bb 14.7% (10/68) for DFG; BB 77.6% (52/67), Bb 22.4% (15/67) for NDFG; and BB 73.3% (66/90), Bb 27.7% (24/90) for CG. No significant difference of Bst BI genotypes was observed among three groups ($P > 0.05$). Serum OC and urine fluoride of children were both significantly higher in DFG and NDFG than in CG ($P < 0.05$, respectively), while a similar situation was not

[191]Wen S1, Li A, Cui L, Huang Q, Chen H, Guo X, Luo Y, Hao Q, Hou J, Ba Y., The relationship of PTH Bst BI polymorphism, calciotropic hormone levels, and dental fluorosis of children in China., Biol Trace Elem Res. 2012 Jun;147(1-3):84-90. doi: 10.1007/s12011-011-9313-5. Epub 2012 Jan 5.

observed between DFG and NDFG in high fluoride areas (P > 0.05). Serum OC level of children with BB genotype was significantly higher compared to those with Bb genotype in high fluoride areas (P < 0.05). However, no significant difference of serum CT or calcium (Ca) was observed. In conclusion, there is no correlation between dental fluorosis and PTH Bst BI polymorphism. Serum OC might be a more sensitive biomarker for detecting early stages of dental fluorosis, and further studies are needed.

The parathyroid gland produces parathyroid hormone (PTH). PTH regulates the amount of calcium in our bones and blood supply. When the calcium level in blood starts to fall, PTH triggers the breakdown of bone tissue as a means of transferring the body's stored supply of calcium into the blood supply. When the parathyroid produces too much PTH a condition known as hyperparathyroidism develops. Hyperparathyroidism has been found to occur as a secondary effect of the fluoride-induced bone disease skeletal fluorosis, and may help to explain some of the bone effects encountered in fluorosis.

When calcium is removed from the bones (osteoclastic activity) the fluoride in the bones increases blood fluoride concentrations.

Gupta et al. (2001)[192] and Suketa (2002) show again that in cases of fluorosis there is hyperparathyroidism, as seen in elevated parathyroid hormone (PTH) levels.

Acevedo (1996)[193] Chardin (1998)[194] When thyroid and parathyroid glands are removed in subjects, same mineral effects occur as can be observed in dental fluorosis patients.

[192] Gupta SK, Khan TI, Gupta RC, Gupta AB, Gupta KC, Jain P, Gupta A - "Compensatory hyperparathyroidism following high fluoride ingestion - a clinico - biochemical correlation" Indian Pediatr 38(2):139-46 (2001)
[193] Acevedo AC, Chardin H, Staub JF, Septier D, Goldberg M - "Morphological study of amelogenesis in the rat lower incisor after thyro-parathyroidectomy, parathyroidectomy and thyroidectomy." Cell Tissue Res 283(1):151-7 (1996)
[194] Chardin H, Acevedo AC, Risnes S - "Scanning electron microscopy and energy-dispersive X-ray analysis of defects in mature rat incisor enamel after thyroparathyroidectomy." Arch Oral Biol 43(4):317-27 (1998)

Stamp (1990)[195]

"1. To determine the relationships between parathyroid hormone activity and long-term sodium fluoride therapy in osteoporosis . . . .

2. Cross-sectional data showed a fourfold mean increase in biologically active parathyroid hormone on fluoride treatment . . . .

3. Fluoride-treated patients were then analysed in two groups according to the level of biologically active parathyroid hormone. . . .

4. Results show that long-term fluoride and calcium therapy increase biologically active parathyroid hormone in osteoporosis and that excessive parathyroid hormone activity may account for certain features of the refractory state."

Chen (1988)[196] "Fluoride ion (F-) alone or in conjunction with aluminum (Al3+) has been shown to stimulate the activity of guanine nucleotide-binding proteins (G proteins) in cell membrane preparations from a variety of cell types and in intact hepatic cells. Several studies have indicated that G proteins are involved in the regulation of parathyroid hormone (PTH) secretion. Intracellular second messengers which modulate PTH secretion (e.g., cAMP) have also been found to be regulated by G proteins. We have, therefore, employed F- as a probe to investigate the possible role of G proteins in the modulation of PTH release and the intracellular second messengers that have been implicated in the control of PTH secretion. F- produces a dose-dependent inhibition of PTH release with a maximal inhibitory effect (67%) at 5 mM. F- exerts its inhibitory effect within 5 min and the degree of suppression of PTH secretion gradually increases over 1 hr. F- (5 mM) inhibits PTH secretion at 0.5 mM Ca2+ to the level observed with 2 mM Ca2+ alone; moreover, the effects of F- and high Ca2+ are not additive. . . . We conclude that F- is a potent inhibitor of PTH secretion."

[195]Stamp TC1, Saphier PW, Loveridge N, Kelsey CR, Goldstein AJ, Katakity M, Jenkins MV, Rose GA. Fluoride therapy and parathyroid hormone activity in osteoporosis. Clin Sci (Lond). 1990 Sep;79(3):233-8.

[196]Chen CJ1, Anast CS, Brown EM. Effects of fluoride on parathyroid hormone secretion and intracellular second messengers in bovine parathyroid cells. J Bone Miner Res. 1988 Jun;3(3):279-88.

Mertz (1987)[197] “Fluorine is known to bind calcium in the body, causing ionic calcium to decrease; this, in turn, causes secondary hyperparathyroidism.”

However, more recent investigations have revealed that a new mechanism of action: hyperparathyroidism is caused by chronically elevated TSH levels. (Fluoride is **the** TSH clone]. Elevated TSH levels are usually seen in hypothyroidism, and therefore explain why hyperparathyroidism is so closely associated with hypothyroidism (Paloyan et al,1997).[198]

Hyperparathyroidism is ten times more frequent in thyroid patients than expected in a general medical population and is especially prevalent in patients with **goiter** (Stoffer, 1982).

Roy (1962) “These experiments may be interpreted to show that the effect of NaF is to reduce the solubility of the apatite complex and thus to lower the basic level of equilibrium of calcium between fluid and solid phases. To compensate for this decreased level, the glands of the intact animals are required to increase secretion with an ultimate increase in osteoclast proliferation.”[199]

[197] [Trace Elements in Human and Animal Nutrition - Fifth Edition, Edited by Walter Mertz, U. S. Dept. of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Beltsville, Maryland, p. 375 (1987)

[198] Paloyan Walker R, Kazuko E, Gopalsami C, Bassali J, Lawrence AM, Paloyan E - "Hyperparathyroidism associated with a chronic hypothyroid state" Laryngoscope 107(7):903-9 (1997)

[199] Roy V. Talmage, S.B. Doty The effect of sodium fluoride on parathyroid function in the rat as studied by peritoneal lavage General and Comparative Endocrinology Volume 2, Issue 5, October 1962, Pages 473–479

C. PANCREAS:

The pancreas produces a hormone called insulin which regulates the uptake of glucose from the bloodstream. Fluoride increases the levels of glucose in the blood. Vinals provides a review and background of the mechanism which fluoride acts on the insulin receptors and is moved to the top of the list of studies to provide a foundation.

Vinals (1993)[200] "Fluoride is a nucleophilic reagent which has been reported to inhibit a variety of different enzymes such as esterases, asymmetrical hydrolases and phosphatases. In this report, we demonstrate that fluoride inhibits tyrosine kinase activity of insulin receptors partially purified from rat skeletal muscle and human placenta. Fluoride inhibited in a similar dose-dependent manner both β-subunit autophosphorylation and tyrosine kinase activity for exogenous substrates. This inhibitory effect of fluoride was not due to the formation of complexes with aluminium and took place in the absence of modifications of insulin-binding properties of the insulin receptor. Fluoride did not compete with the binding site for ATP or Mn2+. Fluoride also inhibited the autophosphorylation and tyrosinekinase activity of receptors for insulin-like growth factor I from human placenta. Addition of fluoride to the pre-phosphorylated insulin receptor produced a slow (time range of minutes) inhibition of receptor kinase activity. Furthermore, fluoride inhibited tyrosine kinase activity in the absence of changes in the phosphorylation of pre-phosphorylated insulin receptors, and the sensitivity to fluoride was similar to the sensitivity of the unphosphorylated insulin receptor. The effect of fluoride on tyrosine kinase activity was markedly decreased when insulin receptors were pre-incubated with the copolymer of glutamate/tyrosine. Prior exposure of receptors to free tyrosine or phosphotyrosine also prevented inhibitory effect of fluoride. However, the protective effect of erosion or phosphotyrosine was maximal at low concentrations, suggesting the interaction of these compounds with the receptor itself rather than with fluoride. These data suggest: (i) that fluoride interacts directly and slowly with the insulin receptor, which causes inhibition of its

[200] VINALS F, TESTAR X, PALACIN M and ZORZANO A. Inhibitory effect of fluoride on insulin receptor autophosphorylation and tyrosinekinase activity, "Biochem.J.(1993)291,615-622(PrintedinGreatBritain) 615

phosphotransferase activity; (ii) that the binding site of fluoride is not structurally modified by receptor phosphorylation; and (iii) based on the fact that fluoride inhibits phosphotransferase activity in the absence of alterations in the binding of ATP, Mn2+ or insulin, we speculate that fluoride binding might affect the transfer of phosphate from ATP to the tyrosine residues of the β-subunite of the insulin receptor and to the tyrosine residues of exogenous substrates.

"The insulin receptor is a disulphide-linked herotetrameric membrane glycoprotein consisting of two alph (M 135000) and two transmembrane beta (M 95000) subunits (Massague et al., 1981); Massage and Czech, 1982; Ullrich et al, 1985; Ebina et al., 1985). The alpha subunits are entirely extracellular and participate in insulin binding, whereas the beta-subunits contain extracellular , transmembrane and intracellular domains. . . . The tyrosine kinase activity of the insulin receptor appears to be essential for certain cellular responses to insulin. Thus anti-insulin-receptor antibodies, which inhibit the kinase activity of the insulin receptors, also block the ability of cells to respond to insulin (Morgan et al., 1986; Morgan and Roth, 1987). In addition, the microinjection of insulin receptors in *Xenopus* oocytes causes an increase in the phosphorylation of ribosomal S6 subunit, which is further increased by prior receptor activation, due to insulin-receptor autophosphorylation (Maller et al., 1986). Studies with receptors mutated at the ATP-binding site (Chou et al., 1987; Ebina et al., 1987; McClain et al., 1987) or at tyrosine residues 1162 and 1163 (Ellis et al., 1986; Decant et al., 1988) have also led to the conclusion that that tyrosine phosphotransferase function of the insulin receptor is an absolute requirement for the hormone to activate the receptor signaling function in cells.

"Based on the pivotal role of insulin-receptor kinase activity on insulin action, the catalytic properties of the insulin-receptor kinase require thorough characterization. In studies initially designed to investigate the interaction between regulatory G-proteins and insulin receptors, we substantiated a potent inhibitory effect of fluoride on insulin-receptor kinase activity. On the basis of this finding and the fact that the use of fluoride , a potent nucleophilic reagent (Edwards and Pearson, 1962), has yielded useful information on the kinetics of a variety of enzymes (Layne and Najjar, 1975; Bunick and Kashket, 1982; Nilsson and Branden, 1982), we have characterized the inhibitory effect

of fluoride on insulin-receptor autophosphorylation and receptor kinase for exogenous substrates."

(A few references primarily in author alphabetical order are provided here. I have not read each article and only a few quotes which were handy, are included here.)

Adebayo 2012[201] "We conclude that fluoride exerts biochemical effect on **lipid peroxidation** and antioxidant enzymes of both PU and well-fed rats. This effect varied widely between the liver and the pancreas but it seems that the liver is more sensitive to the toxic assault of fluoride than the pancreas especially in PU rats."

Agalakova (2012)[202] "The molecular mechanisms underlying fluoride toxicity are different by nature. Fluoride is able to stimulate G-proteins with subsequent activation of downstream signal transduction pathways such as PKA-, PKC-, PI3-kinase-, Ca2+-, and MAPK-dependent systems. G-protein-independent routes include tyrosine phosphorylation and protein phosphatase inhibition. Along with other toxic effects, fluoride was shown to induce oxidative stress leading to excessive generation of ROS, lipid peroxidation, decrease in the GSH/GSSH ratio, and alterations in activities of antioxidant enzymes, as well as to inhibit glycolysis thus causing the depletion of cellular ATP and disturbances in cellular metabolism. Fluoride triggers the disruption of mitochondria outer membrane and release of cytochrome c into cytosol, what activates caspases-9 and -3 (intrinsic) apoptotic pathway. Extrinsic (death receptor) Fas/FasL-caspase-8 and -3 pathway was also described to be implicated in fluoride-induced apoptosis. Fluoride decreases the ratio of antiapoptotic/proapoptotic Bcl-2 family proteins and upregulates the expression of p53 protein. Finally, fluoride changes the expression profile of

[201] Olusegun Lateef Adebayo and Gbenga Adebola Adenuga, 2012. Biochemical Changes in the Liver and the Pancreas of Well-fed and Protein Undernourished Rats Following Fluoride Administration. *Asian Journal of Applied Sciences, 5: 215-223.*

[202] Natalia Ivanovna Agalakova and Gennadii Petrovich Gusev. Molecular Mechanisms of Cytotoxicity and Apoptosis Induced by Inorganic Fluoride, ISRN Cell Biology, Volume 2012 (2012), Article ID 403835, 16 pages http://dx.doi.org/10.5402/2012/403835

apoptosis-related genes and causes endoplasmic reticulum stress leading to inhibition of protein synthesis.

Banu P et al. Toxicity of fluoride to diabetic rats. Fluoride 1997 30(1) 43-50.

Birkner E, et al. Influence of sodium fluoride and caffeine on the concentration of fluoride ions, glucose, and urea in blood serum and activity of protein metabolism enzymes in rat liver. Bill Trace Elem Res. 2006 112(2) 169-74.

Boros I et al. Fluoride intake, distribution, and bone content in diabetic rats consuming fluoridated drinking water. Fluoride 1998 31(1) 33-42.

Bolgul BS et al. Evaluation of caries risk factors and effects of fluoride-releasing adhesive material in children with insulin-dependent diabetes mellitus (IDDM): Initial first-year results. Act Odontological Scandinavia, 2004 62(5) 289-292.

Chehoud KA, Chiba FY, Sassaki Kt, et al. Effects of fluoride intake on insulin sensitivity and insulin signal transduction. Fluoride. October-December 2008 41(4) 270-275.

Chiba FY, Garbin CAS, Sumida DH. Effect of fluoride intake on carbohydrate metabolism, glucose tolerance, and insulin signaling. Fluoride July-September 2012 45(3 Pt 2) 239-241.

Chiba FY, Colombo NH, Shirakashi DJ, Gomes WD, Moimaz SAS, Garbin CAS, Silva CA, Sumida DH. Insulin signal decrease in muscle but not in the liver of castrated male rats from chronic exposure to fluoride. Fluoride January-March 2010. 43(1)25-30.

Chlubek D et al. Activity of pancreatic anti oxidative enzymes and malondialdehyde concentrations in rats with hyperglycemia caused by fluoride intoxication. J. Trace Elem. Med. Bill. 2003 17 57-60.

Chlulnek D, et al. Activity of Pancreatic antioxidative enzymes and malondialdehyde concentrations in rats with hyperglycemia caused by fluoride intoxication. Journal of trace elements in medicine and biology. 2003, vol 17(1)57-60.

Chuba FY, Columbo NH et al. NaF treatment increases TNF-a and resistin concentrations and reduces insulin signal in rats. Journal of Fluorine Chemistry 2012 136 3-7.

Eliud (2009)[203] "Chronic exposure to high fluoride (F^-) may lead to local tissue disturbances, known as fluorosis. F^- is an oxidizing agent and a well-known reversible enzymatic inhibitor that interferes with the enzyme activity of at least 80 proteins. The goals of the current study were to evaluate whether F^- exposure affected the oral glucose tolerance test (OGTT) in C57BL6 mice; and to determine the mechanisms at work in glucose homeostasis at the cellular level, in mouse pancreatic β-cells (βTC-6) exposed to F^-…. Exposure to high levels of F^- in drinking water may decrease insulin mRNA and its secretion from β-cells, and might therefore affect the OGTT."

Garcia-Montalvo EA, Reyes-Perez H, Del Razo LM. Fluoride exposure impairs glucose tolerance via decreased insulin expression and oxidative stress. Toxicology September 19 2009 263(2-3) 75-83.

Greenberg LW, Nelsen CE, Kramer N. Nephrogenic diabetes insipidus with fluorosis. Pediatrics 1974 54 320-322.

[203] Eliud A. García-Montalvo, Hugo Reyes-Pérez, Luz M. Del Razo, Fluoride exposure impairs glucose tolerance via decreased insulin expression and oxidative stress. Toxicology September 2009, 263(2-3) 75-83.

GutowaskI, Baranowska-Bosiack I et al. Changes in the concentration of fluoride in the serum and bones of female rats with strptozotocin induced diabetes. Fluoride 2009. January-March 42(1) 9-16.

Gruck-Mamczar E, et al. Activities of some enzymes and concentration of ammonia in serum of rats with fluoride hyperglycemia. Ann Acad Med Stetin. 2004 50 Suppl 1 36-41.

Hattori Y, Matsuda N, Sato A, Watanuki S, Tomioka H, Kawasaki H, Kanno M. Predominant contribution of the G protein-mediated mechanism to NaF-induced vascular contractions in diabetic rats: association with an increased level of G(qalpha) expression. J Pharmacy Exp there. 2000 292(2) 761-8.

Hu (2012)[204] "Studies on the role of insulin and insulin receptor (InsR) in the process of skeletal fluorosis, especially in osteogenic function, are rare. We evaluated the effect of increasing F^- doses on the marker of bone formation, serum insulin level and pancreatic secretion changes in vivo and mRNA expression of InsR and osteocalcin (OCN) in vitro. . . .To sum up, there existed a close relationship between insulin secretion and fluoride treatment. The insulin signal pathway might be involved in the underlying occurrence or development of skeletal fluorosis."

Irmak (2014)[205] "The incidence of type 1 diabetes (T1D) has increased substantially in Finland, but the exact trigger for the onset of T1D is still unknown. We know that use of amoxicillin and anti-cariogenic fluoride tablets is a common practice for children in Finland. It seems that beta-cell destruction is initiated by modification of the proinsulin by combined effects of fluoride (F2) and amoxicillin. Amoxicillin especially

[204] Hu CY1, Ren LQ, Li XN, Wu N, Li GS, Liu QY, Xu H. Effect of fluoride on insulin level of rats and insulin receptor expression in the MC3T3-E1 cells. Biol Trace Elem Res. 2012 Dec;150(1-3):297-305. doi: 10.1007/s12011-012-9482-x. Epub 2012 Aug 8.

[205] M. Kemal Irmak, Ilknur Senver Ozcelik, Abdullah Kaya. Fluoride toxicity and new-onset diabetes in Finland: a hypothesis. J Exp Integr Med. 2014; 4(1): 3-8
doi: 10.5455/jeim.011113.hp.007

when used together with clavulanic acid results in an acid environment around the beta-cells that promotes the conversion of F2 to hydrogen fluoride (HF). Unlike F2, HF can diffuse easily into the beta-cell cytosol. Because the cytosol has a neutral pH, virtually all HF reverts to F2 in the cytosol and F2 cannot easily diffuse out of the cell. Exposure to excess F2 promotes proinsulin covalent dimerization and simultaneously hyperexpression of MHC Class I molecules. Proinsulin dimers then migrate to the cell membrane with MHC class I molecules, accumulate at the beta-cell membrane and produces a powerful immunogenic stimulus for the cytotoxic T-cells. Production of cytotoxic cytokines from the infiltrating T-cells initiates the destruction of beta-cells. In Finnish children, this might be helped along by a higher beta-cell activity and by a reactive thymus-dependent immune system induced by higher levels of thyroid hormones and calcitonin respectively. After repeated similar attacks, more and more effector T-cells are raised and more and more beta-cells are destroyed, and clinical diabetes occurs."

Lima Leite A, (2014) "Administration of high doses of fluoride (F) can alter glucose homeostasis and lead to insulin resistance (IR)."

Lobo JG, Leite AL, Pereira HA, Fernandes MS, Peres-Buzalaf C, Sumida DH, Rigalli A, Buzalaf MA. Low-Level Fluoride Exposure Increases Insulin Sensitivity in Experimental Diabetes. J Dent Res. 2015 Jul;94(7):990-7. doi: 10.1177/0022034515581186. Epub 2015 Apr 10.

Lombarte, Mercedes Fina, Brenda L Lupo, Maela Buzalaf et al. Physical exercise ameliorates the toxic effect of fluoride on the insulin-glucose system. Journal of Endocrinology. 2013. 218 (1) 99-103.

Lupo M, Buzalaf MA, Rigalli A, Effect of fluoridated water on plasma insulin levels and glucose homeostasis in rats with renal deficiency. Biological Trace Element Research. 2001. 140 198-207.

Menoyo I, Puche RC Rigalli A. Fluoride-induced resistance to insulin in the rat. Fluoride 2008 41 260-269.

MenoyoI Rigalli A, Puche RC. Effect of fluoride on the secretion of insulin in the rat. Arzneimittel Forschung (Drg Res) 2005 55(5) 455-60.

Michaud DS. Epidemiology of pancreatic cancer. Minerva Chir, 2004 59(2)99-111.

Mohammed AHS, Ata S, Dawood EM. Influence of the different does of sodium fluoride on the rabbit exocrine pancreas. Hist-pathological study. Technical Instutitue/Kufa. www.iasj.net/iasj?func=fulltext&aId=39462

National Health and Medical Research Council (NHMRC) 2007. A systematic review of the efficacy and safety of fluoridation Part B: EXCLUDED STUDIES.

NRC (2006) page 214. "OTHER ENDOCRINE ORGANS "The effects of fluoride exposure have been examined for several other endocrine organs, including the adrenals, the pancreas, and the pituitary (for details, see Appendix E, Tables E-16 and E-17). Effects observed in animals include changes in organ weight, morphological changes in tissues, increased mitotic activity, decreased concentrations of pituitary hormones, depressed glucose utilization, elevated serum glucose, and elevated insulin-like growth factor-1 (IGF-1). Effects reported in humans include "endocrine disturbances," impaired glucose tolerance, and elevated concentrations of pituitary hormones. Studies of the effects of fluoride on glucose metabolism and in diabetic animals are discussed below; information on other effects is extremely limited.

Pan (2015)[206] "Two-dimensional gel electrophoresis (2-DE) was used to detect fluoride-induced alterations in the proteome of the rat hippocampus. Male Sprague-Dawley

[206] Pan Y, Lü P, Yin L, Chen K, He Y., Z Effect of fluoride on the proteomic profile of the hippocampus in rats. Naturforsch C. 2015 Jun 13. pii: /j/znc.ahead-of-print/znc-2014-4158/znc-2014-4158.xml. doi: 10.1515/znc-2014-4158. [Epub ahead of print]

rats (n=30) were subjected to treatments three weeks after weaning. Animals of the first group were injected intraperitoneally (i.p.) with aqueous NaF (20 mg/kg/body weight/day), the second group, injected with physiological saline, served as the control. After 30 days, the body weight of the fluoride-treated rats was lower than that of the control, and F- levels in serum were higher than in the control. The hippocampus was subjected to proteomic analysis, and the fluoride-treated group was found to contain 19 up-regulated and eight down-regulated proteins. The proteins, identified by mass-spectroscopic analysis of their fragments obtained after digestion, were found to be involved in amino acid biosynthesis, the insulin signaling pathway and various other crucial functions. Our results also provide useful information on the mechanism of the reduction of the learning ability and memory induced by F."

Pujary UR, Rao P, Mohanthy S, Krishna R, Reedy D. Correlation between serum fluoride and hyperglycemia in endemic fluorosis area. Indian Journal of Clinical Biochemistry. December 2007 22(Suppl) 383.

Prystupa, J. Fluorine—A current literature review. An NRC and ATSDR based review of safety standards for exposure to fluorine and fluorides. Toxicology Mechanisms and Methods. 2011. 21(2) 103-170.

Rashid K1, Sinha K, Sil PC. An update on oxidative stress-mediated organ pathophysiology. Food Chem Toxicol. 2013 Dec;62:584-600. doi: 10.1016

Rasmussen DD, Boldt BM, Wilkinson CW, Yellon SM, Matsumoto AM. Daily melatonin administration at middle age suppresses male rat visceral fat, plasma leptin, and plasma insulin to youthful levels. Endocrinology 1999. 140, 1009-1012.

Rigalli A, et al. Comparative study of the effect of sodium fluoride and sodium monofluorophosphate on glucose homeostasis in the rat. Drug Res 1995. 45(3) 289-92.

Rigalli A, Ballina JC Puche RC. Bone mass increase and glucose tolerance in rats chronically treated with sodium fluoride. Bone and Mineral. 1992. 16, 101-108.

Rigalli A. Inhibitory effect of fluoride on the secretion of insulin. Calico. Tissue Int. 1990. 46, 333-338.

Saber (2000)[207] "Influence of fluoride on exocrine pancreas cells was examined morphologically with traditional and prolonged osmium fixation techniques. . . . These findings indicate that fluoride disrupts the export of zymogens from the rER, resulting in formation of intracisternal granules and autophagosomes, and that the osmiophilic saccules participate in sequestration of cytoplasmic organelles in forming autophagosomes."

Shahed AR, et al. Effect of F on rat serum insulin levels in vivo. Journal of Dental Research. 1986. 65 756.

Tokar VI, Zyryanova VV, Shcherbakov SV. Chronic Fluorides Impact on Pancreas Islet Cells in Workers. Gigiena i Santitariia. November-December 1992, 42-44.

Trivedi N, Mithal A, Gupta SK, Godbole MM, Reversible impairment of glucose tolerance in patients with endemic fluorosis. Diabetologia, 1993 (36) 826-828.

Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Lee DH, Shioda T Soto AM, vom Saal FS, Welshons WV, Zoeller RT, Myers JP. Hormones and endocrine-disrupting chemicals: Low dose effects and nonmonotonic dose responses. Endocrine Reviews, 2012 33(3) 378-455.

[207] Saburou Matsuo, Hiroshi Nakagawa, Ken-ichi Kiyomiya, Masaru Kurebe Fluoride-induced ultrastructural changes in exocrine pancreas cells of rats: fluoride disrupts the export of zymogens from the rough endoplasmic reticulum (rER) Archives of ToxicologyFebruary 2000, Volume 73, Issue 12, pp 611-617

Wang Z, Yang X, Yang S, Ren G, Ferreri M, Su Y, Chen L, Han B. Sodium fluoride suppress proliferation and induce apoptosis through decreased insulin-like growth factor-I expression and oxidative stress in primary cultured mouse osteoblast. Archives of Toxicology, November 2011 85(11) 1407-17

Whitford, GM, Allman DW, Shahed AR. Topical fluorides: effects on physiologic and biochemical processes. J Dent Res. 1987 66(5) 1072-8.

Xie, Yong-ping, Ge Xiang-jin et al, Clinical Study of Effect of High Fluoride on the Function of the Pancreas Islet B Cells, Chinese Journal of Endemiology. 2000, 19(2) 84-85.

D. PINEAL GLAND:

In the seventeenth century, Descartes called the pineal gland the seat of the soul, the connection between the intellect and the body.[208] The pineal gland is about the size of a grain of rice (5mm X 8 mm) the only unpaired midline brain structure. It is located just below the brain in the quadrigeminal cistern and part of the epithalamus. It produces the hormone melatonin which regulates the body's circadian rhythm as well as the onset of puberty (See: Schlesinger ER, Overton DE, Chase HC, Cantwell KT (1956). Newburgh-Kingston caries-fluorine study X111. Pediatric findings after ten years. J Amer Dent Assoc 52: 296-306).

The NRC (2006) review of the literature to that date should be carefully considered and is quoted here.

"Pineal Gland Calcification

> "The pineal gland is a calcifying tissue; in humans, calcified concretions can be found at any age, although the likelihood increases with age (Vígh et al. 1998; Akano and Bickler 2003) and may be associated with menopause (Sandyk et al. 1992). The occurrence of pineal calcifications varies among different populations and nations (Vígh et al. 1998), possibly in association with the degree of industrialization (Akano and Bickler 2003), rates of breast cancer (Cohen et al. 1978), and high circannual light intensity near the equator (Vígh et al. 1998). Osteoporosis might be associated with fewer concretions (Vígh et al. 1998).
>
> "Melatonin secretion is well correlated with the amount of uncalcified pineal tissue (Kunz et al. 1999) but not with the size of pineal calcification (Vígh et al. 1998; Kunz et al. 1999). An increase in calcification of the pineal gland in humans probably represents a decrease in the number of functioning pinealocytes and a

[208] Descartes and the Pineal Gland (Stanford Encyclopedia of Philosophy)
Descartes R. "The Passions of the Soul" excerpted from "Philosophy of the Mind," Chalmers, D. New York: Oxford University Press, Inc.; 2002. ISBN 978-0-19-514581-6

corresponding decrease in the individual's ability to produce melatonin (Kunz et al. 1999). The degree of calcification, relative to the size of an individual's pineal gland, has been suggested as a marker of the individual's decreased capability to produce melatonin (Kunz et al. 1999).

"As with other calcifying tissues, the pineal gland can accumulate fluoride (Luke 1997, 2001). Fluoride has been shown to be present in the pineal glands of older people (14-875 mg of fluoride per kg of gland in persons aged 72-100 years), with the fluoride concentrations being positively related to the calcium concentrations in the pineal gland, but not to the bone fluoride, suggesting that pineal fluoride is not necessarily a function of cumulative fluoride exposure of the individual (Luke 1997, 2001). Fluoride has not been measured in the pineal glands of children or young adults, nor has there been any investigation of the relationship between pineal fluoride concentrations and either recent or cumulative fluoride intakes.

"In Vitro Studies

"Few studies have examined the effects of fluoride on pineal function. NaF (2.5-20 mM, or fluoride at 47.5-380 mg/L) produces markedly increased adenylyl cyclase activity (up to four times control activity) of rat pineal homogenates in vitro (Weiss 1969a,b), as it does in other tissues (Weiss 1969a); ATPase activity in the homogenates was inhibited by up to 50% (Weiss 1969a). Potassium fluoride (7-10 mM, or fluoride at 133-190 mg/L) has been used experimentally to increase adenylyl cyclase activity in rat pineal glands in vitro (Zatz 1977, 1979).

"Animal Studies

"Details of the effect of fluoride on pineal function are presented in Appendix E, Table E- 15. Luke (1997) examined melatonin production as a function of age and time of day in Mongolian gerbils (Meriones unguiculatus). On an absolute basis, melatonin production by the low-fluoride group was constant at ages 7-28 weeks, with no difference between males and females. Relative to body weight, melatonin output declined progressively with age until adulthood (by 11.5 weeks in females

and 16 weeks in males). In contrast, prepubescent gerbils fed the high-fluoride diet had significantly lower pineal melatonin production than prepubescent gerbils fed the low-fluoride diet. Relative to body weight, the normal higher rate of melatonin production in sexually immature gerbils did not occur.

“Sexual maturation in females occurred earlier in the high-fluoride animals (Luke 1997); males had increases in melatonin production relative to body weight between 11.5 and 16 weeks (when a decrease normally would occur), and testicular weight at 16 weeks (but not at 9 or 28 weeks) was significantly lower in high-fluoride than in low-fluoride animals. The circadian rhythm of melatonin production was altered in the high-fluoride animals at 11.5 weeks but not at 16 weeks. In high-fluoride females at 11.5 weeks, the nocturnal peak (relative to body weight) occurred earlier than in the low-fluoride animals; also, the peak value was lower (but not significantly lower) in the high-fluoride animals. In males, a substantial reduction ($P < 0.00001$) in the nocturnal peak (relative to body weight) was observed in the high-fluoride animals.

“Human Studies

“Although no studies are available that specifically address the effect of fluoride exposure on pineal function or melatonin production in humans, two studies have examined the age of onset of menstruation (age of menarche) in girls in fluoridated areas (Schlesinger et al. 1956; Farkas et al. 1983; for details, see Appendix E, Table 12

E-15) ; the earlier study was discussed by Luke (1997) as part of the basis for her research. No comparable information on sexual maturation in boys is available.”

12

Both Schlesinger et al. (1956) and Farkas et al. (1983) referred to tables of the distribution of ages at the time of first menstruation, but, in fact, both studies provided only frequencies by age (presumably at the time of study, in either 1-year or 0.5-year increments) of girls having achieved menarche by the stated age. Farkas et al. (1983) specifically indicated use of the probit method for ascertainment of the

median age at menarche; the data provided by Schlesinger et al. (1956) appear to correspond to that method, but they do not specifically mention it. The probit (or status quo) method appears to be routinely used to estimate the median (or other percentiles of) age at menarche, sometimes in conjunction with an estimated mean age at menarche based on recall data (e.g., Wu et al. 2002; Anderson et al. 2003; Chumlea et al. 2003; Padez and Rocha 2003). According to Grumbach and Styne (2002), “The method of ascertainment of the age of menarche is of importance. Contemporaneous recordings are performed with the probit method of asking, ‘yes’ or ‘no,’ are you menstruating? These may be incorrect because of social pressures of the culture and socioeconomic group considered. Recalled ages of menarche are used in other studies and considered to be accurate within 1 year (in 90% of cases) during the teenage years and in older women, too.”

“In girls examined approximately 10 years after the onset of fluoridation (1.2 mg/L, in 1945) in Newburgh, New York, the average age at menarche was 12 years, versus 12 years 5 months among girls in unfluoridated Kingston (Schlesinger et al. 1956). The authors stated that this difference was not statistically significant. Note that those girls who reached menarche during the time period of the study had not been exposed to fluoride over their entire lives, and some had been exposed perhaps for only a few years before menarche (they would have been 8-9 years old at the time fluoridation was started). Those girls in Newburgh who had been exposed to fluoridated water since birth (or before birth) had not yet reached menarche by the time of the study.

“A later study in Hungary (Farkas et al. 1983) reported no difference in the menarcheal age of girls in a town with “optimal” fluoride concentration (1.09 mg/L in Kunszentmárton, median menarcheal age 12.779 years) and a similar control town (0.17 mg/L in Kiskunmajsa; median menarcheal age 12.79 years). This study shows postmenarcheal girls present at younger ages in the higher fluoride town than in the low-fluoride town, although the reported median ages were the same (Farkas et al. 1983).

"Discussion (Pineal Function)

"Whether fluoride exposure causes decreased nocturnal melatonin production or altered circadian rhythm of melatonin production in humans has not been investigated. As described above, fluoride is likely to cause decreased melatonin production and to have other effects on normal pineal function, which in turn could contribute to a variety of effects in humans. Actual effects in any individual depend on age, sex, and probably other factors, although at present the mechanisms are not fully understood."

Luke (2001)[209] "By old age, the pineal gland has readily accumulated F and its F/Ca ratio is higher than bone. . . The pineal gland is a mineralizing tissue. . . The concretions are composed of hydroxyapatitie (HA). . . calcium is distributed throughout the pinealocytes: in the mitochondria, golgi apparatus, cytoplasm, and nucleus. Fluoride does not accumulate in the brain. Of all tissues, brain has the lowest fluoride concentrations. It is generally agreed that the blood-brain barrier restricts the passage of fluoride into the central nervous system. The human pineal gland is outside the blood-brain barrier. . . . pinealocytes have free access to fluoride in the bloodstream. This fact, coupled with the presence of HA, suggest that the pineal gland may sequester fluoride from the bloodstream." See Luke's graph below.

[209] Luke, J., Fluoride deposition in the human Pineal Gland. Caries Research | 2001; 35(2):125-128 | School of Biological Sciences, University of Surrey, Guildford, UK.

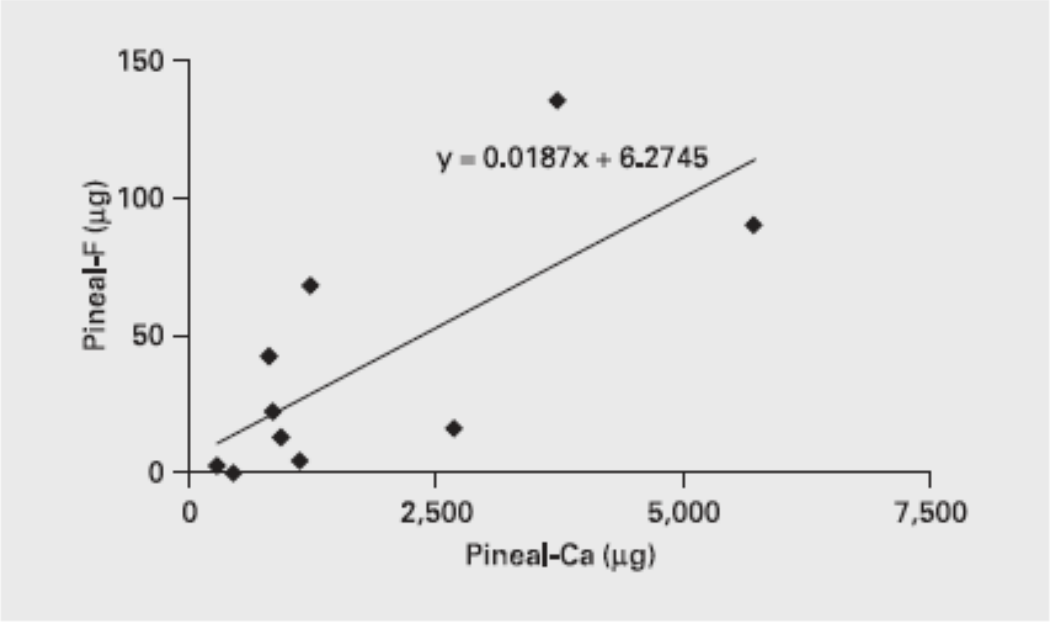


Fig. 1. The relationship between the calcium and fluoride contents of ten aged human pineal glands.

The pineal gland is bathed in cerebrospinal fluid but is not isolated by the blood brain barrier and is second only to the kidneys in blood profusion. (After the blood brain barrier is formed, the barrier mitigates fluoride transmission, but not for the pineal gland who's blood source is outside the blood brain barrier.) Innervation is sympathetic, parasympathetic, from the otic ganglia and trigeminal ganglion with nerve fibers containing the neuropeptide PACAP.

The pineal gland consists mainly of two types of pinealocytes, like photoreceptors, and decline by way of apoptosis as the age of the organism increases.[210] High concentrations of fluoride and other toxins cause apoptosis. Type 1 cells are high in mitochondria and convert the amino acid tryptophan to serotonin then N-acetyl-

[210] Polyakova, V. O., N. S. Linkova, and S. A. Pichugin (2011). "Changes in Apoptosis and Cell Proliferation in Human Pineal Gland during Aging". *Bulletin of Experimental Biology and Medicine* **150** (4): 468–70. doi:10.1007/s10517-011-1170-x. PMID 22268045.

serotonin and then to melatonin. Type 2 contain vacuoles, melatonin and are thought to act like endocrine and neuronal cells.[211]

Pinealocytes contain synaptic ribbons in children and adults but not human fetuses. Synaptic ribbons are important in neurotransmitter release.[212]

One of the difficulties in studying the pineal gland is the significant difference between rodents and higher vertebrates with rodent pineal gland lacking pineal gland neurons.

Although the effects of high concentrations of fluoride remain poorly understood, animal experiments have found that high doses of fluoride had a reduced melatonin production and an earlier onset of puberty.

The abundant melatonin levels in children are believed to inhibit sexual development which maybe a mechanism for early puberty with increased fluoride exposure.

> "Studies on rodents suggest that the pineal gland may influence the actions of recreational drugs, such as cocaine,[213] and antidepressants, such as fluoxetine (Prozac),[214] and its hormone melatonin can protect against neurodegeneration."[215]

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[211] Khavinson, V. Kh, N. S. Linkova, I. M. Kvetnoy, T. V. Kvetnaia, V. O. Polyakova, and H. W. Korf (2012). "Molecular Cellular Mechanisms of Peptide Regulation of Melatonin Synthesis in Pinealocyte Culture". *Bulletin of Experimental Biology and Medicine* **153** (2): 255–58. doi:10.1007/s10517-012-1689-5.

[212] Spiwoks-Becker, I., C. Maus, S. Dieck, A. Fejtová, L. Engel, T. Wolloscheck, U. Wolfrum, L. Vollrath, and R. Spessert (2008). "Active Zone Proteins Are Dynamically Associated with Synaptic Ribbons in Rat Pinealocytes". *Cell and Tissue Research* **333** (2): 185–95. doi:10.1007/s00441-008-0627-3. PMC 2757586. PMID 18523806.

[213] Uz T, Akhisaroglu M, Ahmed R, Manev H (2003). "The pineal gland is critical for circadian Period1 expression in the striatum and for circadian cocaine sensitization in mice". *Neuropsychopharmacology* **28** (12): 2117–23. doi:10.1038/sj.npp.1300254. PMID 12865893

[214] Uz T, Dimitrijevic N, Akhisaroglu M, Imbesi M, Kurtuncu M, Manev H (2004). "The pineal gland and anxiogenic-like action of fluoxetine in mice". *Neuroreport* **15** (4): 691–4. doi:10.1097/00001756-200403220-00023. PMID 15094477.

[215] Manev H, Uz T, Kharlamov A, Joo J (1996). "Increased brain damage after stroke or excitotoxic seizures in melatonin-deficient rats". *FASEB J* **10** (13): 1546–51. PMID 8940301.

It is only a matter of time before researchers more clearly elucidate whether fluoride's effect is a contributing or causative factor for calcification and apoptosis of the pineal gland and the resulting decrease in melatonin production, early puberty and insomnia.

Kalisinska (2014) "Fluoride concentration in the pineal gland was significantly greater than in the bone and the brain of the duck."[216]

[216] Kalisinska E1, Bosiacka-Baranowska I, Lanocha N, Kosik-Bogacka D, Krolaczyk K, Wilk A, Kavetska K, Budis H, Gutowska I, Chlubek D. Fluoride concentrations in the pineal gland, brain and bone of goosander (Mergus merganser) and its prey in Odra River estuary in Poland. Environ Geochem Health. 2014 Dec;36(6):1063-77. doi: 10.1007/s10653-014-9615-6. Epub 2014 Apr 18.

E. Adrenal Gland

Schetinina 1997)[217] The activity of carboxypeptidase (CP) H, the enzyme taking part in neuropeptide formation, and activity of recently described phenylmethylsulfonyl fluoride (PMSF)--inhibiting CP in males and females of white mongrel rats were studied. Minor differences between the CPH activities in brain regions were found in hippocampus. PMSF-inhibited activity of carboxypeptidase was significantly higher in females than in males in pituitary gland, adrenal gland, olfactory bulbus, optic and auditory bills, cerebellum, hippocampus, striatum, cerebral hemispheres and spleen. The CPH activity was 5-fold higher in ovaries than in testicles. PMSF-inhibited CP activity in testicles was 3.7-fold lower than in ovaries. Possible participation of basic CP in determination of sexual differences of some neuropeptide level and protein catabolism is studied.

Juska (1995)[218] A mathematical model relating the activity of adenylate cyclase (AC) with concentrations of stimulators, equilibrium dissociation constants, specific activity and efficacies of AC depending on the states of its binding sites has been developed and used for analysis of the data on activation of AC of bovine adrenal cortex plasma membranes presented in (De Foresta et al. (1987) FEBS Lett. 216, 107-112). Equilibrium dissociation constants. chi h and chi l, corresponding to high- and low-affinity forskolin-binding sites were estimated to be 0.37 and 17 microM: these constants characterize forskolin's potency more adequately than does ED50, the concentration eliciting half-asymptotic activity of AC. Corticotropin does not affect the affinity of AC for forskolin whereas fluoride increases this affinity, thus augmenting forskolin's potency. . . .”

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217 Shchetinina NVVernigora ANGengin MTAuthor information [Basic carboxypeptidase activity in rats of both sexes]. [Article in Russian] Ukr Biokhim Zh (1978). 1997 May-Jun;69(3):115-8.

218 Juska A, de Foresta B .Analysis of effects of corticotropin, forskolin and fluoride on activity of adenylate cyclase of bovine adrenal cortex. Biochim Biophys Acta. 1995 Jun 14;1236(2):289-98

Cannon (1994)[219] “Guanine nucleotide binding proteins (G proteins) act as signal transducers between membrane receptors and ion channels. In the present study, the whole-cell arrangement of the patch clamp technique was used to examine the effect of G proteins on K+ channels in cultured bovine adrenal chromaffin cells . . . . Treatment of the chromaffin cells with fluoride decreased nicotine-evoked secretion of catecholamines in a concentration-dependent manner. . . .”

Vitale (1993)[220] **“**The use of non-hydrolyzable analogues of GTP in permeabilized secretory cells suggests that guanine nucleotide-binding regulatory proteins (G proteins) may be involved in regulated exocytosis. . . . These results suggest that the secretory machinery in chromaffin cells can be blocked by activating a G(o) protein. Consistent with this finding, two other known activators of heterotrimeric G proteins, aluminum fluoride and benzalkonium chloride, inhibited calcium-evoked catecholamine secretion in streptolysin O-permeabilized chromaffin cells. We conclude that an inhibitory G(o) protein, possibly located on the membrane of secretory granules, is involved in the final stages of exocytosis in chromaffin cells.”

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[219] Cannon SD[1], Wilson SP, Walsh KB. A G protein-activated K+ current in bovine adrenal chromaffin cells: possible regulatory role in exocytosis. Mol Pharmacol. 1994 Jan;45(1):109-16

[220] Vitale N[1], Mukai H, Rouot B, Thiersé D, Aunis D, Bader MF. J Biol Chem. Exocytosis in chromaffin cells. Possible involvement of the heterotrimeric GTP-binding protein G(o).
1993 Jul 15;268(20):14715-23.

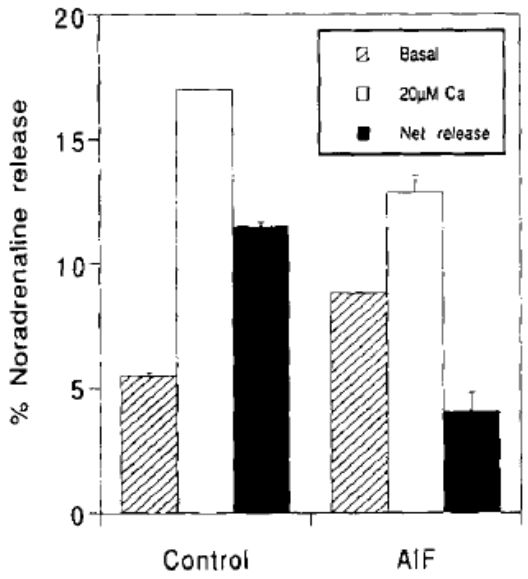

FIG. 6. **Effect of AlF_4^- on secretion from SLO-permeabilized chromaffin cells.** SLO-permeabilized cells were preincubated for 10 min in calcium-free KG medium in the presence (*AlF*) or absence (*Control*) of 20 mM NaF and 50 μM $AlCl_3$. Cells were then stimulated for 10 min with KG medium containing 20 μM free calcium (*open columns*). The basal release was estimated in calcium-free KG medium (*scratched columns*) and subtracted to obtain the net noradrenaline release (*closed columns*). AlF_4^- inhibited calcium-dependent noradrenaline release in chromaffin cells.

Ito (1991)[221] We have reported recently that prostaglandin E2 (PGE2) stimulated phosphoinositide metabolism in bovine adrenal chromaffin cells and that PGE2 and ouabain, an inhibitor of Na+, K(+)-ATPase, synergistically induced a gradual secretion of catecholamines from the cells. Here we examined the involvement of a GTP-binding protein(s) in PGE receptor-induced responses by using NaF. In the presence of Ca2+ in the medium, NaF stimulated the formation of all three inositol

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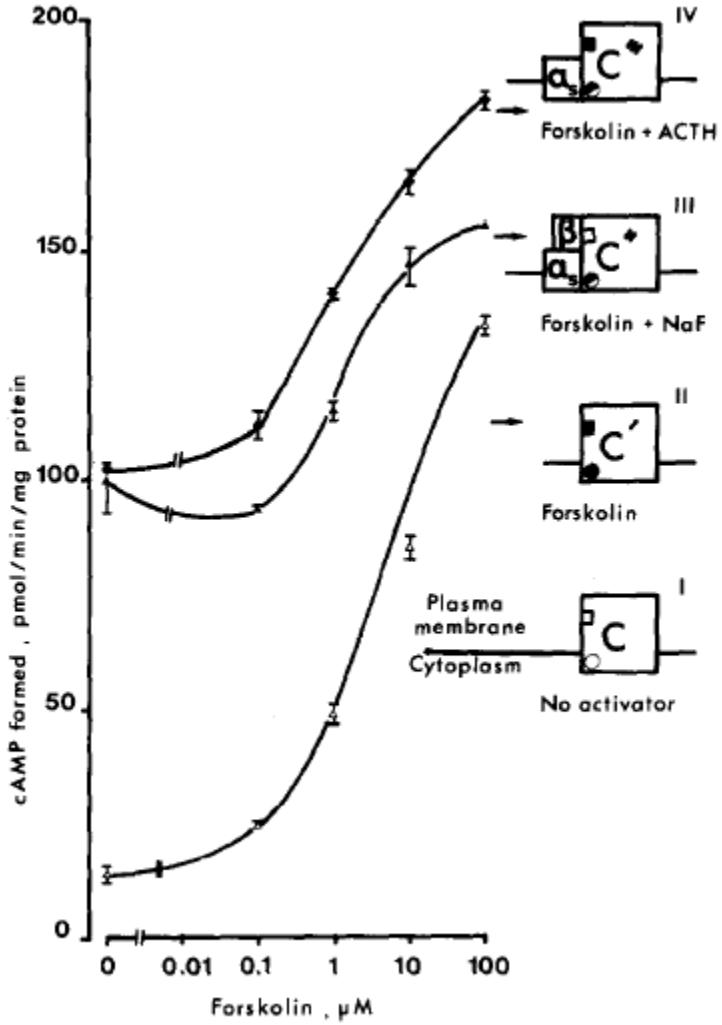
221 Ito S[1], Negishi M, Mochizuki-Oda N, Yokohama H, Hayashi O., Sodium fluoride mimics the effect of prostaglandin E2 on catecholamine release from bovine adrenal chromaffin cells. J Neurochem. 1991 Jan;56(1):44-51.

phosphates, i.e., inositol monophosphate, bisphosphate, and trisphosphate, linearly over 30 min in a dose-dependent manner (15-30 mM). This effect on phosphoinositide metabolism was accompanied by an increase in cytosolic free Ca2+. NaF also induced catecholamine release from chromaffin cells, and the dependency of stimulation of the release on NaF concentration was well correlated with those of NaF-enhanced inositol phosphate formation and increase in cytosolic free Ca2+. Although the effect of NaF on PGE2-induced catecholamine release in the presence of ouabain was additive at concentrations below 20 mM, there was no additive effect at 25 mM NaF. Furthermore, the time course of catecholamine release stimulated by 20 mM NaF in the presence of ouabain was quite similar to that by 1 microM PGE2, and both stimulations were markedly inhibited by amiloride, with half-maximal inhibition at 10 microM. Pretreatment of the cells with pertussis toxin did not prevent, but rather enhanced, PGE2-induced catecholamine release over the range of concentrations examined. These results demonstrate that NaF mimics the effect of PGE2 on catecholamine release from chromaffin cells and suggest that PGE2-evoked catecholamine release may be mediated by the stimulation of phosphoinositide metabolism through a putative GTP-binding protein insensitive to pertussis toxin.

De Foresta (1987)[222] "The diterpene forskolin maximally stimulated bovine adrenal cortex adenylate cyclase activity 9-fold with a concentration producing half-maximum effect (ED50) of about 4 microM. The effects of forskolin and the fully active corticotropin fragment ACTH (I 24) were additive over nearly the whole range of concentration of both effectors, indicating separate and independent mechanisms of action. By contrast, 10 mM NaF blocked forskolin action in the nanomolar range of the diterpene concentration, while it allowed a partial stimulation by forskolin in the micromolar range. NaF thus reveals a heterogeneity of forskolin action in the adrenal cortex plasma membranes. Moreover, our data suggest that ACTH and NaF

[222] de Foresta B, Rogard M, Gallay J., Adenylate cyclase of bovine adrenal cortex plasma membranes. Divergence between corticotropin and fluoride combined effects with forskolin. FEBS Lett. 1987 May 25;216(1):107-12.

activation effects, both mediated by the stimulatory regulatory protein Gs, proceed through different mechanisms."



Suketa (1985)[223] "Changes in adrenal function as a possible mechanism for elevated serum glucose by a single large dose of fluoride."

Wolff (1970)[224] "Chlorpromazine (3 x 10(-4)M) prevents the stimulation of adenyl cyclase activity in thyroid membranes produced by thyrotropin and prostaglandin,

[223] Suketa Y, Asao Y, Kanamoto Y, et al. "Changes in adrenal function as a possible mechanism for elevated serum glucose by a single large dose of fluoride." To Appl Pharm. 1985. 80 199-205.

[224] Wolff J, Jones ABInhibition of hormone-sensitive adenyl cyclase by phenothiazines. Proc Natl Acad Sci U S A. 1970 Feb;65(2):454-9

ACTH stimulation of adenyl cyclase in adrenal tissue, and glucagon- and epinephrine-stimulation of adenyl cyclase activity in liver. Baseline activity is unaffected. Parathyroid hormone stimulation of kidney preparations was not inhibited under these conditions. At chlorpromazine concentrations >3 x 10(-4)M F(-)-stimulated cyclase activity of thyroid and adrenal tissue was increased. Other phenothiazines, trifluoperazine, and prochlorperazine, have similar effects on thyrotropin and F(-)-stimulated cyclase activity of thyroid. Na(+)- K(+)-dependent ATPase of thyroid is also inhibited by chlorpromazine. Since thymol causes a similar dissociation of hormone- and F(-)-stimulated adenyl cyclase, it is concluded that the surface properties of these agents best account for their effects on adenyl cyclase."

F. GONADS

Ovaries: The first study is by Yin (2015), and a significant portion is presented here because it illustrates the risks better and confirms earlier studies with depth.

Yin (2015)[225] "Reproductive toxicity has been an exciting topic of research in reproductive biology in recent years. Soluble fluoride salts are toxic at high concentrations; their reproductive toxicity was assessed in this study by administering different fluoride salt concentrations to mice. Continuous feeding for five weeks resulted in damage to the histological architecture of ovaries. The expression of genes, including Dazl, Stra8, Nobox, Sohlh1, and ZP3 gene, associated with oocyte formation were much lower in the experimental group as compared with the control group. The number of in vitro fertilization of mature oocytes were also much lower in the experimental group as compared with control. Moreover, the fertility of female mice, as assessed by mating with normal male mice, was also lower in experimental compared with control groups. The expression of the oocyte-specific genes: Bmp15, Gdf9, H1oo, and ZP2, which are involved in oocyte growth and the induction of the acrosome reaction, decreased with the fluoride administration. DNA methylation and histone acetylation (H3K18ac and H3K9ac) are indispensable for germline development and genomic imprinting in mammals, and fluoride administration resulted in reduced levels of H3K9ac and H3K18ac in the experimental group as compared with the control group, as detected by immunostaining. Our results indicate that the administration of high concentrations of fluoride to female mice significantly reduced the number of mature oocytes and

[225] Yin S[1], Song C[1], Wu H[1], Chen X[1], Zhang Y[1]. Adverse Effects of High Concentrations of Fluoride on Characteristics of the Ovary and Mature Oocyte of Mouse. PLoS One. 2015 Jun 8;10(6):e0129594. doi: 10.1371/journal.pone.0129594. eCollection 2015.

hampered their development and fertilization. Thus, this study lays a foundation for future studies on fluoride-induced reproductive disorders in women.

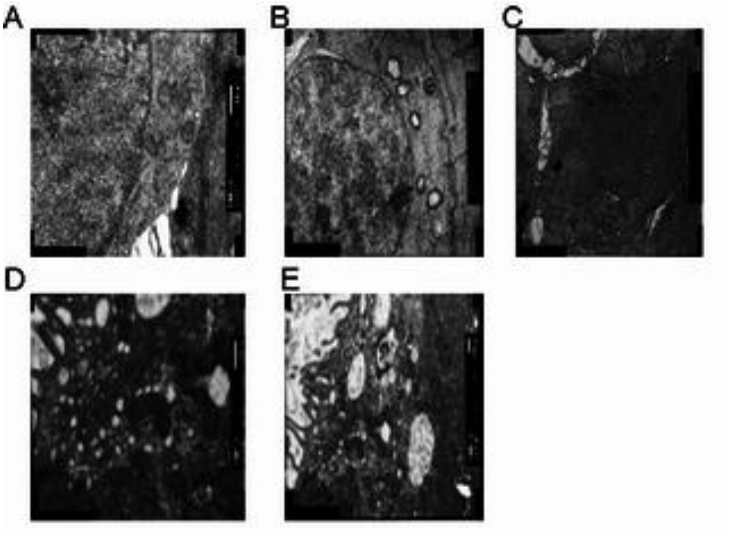


Fig 1. Effect of fluoride administration on ultrastructural features of ovary. (A-E): Ovaries were removed from female mice and ultrathin sections were cut. The histological architecture of ovaries from the control group (A, administered 0 mg/L NaF) and experimental (B-E; administered 50, 100, 150, and 200 mg/L NaF, respectively) groups was examined by transmission electron microscopy.

Effect of fluoride administration on expression of germline-specific genes in the ovary

RNA was isolated from ovaries of mice from the control and experimental groups, and the expression of potential germline-specific genes, particularly Dazl, Stra8, Sohlh1, Nobox, and Zp3, was analysed by RT-PCR. As observed in Fig 2A–2E, the expression of these genes was lower in the experimental groups (administered 50, 100, 150, or 200mg/L NaF) compared with the control group (administered 0mg/L NaF). Increase in fluoride concentration resulted in the decreased expressions of

these genes, particularly Nobox, which was rarely detected in the experimental groups (Fig 2D).

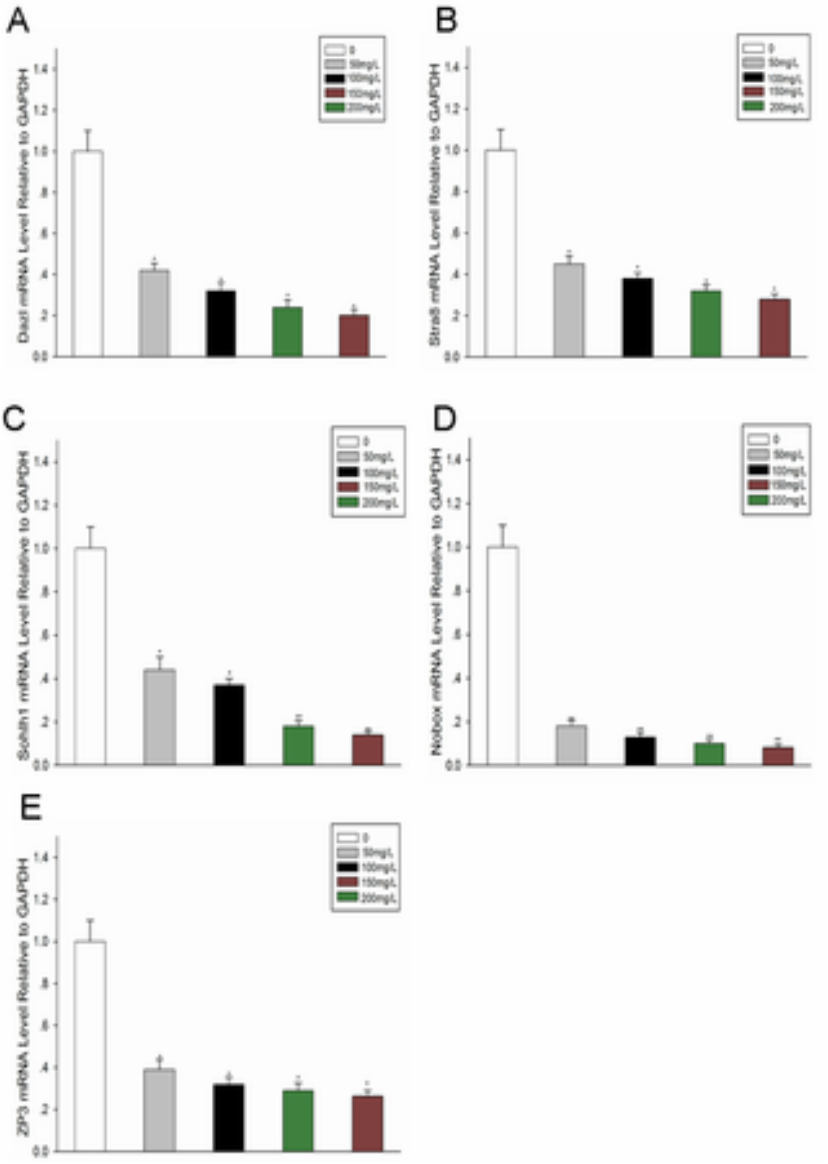


Fig 2. Effect of fluoride administration on expression of germline-specific genes in the ovary.

(A-E): mRNA was harvested from ovaries of mice from the control and experimental groups. qPCR was performed for assessing the relative expression levels of germline-specific genes (A: Dazl, B: Stra8, C: Sohlh1, D: Nobox, and E: Zp3) in the ovary. All data are presented as the mean ± SD and are derived from three independent experiments. *P<0.05; **P<0.01.

Effect of fluoride administration on the formation and in vitro/in vivo fertilization of mature oocytes

The effect of high concentrations of fluoride on the formation and in vitro fertilization of mature oocytes was investigated; furthermore, the fertility of female mice exposed to fluorides was examined by mating with normal male mice. Superovulation was achieved by the administration of 10 IU pregnant mare serum gonadotropin and 10 IU human chorionic gonadotropin before mating or harvesting of mature oocytes from the oviduct ampullae, as detailed in Materials and Methods. Fig 3A shows that the number of mature oocytes per ovary was significantly lower in the experimental groups (administered 50, 100, 150, or 200 mg/L NaF) compared with the control group (administered 0 mg/L NaF). This result is also reflected in the lower fertility of fluoride-administered female mice, as assessed by mating with normal male mice (Fig 3B), and in the lower efficiency of in vitro fertilization for the experimental groups compared with the control group (Fig 3C).

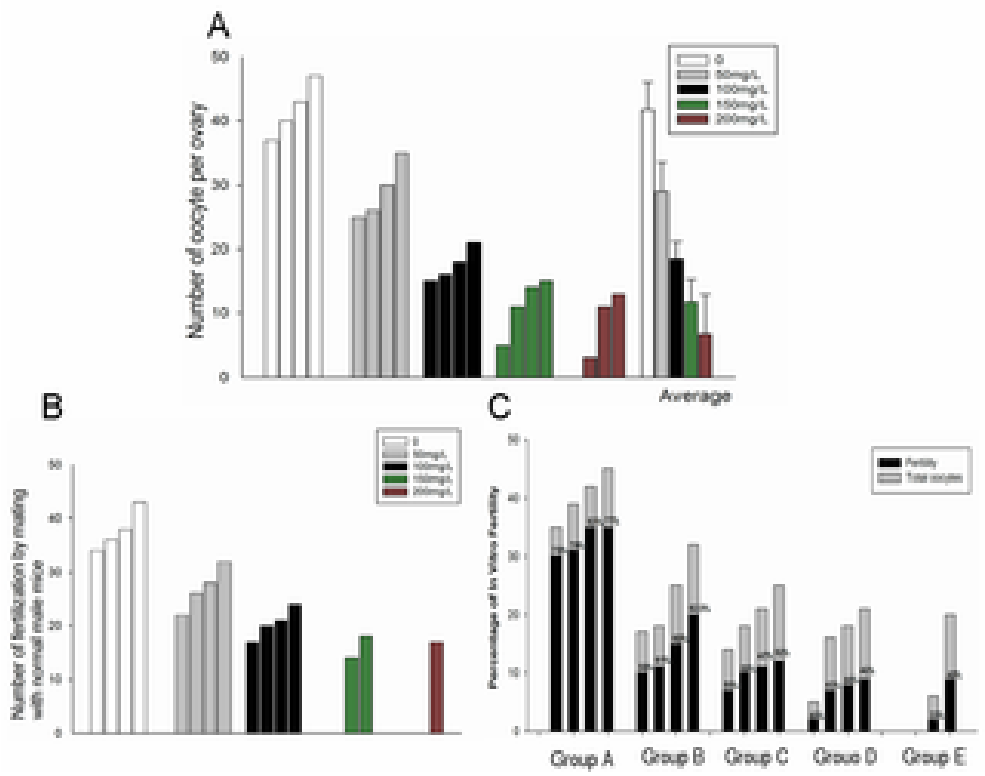


Fig 3. Effect of fluoride administration on formation and in vitro/in vivo fertilization of mature oocytes.

Mature oocytes were released from oviduct ampullae of superovulated mice ~14–16 h following the administration of human chorionic gonadotropin, and the number of the mature oocytes in the ovaries (A) and the efficiency of in vitro fertilization (C)were estimated. Mice from the control and experimental groups were mated with normal male mice following the administration of human chorionic gonadotropin for detecting the in vivo fertilization efficiency (B). (Data are presented as mean ± SD, with four mice (n = 4) per group).

Effect of fluoride administration on the expression of oocyte-specific genes

The results mentioned above indicate that the number and fertilization of mature oocytes are affected by high concentrations of fluoride. Therefore, the expression of oocyte-specific genes was evaluated by RT-PCR following the direct synthesis of cDNA from mature oocytes, as detailed in Materials and Methods. Four oocyte-specific genes, Bmp15, Gdf-9, Zp2, and H1oo, were focused on in this study

because of their crucial functions. Expression of all these genes was found to be lower in the experimental groups compared with the control group, with negative association observed between the expression of these genes and fluoride concentration (Fig 4A–4D).

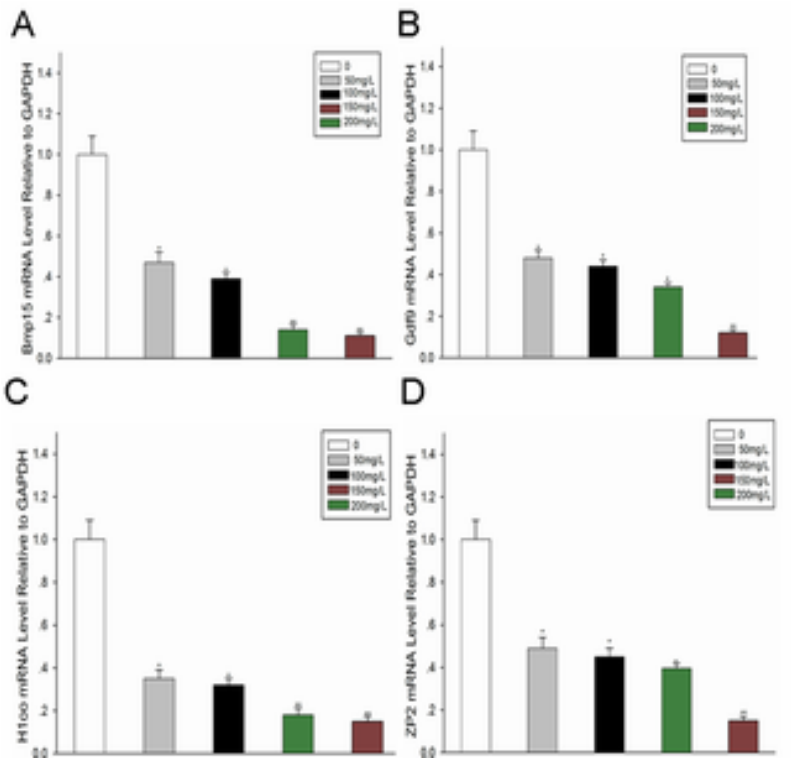


Fig 4. Effect of fluoride administration on the expression of oocyte-specific genes.

(A-D): mRNA was harvested from oocytes of mice from the control and experimental groups. RT-PCR was performed for assessing the relative expression levels of oocyte-specific genes (A: Bmp15, B: Gdf9, C: H1oo, and D: Zp2) in the oocytes. All data are presented as the mean ± SD and are derived from three independent experiments. *P<0.05; **P<0.01.

Effect of fluoride administration on DNA methylation and histone acetylation in mature oocytes

Immunostaining was performed to assess the effect of fluoride administration on global DNA methylation and histone acetylation (notably, H3K18ac and H3K9ac) in mature oocytes. As seen in Fig 5A, significant differences were not observed in 5-methylcytosine levels between the experimental (administered various fluoride concentrations) and control groups. In contrast, lower levels of H3K18ac and of the H3K9ac were observed in the experimental groups (Fig 5B and 5C). (Not included)

Fig 5. Effect of fluoride administration on DNA methylation and histone acetylation in mature oocytes.

Mature oocytes were released from the oviduct ampullae of superovulated mice ~14–16 h following the administration of human chorionic gonadotropin. Immunofluorescence was performed for the detection of levels of 5-methylcytosine (A), H3K9ac (B), and H3K18ac (C). Each sample was stained with anti-5-methylcytosine (green), anti-H3K9ac (green), or anti- H3K18ac (green) antibodies and counterstained with DAPI (blue) to allow DNA visualization. Samples were visualized at (original magnification × 200) for exposure time of 200 ms (anti-5-methylcytosine, anti-H3K9ac and anti-H3K18ac).

Discussion

Fluorides are well recognized as pollutants, with a great deal of research focused on the environmental hazard that they cause [22, 23]. While the effects of fluoride exposure on fertility are known, its exact effect on the production of mature oocytes in mammalian ovaries remains to be investigated. The objective of this study is to explicitly assess the adverse effects of high concentrations of fluoride on the characteristics of mouse ovary and mature oocyte.

The consumption of large quantities of fluoride administration resulted in obvious damage to the histological architecture of mouse ovaries, as reported previously [14, 24]. Further, the effect of fluoride administration on the expression of germline-specific genes was investigated. Previous studies have reported the association

between expression of particular ovary-specific genes and oocyte formation. Dazl, expressed during embryonic development in the female gonads of mice well before the onset of meiosis, functions in the first phase of gametogenesis during the differentiation, proliferation and maintenance of primordial germ cells and their substitutes [25]; Stra8 is required for meiotic progression in the mouse ovary, previous studies demonstrated that meiosis is a sex-specific event where germ cells undergo cellular differentiation to form oocytes or spermatozoa, with abnormal gene expression during meiosis leading to aberrant gamete formation, which is often a major cause of infertility in both males and females [26]; Nobox deficiency has been shown to disrupt early folliculogenesis and expression of oocyte-specific genes [27]; Sohlh1 is a transcription factors of the bHLH family and is specifically expressed in germ cells; it plays a role in oocyte differention, in female, such that Sohlh1 ablation causes oocyte loss in the neonatal ovary [28]; Zp3 plays an important role in the development of mouse zona pellucida, which is critical for fertilization [29]. This study revealed that the expression of these genes was much lower in the experimental groups compare with the control group and showed an inverse association with the concentration of fluoride adminstratered. The changes in histological architecture and expression of germline-specific genes in the ovary are likely to affect the formation and fertilization of mature oocytes. The effect of high concentrations of fluoride on the formation of mature oocytes was investigated by inducing superovulation followed by collection of mature oocytes; moreover, in vitro fertilization and in vivo fertilization following mating with normal male mice were also assessed. The results obtained showed that increase in fluoride concentration resulted in lower yield of mature oocytes as well as lower efficiency of in vivo and in vitro fertilization in the experimental groups compared with the control group, which is in agreement with the observed expression of germline-specific genes, as detailed above.

The expression of the following oocyte-specific genes was also assessed following fluoride administration: Bmp15, which is involved in oocyte maturation and follicular development; Gdf-9, which regulates the oocyte growth and function of oocytes as well as growth and differention of granulose cell; zp2, which mediates species-

specific sperm binding, induces acrosome reaction, and prevents post fertilization polyspermy; and H1oo, whose expression is restricted to the growing/maturing oocyte and to the zygote [30]. The expression of these oocyte-specific genes was decreased upon fluoride administration, which is expected to disrupt the normal maturation of oocyte.

The important role played by histone acetylation and DNA methylation in oogenesis is widely accepted. Previous studies have shown that occurrence of 5-methylcytosine in mammals genomes is crucial for normal mammalian development, while histone acetylation is associated with a transcriptionally active state and allows access of transfactor to DNA sequence. Abnormal epigenetic modification is expected to be detrimental to offspring as a consequence of DNA damage [31]. Therefore, the levels of global DNA methylation, and the active histone marks H3K9ac and H3K18ac were assessed in mature oocytes following the administration of fluoride to mice. The results revealed the absence of significant differences in the level of 5-methylcytosine between the experimental and control groups. However, the levels of H3K9ac and H3K18ac were lower in the experimental compared with the control groups and decreased with increase in fluoride concentration. Such abnormal epigenetic modification is likely to be particularly detrimental to offspring.

Behavioral differences were also observed in mice belonging to various experimental groups. Mice belonging to the experimental group D (administered 150 mg/L NaF) were observed to be thinner compared with the other groups, while the mice of group E (administered 200 mg/L NaF) consumed a much greater quantity of water; moreover, the mice of groups C, D, and E (administered 100, 150, and 200 mg/L NaF, respectively) displayed a tendency to closely approach one another. This is attributable to the neurotoxicity and behavioral changes caused upon fluoride consumption in animals [32, 33].

Taken together, this study suggests that the administration of high concentrations of fluoride to female mice not only results in ovarian damage but also significantly reduces the number and the fertilization potential of mature oocytes by reducing the expression of genes that play an important role in the normal development and maturation of oocytes. The results obtained in this study could thus be employed for

statistical analysis of the association between exposure to high concentrations of fluoride and reproductive disorders in women."

Geng (2014)[226] The toxicity of sodium fluoride (NaF) to female fertility is currently recognized; however, the mechanisms are unclear. Previously, we reported a reduction in successful pregnancy rates, ovarian atrophy and dysfunction following exposure to NaF. The purpose of this study was to elucidate the underlying molecular mechanisms. Female Sprague-Dawley rats (10 rats/group) received 100 or 200mg/L NaF in their drinking water for 6 months or were assigned to an untreated control group. Apoptotic indices and oxidative stress indicators in blood and ovarian tissue were analyzed following sacrifice. The results confirmed the NaF-induced ovarian apoptosis, with concomitant activation of oxidative stress. Further investigations in ovarian granular cells showed that exposure to NaF activated extracellular regulated protein kinase (ERK) and c-Jun NH2 kinase (JNK), disrupting the ERK and JNK signaling pathways, while p38 and PI3K remained unchanged. These data demonstrated that oxidative stress may play a key role in NaF-induced ovarian dysfunction by activating the apoptotic ERK and JNK signaling pathways.

Zhou (Feb 2013)[227] "The aim of this study was to investigate the effects of sodium fluoride (NaF) on female reproductive function and examine the morphology of the ovaries and uteri of rats exposed to NaF. . . . These results suggest that female reproductive function is inhibited by NaF and that exposure to NaF causes ovarian and uterine structural damage. NaF may thus significantly reduce the fertility of female rats."

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[226] Geng Y[1], Qiu Y[2], Liu X[3], Chen X[4], Ding Y[5], Liu S[6], Zhao Y[7], Gao R[8], Wang Y[9], He J[10]. Sodium fluoride activates ERK and JNK via induction of oxidative stress to promote apoptosis and impairs ovarian function in rats. J Hazard Mater 2014 May 15;272:75-82. doi: 10.1016/j.jhazmat.2014.03.011. Epub 2014 Mar 18.

[227] Zhou Y[1], Zhang H, He J, Chen X, Ding Y, Wang Y, Liu X. Effects of sodium fluoride on reproductive function in female rats. Food Chem Toxicol. 2013 Jun;56:297-303. doi: 10.1016/j.fct.2013.02.026. Epub 2013 Feb 28.

Zhou (Sept 2013),[228] "Recognition of the harmful effects of sodium fluoride (NaF) on human reproduction is increasing, especially as it relates to female reproduction. However, the mechanism by which NaF interferes with female reproduction is unclear. The aims of the present study were to investigate the effects of fluoride exposure on female fertility and to elucidate the mechanisms underlying these effects. . . . These results suggest that the reproductive hormone reduction and the abnormalities of related receptor proteins expression are important factors underlying the decreased fertility observed in female rats that have been exposed to NaF."

Johanna (2013)[229] The effects of oral administration of sodium fluoride (NaF) and/or arsenic trioxide (As(2)O(3)) (5 mg and 0.5 mg/kg body weight, respectively) for 30 days were investigated on free radical induced toxicity in the mouse ovary. The reversibility of the induced effects after withdrawal of NaF+As(2)O(3) treatment and by administration of antioxidant vitamins (C, E) and calcium alone as well as in combination were also studied. The combined treatment of NaF and As(2)O(3) impaired significantly ($p<0.001$) the production of free radical scavengers such as glutathione and ascorbic acid as well as antioxidant enzymes, namely, glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and catalase (Cat), thereby increasing ovarian lipid peroxides (LPO) which might have rendered the ovary susceptible to injury. The withdrawal of the combined (NaF and As(2)O(3) for 30 days) treatment caused partial recovery in the ovary, which was more pronounced ($p<0.001$) by treatment with vitamin C, calcium, or vitamin E alone and in combination. Hence the induced toxicity was transient and reversible.

Hou (2013) "To explore the influence of water fluoride exposure on reproductive hormones in female. Cross-sectional study was conducted in seven villages of a

[228] Zhou Y[1], Qiu Y, He J, Chen X, Ding Y, Wang Y, Liu X. The toxicity mechanism of sodium fluoride on fertility in female rats. Food Chem Toxicol. 2013 Dec;62:566-72. doi: 10.1016/j.fct.2013.09.023. Epub 2013 Sep 23.

[229] Jhala DD[1], Chinoy NJ, Rao MV. Mitigating effects of some antidotes on fluoride and arsenic induced free radical toxicity in mice ovary. Food Chem Toxicol. 2008 Mar;46(3):1138-42. doi: 10.1016/j.fct.2007.11.009. Epub 2007 Nov 23.

county in Henan province by using simple random sampling including high fluoride area, defluoridation project area and control area on April, 2011 based on the preliminary study results of fluoride concentration in drinking water. Women who were born and growth or lived in the village at least 5 years and aged 18-48 years old were recruited using cluster sampling. They were divided into high fluoride group (HFG, 116 subjects), defluoridation project group (DFPG, 132 subjects) and control group (CG, 227 subjects) in accordance with the above areas. All subjects accepted questionnaire and physical checkup. . . Fluoride exposure may influence reproductive hormones in female, especially in ovulatory and luteal phase of menstrual cycle."[230]

The Oxford Journals (2006)[231] is many pages in length and a good source for review of the ovary and developing follicle. In part, they report:

"Ovarian follicle development is a complex process that begins with the establishment of what is thought to be a finite pool of primordial follicles and culminates in either the atretic degradation of the follicle or the release of a mature oocyte for fertilization. This review highlights the many advances made in understanding these events using transgenic mouse models. Specifically, this review describes the ovarian phenotypes of mice with genetic mutations that affect ovarian differentiation, primordial follicle formation, follicular growth, atresia, ovulation and corpus luteum (CL) formation. In addition, this review describes the phenotypes of mice with mutations in a variety of genes, which affect the hormones that regulate folliculogenesis. Because studies using transgenic animals have revealed a variety of reproductive abnormalities that resemble many reproductive disorders in women, it is likely that studies using transgenic mouse models will impact our understanding of ovarian function and fertility in women."

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[230] Hou JX1, Yang YJ, Gong B, Li SH, Ding Z, Wen SB, Li SQ, Cheng XM, Cui LX, Ba Y. [The influence of high fluoride exposure in drinking water on endocrine hormone in female]. [Article in Chinese] Zhonghua Yu Fang Yi Xue Za Zhi. 2013 Feb;47(2):142-6.

[231] Ovarian follicle development and transgenic mouse models, Hum. Reprod. Update Oxford Journals (September/October 2006) 12 (5): 537-555. doi: 10.1093/humupd/dml022 First published online: May 25, 2006 Update (September/October 2006) 12 (5): 537-555. doi: 10.1093/humupd/dml022

Stan (1994)[232] “A review of fluoride toxicity showed decreased fertility in most animal species studied. The current study was to see whether fluoride would also affect human birth rates. A U.S. database of drinking water systems was used to identify index counties with water systems reporting fluoride levels of at least 3 ppm. These and adjacent counties were grouped in 30 regions spread over 9 states. For each county, two conceptionally different exposure measures were defined, and the annual total fertility rate (TFR) for women in the age range 10–49 yr was calculated for the period 1970–1988. For each region separately, the annual TFR was regressed on the fluoride measure and sociodemographic covariables. Most regions showed an association of decreasing TFR with increasing fluoride levels. Meta-ana/ysis of the region-specific results confirmed that the combined result was a negative TFR/fluoride association with a consensus combined p value of .0002-.0004, depending on the analytical scenario. There is no evidence that this outcome resulted from selection bias, inaccurate data, or improper analytical methods. However, the study is one that used population means rather than data on individual women. Whether or not the fluoride effect on the fertility rate found at the county level also applies to individual women remains to be investigated.”

[232] Stan C. Freni., Exposure to high fluoride concentrations in drinking water is associated with decreased birth rates. Journal of Toxicology and Environmental Health, 1994, Volume 42, Issue 1, pages 109-121

TESTES:

Han (2015)[233] "Numerous studies have shown that fluoride exposure adversely affected the male reproductive function, while the molecular mechanism is not clear. The present study was to investigate the effects of fluoride exposure (60days) on the expressions of reproductive related genes, serum sex hormone levels and structures of the hypothalamus-pituitary-testicular axis (HPTA), which plays a vital role in regulating the spermatogenesis in male mice. In this study, 48 male mice were administrated with 0, 25, 50, and 100mg/L NaF through drinking water. Results showed that the malformation ratio of sperm was significantly increased ($P<0.05$). At transcriptional level, the expression levels of follicle-stimulating hormone receptor (FSHR), luteinizing hormone receptor (LHR), inhibin alpha (INHα), inhibin beta-B (INHβB), and sex hormone binding globulin (SHBG) mRNA in testis were significantly decreased ($P<0.05$). Moreover, histological lesions in testis and ultrastructural alterations in hypothalamus, pituitary and testis were obvious. However, the same fluoride exposure did not lead to significant changes of related mRNA expressions in hypothalamus and pituitary ($P>0.05$). Also, there were no marked changes in serum hormones. Taken together, we conclude that the mechanism of HPTA dysfunction is mainly elucidated through affecting testes, and its effect on hypothalamus and pituitary was secondary at exposure for 60days."

Hamza (2015)[234] "Sodium fluoride (NaF) intoxication is associated with oxidative stress and altered antioxidant defense mechanism. The present study was carried out to evaluate the potential protective role of blackberry and quercetin (Q) against NaF-induced oxidative stress and histological changes in liver, kidney, testis and brain

[233] Han H1, Sun Z1, Luo G2, Wang C3, Wei R1, Wang J4., Fluoride exposure changed the structure and the expressions of reproductive related genes in the hypothalamus-pituitary-testicular axis of male mice. Chemosphere. 2015 Sep;135:297-303.

[234]Hamza RZ, El-Shenawy NS, Ismail HA. Protective effects of blackberry and quercetin on sodium fluoride-induced oxidative stress and histological changes in the hepatic, renal, testis and brain tissue of male rat. J Basic Clin Physiol Pharmacol. 2015 May;26(3):237-51.

tissues of rats. . . .RESULTS AND CONCLUSIONS: NaF caused an elevation in lipid peroxidation level paralleled with significant decline in glutathione peroxidase, glutathione reductase, glutathione S-transferase, superoxide dismutase and catalase activities as well as the total antioxidant activity in liver, kidney, testes and brain. Some histopathological changes were detected in all tested tissues of the NaF treated group. Q and BBJ had successfully maintained normal histological architecture and mitigated the induction of oxidative stress caused by NaF. Q effectively reduced the elevation in thiobarbituric acid reactive substances level and restored the activities of antioxidant enzymes in liver, kidney, testis and brain. Less histopathological changes were observed in Q+NaF and BBJ+NaF treated groups. As a result, BBJ and Q significantly reduced NaF-induced oxidative and histological changes in rats. In the combination of BBJ and Q against NaF toxicity, the effects were more severe than from separate exposure, thus indicating that these flavonoids exhibited synergistic effects on all antioxidant and histological parameters."

Song (2014)[235] '"The biological effects of fluoride on human health are often extensive, either beneficial or detrimental. Among the various effects of fluoride exposure in different organs, the reproductive tract is particularly susceptible to disruption by fluoride at a sufficient concentration. It has attracted much attention to the effect of sodium fluoride on male fertility, gestational female, and offspring. Herein, we applied a widespread natural compound sodium fluoride (NaF) and investigated the effects of acute NaF exposure on Leydig cells, including their proliferation, apoptosis, and signal pathway changes. Our results demonstrated that high dosage of NaF could inhibit cell proliferation by stress-induced apoptosis, which was confirmed by cellular and molecular evidences. We found that fluoride exposure affected the expression levels of stress response factors, signal transduction components, and apoptosis-related proteins, including caspase-3/caspase-9, B-cell

[235] Song Gh[1], Wang RL, Chen ZY, Zhang B, Wang HL, Liu ML, Gao JP, Yan XY. Toxic effects of sodium fluoride on cell proliferation and apoptosis of Leydig cells from young mice. J Physiol Biochem. 2014 Sep;70(3):761-8. doi: 10.1007/s13105-014-0344-1. Epub 2014 Jul 30.

lymphoma 2 (Bcl-2), and Bax. This study suggests that the complex effects of fluoride on Leydig cells are closely related to its dosage."

Geng (2014) "The toxicity of sodium fluoride (NaF) to female fertility is currently recognized; however, the mechanisms are unclear. Previously, we reported a reduction in successful pregnancy rates, ovarian atrophy and dysfunction following exposure to NaF. The purpose of this study was to elucidate the underlying molecular mechanisms. . . The results confirmed the NaF-induced ovarian apoptosis, with concomitant activation of oxidative stress. Further investigations in ovarian granular cells showed that exposure to NaF activated extracellular regulated protein kinase (ERK) and c-Jun NH2 kinase (JNK), disrupting the ERK and JNK signaling pathways, while p38 and PI3K remained unchanged. These data demonstrated that oxidative stress may play a key role in NaF-induced ovarian dysfunction by activating the apoptotic ERK and JNK signaling pathways."[236]

Wang (2014) "Sodium fluoride (NaF) has been found to interfere with the reproductive system of animals. However, the cellular mechanisms underlying the reproductive toxicity of fluoride are unclear. The present study aims to define a possible mechanism of NaF-induced reproductive toxicity with respect to mineral, oxidative stress and c-Fos expression and the role of aluminum (Al) in intervening the toxic effect of NaF on rat testes. . . The present study suggested that NaF could decrease the contents of Ca, Fe and Mg and enhance oxidative stress leading to c-Fos overexpression, and some deleterious effects were more prominent at lower NaF intake. Furthermore, Al within the research concentration could minimize reproductive toxicity caused by fluoride."[237]

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[236] Geng Y1, Qiu Y2, Liu X3, Chen X4, Ding Y5, Liu S6, Zhao Y7, Gao R8, Wang Y9, He J10. Sodium fluoride activates ERK and JNK via induction of oxidative stress to promote apoptosis and impairs ovarian function in rats. J Hazard Mater. 2014 May 15;272:75-82. doi: 10.1016/j.jhazmat.2014.03.011. Epub 2014 Mar 18.

[237] Wang J1, Zhang H, Xu F, Xu F, Zhang K, Zhang Y. The antagonism of aluminum against fluoride-induced oxidative stress and c-Fos overexpression in rat testes. Toxicol Mech Methods. 2014 Feb;24(2):136-41. doi: 10.3109/15376516.2013.869779. Epub 2013 Dec 16.

Yang (2014)[238] “Investigated the effects of N-acetylcysteine (NAC) on endoplasmic reticulum stress of sertoli cells induced by sodium fluoride (NaF). METHODS: Rat sertoli cells were exposed to various concentration of (0, 6, 12, 24 μg/ml) sodium fluoride with or without 2 mmol/L NAC for 24 hours. The cell viability was evaluated using trypan blue exclusion test. Intracellular reactive oxygen species (ROS) was measured using the fluorescent probe DCFH-DA. Western blot was used to test the expression of GRP78, PERK and CHOP. RESULTS: It was found that treatment with NAC (2 mmol/L) restored the reduced cell viability and excessive oxidative stress (P < 0.01). Moreover, fluoride exposure upregulated the expression of GRP7 8, PERK and CHOP protein (P <0. 01). NAC was also found to suppress the levels of GRP78, PERK and CHOP expression in NaF-treated cells (p<0.01). CONCLUSION: Endoplasmic reticulum stress signaling pathways were activated by ROS, and NAC attenuate endoplasmic reticulum stress through inhibiting the levels of ROS in NaF-treated sertoli cells.”

Zhang (2013)[239] “Long-term excessive fluoride intake is known to be toxic and can damage a variety of organs and tissues in the human body. However, the molecular mechanisms underlying fluoride-induced male reproductive toxicity are not well understood. In this study, we used a rat model to simulate the situations of human exposure and aimed to evaluate the roles of endoplasmic reticulum (ER) stress and inflammatory response in fluoride-induced testicular injury. Sprague-Dawley rats were administered with sodium fluoride (NaF) at 25, 50 and 100mg/L via drinking water from pre-pregnancy to gestation, birth and finally to post-puberty. And then the testes of male offspring were studied at 8weeks of age. Our results demonstrated that fluoride treatment increased MDA accumulation, decreased SOD activity, and enhanced germ cell apoptosis. In addition, fluoride elevated mRNA and protein levels of glucose-regulated protein 78 (GRP78), inositol requiring ER-to-nucleus

[238]Yang Y, Huang H, Feng D, Liu W, Cheng X, Ba Y, Cui L.[Effects. of N-acetylcysteine on fluoride-induced endoplasmic reticulum stress in sertoli cells]. [Article in Chinese] Wei Sheng Yan Jiu. 2014 Sep;43(5):805-8, 813.
[239]Zhang S[1], Jiang C, Liu H, Guan Z, Zeng Q, Zhang C, Lei R, Xia T, Gao H, Yang L, Chen Y, Wu X, Zhang X, Cui Y, Yu L, Wang Z, Wang A. Fluoride-elicited developmental testicular toxicity in rats: roles of endoplasmic reticulum stress and inflammatory response. Toxicol Appl Pharmacol. 2013 Sep 1;271(2):206-15. doi: 10.1016/j.taap.2013.04.033. Epub 2013 May 22.

signal kinase 1 (IRE1), and C/EBP homologous protein (CHOP), indicating activation of ER stress signaling. Furthermore, fluoride also induced testicular inflammation, as manifested by gene up-regulation of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), in a nuclear factor-κB (NF-κB)-dependent manner. These were associated with marked histopathological lesions including injury of spermatogonia, decrease of spermatocytes and absence of elongated spermatids, as well as severe ultrastructural abnormalities in testes. Taken together, our results provide compelling evidence that ER stress and inflammation would be novel and significant mechanisms responsible for fluoride-induced disturbance of spermatogenesis and germ cell loss in addition to oxidative stress."

Deng (2013) "To discuss the significance of calcineurin (CaN) and nuclear factor of active T cells 1 (NFATc1) in the damage mechanism of the testis of rats with chronic fluorosis. . . The changes in the signaling pathway of expression of CaN may be involved in the injury mechanism of testis tissues of rats with chronic fluorosis."[240]

Dimcevici (2013) "It has been revealed that excessive fluoride intake on long-term is associated with toxic effects and can damage a variety of organs and tissues in the human body, including the male reproductive system. . . The results indicate that natrium fluoride administered in different doses, even at homeopathic dose or at allopathic-homeopathic dose, determined vacuolar dystrophy of epididymal epithelial cells, vacuolar dystrophy of linear seminal cells and necrosis."[241]

[240] Deng CN1, Yu YN2, Xie Y1, Zhao LN1. [Expression of calcineurin and nuclear factor of activated T cells 1 in testis of rats with chronic fluorosis]. [Article in Chinese] Zhonghua Yu Fang Yi Xue Za Zhi. 2013 Dec;47(12):1142-7.
[241] Dimcevici Poesina N1, Bălălău C, Bârcă M, Ion I, Baconi D, Baston C, Băran Poesina V. Testicular histopathological changes following sodium fluoride administration in mice. Rom J Morphol Embryol. 2013;54(4):1019-24.

Xiao (2011)[242] "The rat fluorosis models were successfully established. The fluoride content in testis was significantly increased in all the fluorosis groups(P<0.01). Testicular structures were damaged in all of fluoride groups. The TNOS, iNOS activities, and MDA content of each fluoride group were significantly higher than that of the control group on day 120 and 180 (P<0.05 or 0.01). The TNOS, iNOS activities, and MDA content significantly increased in a dose dependent manner (P<0.05 or 0.01). The SOD activities significantly decreased in all the fluoride groups (P<0.05 or 0.01). **CONCLUSIONS:** Endemic fluoride poisoning caused by coal burning can cause disorders in the oxidative system and antioxidative system in rat testis. The oxidative stress may play an important role in the fluorides induced reproductive toxicity in male rats.

Hao (2010)[243] **OBJECTIVE:** To study of endocrine disturbing effect of fluoride on human hypothalamus-hypophysis-testis axis hormones. **METHODS:** Sunying County, Kaifeng City was selected as polluted district which the fluoride in drinking water was 3.89 mg/L, and Shenlilou county was selected as control district which the fluoride was less than 1.0 mg/L. 150 individual lived there more than 5 years were selected randomly. And investigated by medical examination, then blood and urine sample were collected, and the serum level of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), testosterone (T) and estradiol (E2) were measured by RIA method, and the urine level of fluoride were measured. Other than that, the concentration of fluoride in the water, food, soil and air were detected by the standard methods. **RESULTS:** The concentrations of fluoride in the water, food and soil of the fluoride polluted district were significantly higher than those of control district (P < 0.05), and the concentration fluoride in the air of two district were not found. There was no significant difference of serum level of GnRH between fluoride polluted district and control district (P > 0.05). The serum level of LH in men of

[242] Xiao YH[1], Sun F, Li CB, Shi JQ, Gu J, Xie C, Guan ZZ, Yu YN.[Effect of endemic fluoride poisoning caused by coal burning on the oxidative stress in rat testis]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2011 Aug;33(4):357-61. doi: 10.3881/j.issn.1000-503X.2011.04.002 [Article in Chinese]

[243] Hao P[1], Ma X, Cheng X, Ba Y, Zhu J, Cui L.[Effect of fluoride on human hypothalamus-hypophysis-testis axis hormones]. Wei Sheng Yan Jiu. 2010 Jan;39(1):53-5. [Article in Chinese]

fluoride polluted district was significantly higher than that of control group (P < 0.05), and the serum level of T in men of fluoride polluted district was significantly less than that of control group (P < 0.05). There was no significant difference of serum level of LH between fluoride polluted district and control district (P > 0.05), and the serum level of T in women of fluoride polluted district was significantly higher than that of control group (P < 0.05). There was no significant difference of serum level of E2 between fluoride polluted district and control district (P > 0.05). **CONCLUSION:** Fluoride could effect hormone levels of each layer of the hypothalamus-hypophysis-testis axis, and show the reproductive endocrine disturbing effects. The reproductive endocrine disturbing effects of male maybe more severe than those of female.

Ma (2008)[244] **OBJECTIVE:** To study the endocrine disturbing effect of fluorin on Hypothalamus-Hypophysis-Testis axis in male rats. **METHODS:** A total of 36 Wister male rats weighting 60-70 g were randomly divided into group I (high fluoride group of F-100 mg/l), group II (low fluoride group of F- 30 mg/l), group III (control group with pure water), with 12 rats in each group. Fluoride was administered with drinking water for 8 weeks. Then the level of procreation hormone in serum was detected by RIA method. And the spermatozoa quality was analysized. **RESULTS:** There was difference between group I, group II and group III each other (P < 0.05) in body weight. As to right testis weight, there was difference between group I, group II and group III each other (P < 0.05). Epididymide organic coefficient in group II and group I were lower than that in group III (P > 0.05). Compared with group III, the counts amount of sperm and the rates of sperm mobility in group II and group I singnificantly increased (P < 0.05), and the rates of sperm aberration in group II and group I significantly decreased (P < 0.05), compared with group II, the sperm quality of group I descreased significantly (P < 0.05). The level of GnRH in three groups were significant difference between each groups (P <0.05). The level of FSH in three groups were significant difference between each groups (P < 0.05). The level of ICSH in three groups were no significant difference between each groups (P > 0.05).

[244] Ma X[1], Cheng X, Li F, Guo J.[Experimental research on endocrine disturbing effect of fluorin on hypothalamus-hypophysis-testis axis in male rats]. Wei Sheng Yan Jiu. 2008 Nov;37(6):733-5. [Article in Chinese]

The level of T in Group I is significant lower than that of in Group II and Group III ($P < 0.05$). The level of E2 in Group I is significant higher than that of in Group II and Group III ($P < 0.05$).

Gupta (2007)[245] "The present study was undertaken to evaluate the effect of fluoride toxicity on the reproductive system of male rats. Sexually mature male Wistar rats were exposed to 2, 4, and 6 ppm sodium fluoride in their drinking water for 6 months ad libitum. Sperm motility and density in cauda epididymis were assessed. Biochemical and histological analysis were performed in reproductive organs. Fluoride treatment brought about a significant decrease in the weight of testis, epididymis, and ventral prostate. The sperm motility and density were significantly reduced. There was a marked reduction in the number of primary spermatocyte, secondary spermatocyte, and spermatids. The Sertoli cell counts and their cross sectional surface areas were significantly decreased. The Leydig cell nuclear area and the number of mature Leydig cells were also significantly decreased. The protein content of the testis and epididymis were significantly reduced. Fructose in the seminal vesicles and cholesterol in testes were increased significantly. In conclusion, sodium fluoride administrated in drinking water of 2, 4, and 6 ppm concentration for 6 months to male rats adversely affected their fertility and reproductive system."

Jiang (2007)[246] OBJECTIVE: To study the damages of fluoride on the male reproductive system in rat testes. METHODS: A total of 30 male SD rats were randomly divided into control group, high, low dose fluorine treated groups, which were given normal saline ,20 mg/kg sodium fluoride, and 10mg/kg sodium fluoride respectively. After 39 days the change of the weight of rats and the number of sperms were observed. The change of telomerase reverse transcriptase(TERT) and proliferating cell nuclear

[245] Gupta RS[1], Khan TI, Agrawal D, Kachhawa JB. The toxic effects of sodium fluoride on the reproductive system of male rats. Toxicol Ind Health. 2007 Oct;23(9):507-13.
[246] Jiang Q[1], Song XK, Cui QH, Chen LJ. [Effect of fluoride on expression of telomerase reverse transcriptase expression and proliferating cell nuclear antigen in germ cells of rats' testes]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2007 Feb;25(2):96-9. [Article in Chinese]

antigen (PCNA) were observed by using in situ hybridization and radioimmunoassay respectively.RESULTS: The weight was (273.39 +/- 20.68), (240.00 +/- 21.39) g in NaF treated groups, which was lower than that in control group(P < 0.05); The rate of TERT expression in germ cells of testes in NaF treated groups was (13.89 +/- 4.86)% and (6.33 +/- 4.42)% respectively, which was significantly lower than that in control group (P < 0.05). The rate of PCNA expression in germ cells of tests in NaF treated groups was (0.71 +/- 0.05)%, (0.60 +/- 0.08)% respectively, which also was significant lower than that in control group(P < 0.05). The number of sperms was (18.31 +/- 1.20)10(10)/L, (9.17 +/- 1.38)10(10)/L, which was lower than that in control group (P < 0.05). CONCLUSION: Fluorine possibly damages the male reproductive system by reducing the expression of TERT and PCNA.

Oncu (2007)[247] (Note: Oncu's rats were given 0.7 mg/l NaF, the same as USPHS recommended "This experiment was designed to investigate the histological and lipid peroxidation effects of chronic fluorosis on testes tissues of first- and second-generation rats. Sixteen virgin female Wistar rats were mated with eight males (2:1) for approximately 12 h to obtain first-generation rats. Pregnant rats were divided into two groups: controls and fluoride-given group, each of which containing five rats. Pregnant rats in the fluoride-given group were exposed to a total dose of 30 mg/l sodium fluoride (NaF) in commercial drinking water containing 0.07 mg/l of NaF throughout the gestation and lactation periods. After the lactation period, the young animals (first generation, F1) were exposed to the same dose of NaF in drinking water for 4 months. At the end of the 4 months of experimental period, nine randomly chosen male rats (F1) were killed and testes tissues were taken for histopathological and biochemical analysis. The remaining eight female rats were mated with four males (2:1) for approximately 12 h to obtain second-generation rats. Six female were identified as pregnant and treated with similarly throughout the gestation and the lactation periods. After the lactation period, the young male animals (second generation, F2) were also treated in the same way for 4 months. At

[247] Oncü M[1], Kocak A, Karaoz E, Darici H, Savik E, Gultekin F. Effect of long-term fluoride exposure on lipid peroxidation and histology of testes in first- and second-generation rats. Biol Trace Elem Res. 2007 Sep;118(3):260-8.

the end of the 4 months of experimental period, nine randomly chosen male rats (F2) were killed and testes tissues were collected for histopathological and biochemical analysis. The rats in the control group were applied the same procedure without NaF administration. In biochemical analysis of the fluoride given F1 and F2 rats, it has been found that plasma fluoride levels and testes thiobarbituric acid reactive substance levels were significantly increased when compared with the control group. In F1 and F2 rats, similar histopathological changes were observed. In both groups, spermatogenesis was severely reduced. Spermatogonia and primary spermatocytes were normal, however, there was a widespread degeneration in other spermatogenic cell lines of the seminiferous epithelium. The histological structures of the Sertoli and interstitial Leydig cells were normally observed. It is concluded that chronic fluorosis exposure leads to a remarkable destruction in testes tissues of F1 and F2 rats via lipid peroxidation."

Dvoráková-Hortová K (2007)[248] Increasing infertility, due to pathological changes on sperm, has become a serious issue. Eco-toxicological effect of rising concentration of fluorides can be enhanced in the presence of aluminium ions by forming fluorometallic complexes, analogues of phosphate groups that interfere with the activity of G-proteins and P-type ATPases, which are part of several signalling pathways during sperm maturation. In order for sperm to gain fertilizing ability, they must undergo in the female reproductive tract, capacitation that includes tyrosine phosphorylation and consequent actin polymerization. The present paper reports the findings of 3-month oral toxicity in mice of fluorides at the concentrations 0, 1, 10, and 100ppm and their synergic action with aluminium at dose of 10ppm. There were no mortalities, clinical signs of discomfort or body weight loss during the experiment. The analysis revealed, for the concentrations of 10 and 100ppm, abnormalities of spermatogenesis and ability of epididymal spermatozoa to capacitate in vitro, as the result of decreased sperm head tyrosine phosphorylation and actin polymerization. The enhancing overload caused by fluorides represents a potential factor, having an

[248] Dvoráková-Hortová K[1], Sandera M, Jursová M, Vasinová J, Peknicová J. The influence of fluorides on mouse sperm capacitation. Anim Reprod Sci. 2008 Oct;108(1-2):157-70. Epub 2007 Aug 6.

impact on function of sperm, hence contributing to a growing infertility in the human population.

Zakrzewska (2006)[249] “RESULTS: The semen was diluted in 0.9% NaCl and was found to contain 12.4 micromol ATP 10-(-9) spermatozoa. ATP content was reduced with rising concentrations of NaF: by 74.6% at 20 tmol/L; by 75.5% at 100 micromol/L; by 90.8% at 200 imol/L; and by 99.9% at 10(5) micromol/L. The correlation between ATP content and sperm motility was significant (r = 0.4990). There was no correlation between ATP content and sperm density.”

Krasowska (2004)[250] “Previous work has shown that a high fluoride intake in rodents leads to histopathological changes in the germinal epithelium of testes that is associated with zinc deficiency. The purpose of this study was to determine whether supplemental dietary Zn would protect against testicular toxicity induced by fluoride in a small rodent, the bank vole. The 4-month exposure period to fluoride (200 microg/ml of drinking water) induced histopathological changes (hemorrhage in interstitium, necrosis and apoptosis in seminiferous tubule epithelium) which were accompanied by decreased testicular zinc concentration and increased lipid peroxidation. Supplemental dietary zinc (110-120 microg/g) together with fluoride treatment resulted in complete reversal of the fluoride-mediated effects. However, supplemented dietary Zn did not affect the accumulation of fluoride in the testes and bone. These data suggest that a zinc-enriched diet protects seminiferous tubules against fluoride toxicity by preventing the fluoride-induced testicular zinc deprivation.”

[249] Zakrzewska H, Udala J. (2006). [In vitro influence of sodium fluoride on adenosine triphosphate (ATP) content in ram semen]. [Article in Polish]. Ann Acad Med Stetin. 52 Suppl 1:109-11

[250] Krasowska A[1], Włostowski T, Bonda E. Zinc protection from fluoride-induced testicular injury in the bank vole (Clethrionomys glareolus). Toxicol Lett. 2004 Mar 7;147(3):229-35.

Zakrzewska (2002)[251] "The activities of androgen-dependent enzymes—acid phosphatase (ACP), lactate dehydrogenase (LDH), and gamma-glutamyl transferase (y-GT-10S)—decreased significantly when the ejaculate was treated with NaF at concentrations of 20, 100, 200 µmol/L (0.38; 1.9; 3.8 ppm F-), but they returned to the initial value of the control at 0.1 mol/L (1900 ppm F-). . . . These changes undoubtedly affect the physiological functions of the sperm."

Ghosh (2002)[252] "This study examined the effect of sodium fluoride, a water pollutant important through the world, including India, on testicular steroidogenic and gametogenic activities in relation to testicular oxidative stress in rats. Sodium fluoride treatment at 20mg/kg/day for 29 days by oral gavage resulted in significant diminution in the relative wet weight of the testis, prostate, and seminal vesicle without alteration in the body weight gain. Testicular delta(5),3beta-hydroxysteroid dehydrogenase (HSD) and 17beta-HSD activities were decreased significantly along with significant diminution in plasma levels of testosterone in the fluoride-exposed group compared to the control. Epididymal sperm count was decreased significantly in the fluoride-treated group and qualitative examination of testicular sections revealed fewer mature luminal spermatozoa in comparison to the control. The seminiferous tubules were dilated in treated animals. Fluoride treatment was associated with oxidative stress as indicated by an increased level of conjugated dienes in the testis, epididymis, and epididymal sperm pellet with respect to control. Peroxidase and catalase activities in the sperm pellet were decreased significantly in comparison to the control. The results of this experiment indicate that fluoride at a dose encountered in drinking water in contaminated areas exerts an adverse effect on the male reproductive system and this effect is associated with indicators of oxidative stress."

[251] Zakrzewska H, et al. (2002). In vitro influence of sodium fluoride on ram semen quality and enzyme activities. Fluoride 35: 153-160.

[252] Ghosh D[1], Das Sarkar S, Maiti R, Jana D, Das UB. Testicular toxicity in sodium fluoride treated rats: association with oxidative stress. Reprod Toxicol. 2002 Jul-Aug;16(4):385-90.

Susheela (1996)[253] "OBJECTIVE: The present study focuses on serum testosterone concentrations in patients with skeletal fluorosis, in order to assess the hormonal status in fluoride toxicity. METHODS: Serum testosterones were compared for patients afflicted with skeletal fluorosis (n = 30) and healthy males consuming water containing less than 1 ppm fluoride (Control 1, n = 26) and a second category of controls (Control 2, n = 16): individuals living in the same house as the patients and consuming same water as patients but not exhibiting clinical manifestations of skeletal fluorosis. RESULTS: Circulating serum testosterones in skeletal fluorosis patients were significantly lower than those of Control 1 at $p < 0.01$. Testosterone concentrations of Control 2 were also lower than those of Control 1 at $p < 0.05$ but were higher than those of the patient group. CONCLUSIONS: Decreased testosterone concentrations in skeletal fluorosis patients and in males drinking the same water as the patients but with no clinical manifestations of the disease compared with those of normal, healthy males living in areas nonendemic for fluorosis suggest that fluoride toxicity may cause adverse effects in the reproductive system of males living in fluorosis endemic areas."

Chinook (1994)[254] "Fluoride-treated sperm [4,750 ppm for 20 minutes] exhibited a high percent of morphologic abnormalities, including a large number (10.59%) of elongated heads and 2.1% amorphous heads. The tail also revealed splitting (2.19%), coiling (11.6%) and deflagellation (22.43%). A few sperm had bent necks, and 16.75% of spermatozoa showed a diminutive acrosome. . . . These changes may have caused loss of membrane integrity and reduced metabolic activity, which ultimately resulted in deterioration of forward progression rating. The treatment caused a significant enhancement in poor to fair forward progression and failure of good and excellent forward progression, leading to a significant decline in sperm motility. . . . The depleted sperm GSH in the present investigation strongly suggests

[253]Susheela AK1, Jethanandani P., Circulating testosterone levels in skeletal fluorosis patients. J Toxicol Clin Toxicol. 1996;34(2):183-9.

[254] Chinoy NJ, Narayana MV. (1994). In vitro fluoride toxicity in human spermatozoa. Reprod Toxicol. 8(2):155-9.

that, like several exogenous compounds, fluoride is largely dependent upon glutathione for detoxification."

Chubb (1985a)[255] "Our studies indicate that 3 ppm fluoride ions significantly inhibit testosterone secretion by rat testes perfused in vitro. . . . In conclusion, Oxypherol-E.T. contains contaminants that are toxic to endocrine organs. Fluoride ion may be the primary endocrine toxicant."

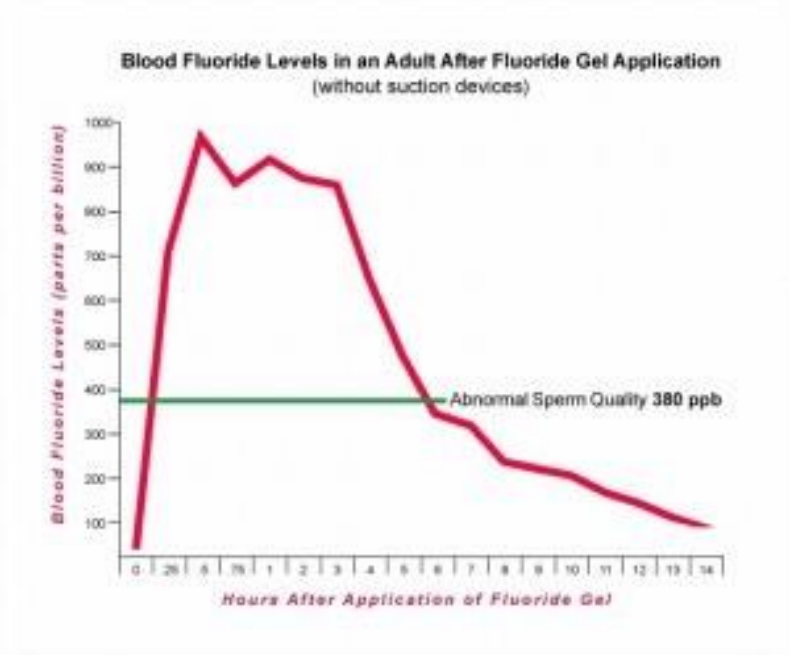
REVIEW BY FAN (2011)[256] "The enhancing overload caused by fluorides represents a potential factor, having an impact on function of sperm, hence contributing to a growing infertility in the human population." (Animal Reproduction Science, 2008

"Male infertility is responsible for about 50% of the fertility problems that couples face. Infertility in males is often the result of reduced sperm court, abnormal sperm quality (e.g., reduced motility and altered morphology), or altered levels of sex hormones (e.g., reduced testosterone). A review of over 100 studies of sperm density from 1938 to 1996 found that human sperm count has significantly declined in North America and Europe since the 1940s. (Swan 2000) While the causes of this decline are not entirely known, fluoride exposure — particularly from high-concentration topical fluoride gels — must be considered as one of the potential contributing factors.

"In 2002 and again in 2006, researchers from Poland reported that exposing ram semen to 0.38 parts per million (20 umol/L) of fluoride for 5 hours was sufficient to "cause a statistically significant decrease in the motility of spermatoza and the number of intact acrosomes." (Zakrzewska 2002). As the authors noted, these changes would "undoubtedly affect the physiological function of the sperm." Prior to the Polish team's findings, researchers from Texas found that infusing testis with

[255] Chubb C. (1985a). Reversal of the endocrine toxicity of commercially produced perfluorochemical emulsion. Biology of Reproduction 33(4):854-8.
[256] http://fluoridealert.org/issues/health/fertility/

higher, but still relatively modest, levels of fluoride (4.75 ppm) “unequivocally” inhibited the synthesis of testosterone. (Chubb 1985).



“The Polish team’s findings are of particular importance when considering that from the 1960s to the 1990s, the use of high-concentration topical fluoride gels produced blood concentrations in boys and men that far exceeded 0.38 ppm. In tests on both children and adults, the use of topical fluoride gels at the dental office has been found to produce blood fluoride concentrations as high as 1.2 ppm, or four times higher than the concentration found to damage sperm. (Ekstrand 1980, 1981). Further, the blood fluoride concentrations have been found to exceede 0.38 ppm for up to six hours after treatment (longer than the length of time that the Polish researchers exposed the semen). Although most dentists now use precautionary procedures (e.g., suction devices) to reduce blood fluoride concentrations following application of fluoride gels, available data shows that children will still routinely ingest enough fluoride from topical gels to reach blood fluoride concentrations exceeding 0.38 ppm.

“Consistent with the in vitro research, over 60 animal studies have found that fluoride adversely impacts the male reproductive system. The effects — which have been observed in rats, mice, chickens, and rabbits — include: (1) decreases in testosterone levels; (2) reduced sperm motility; (3) altered sperm morphology; (4)

reduced sperm quantity; (5) increased oxidative stress; (6) and reduced capacity to breed. While the studies have generally used high doses, many of the studies have found effects at dosages that would produce blood fluoride concentrations far lower than the concentrations used in the in vitro research. See, e.g., Sun (2010); Dvoráková-Hortová (2008); Sharma (2008); Reddy (2007); Gupta (2007); Pushpalatha (2005). In one of the few studies to report blood fluoride concentrations, Mexican researchers reported that blood fluoride levels of 0.2 to 0.26 ppm for an eight week period caused increased oxidative stress, reductions in sperm motility and reduced fertility in male rats. Izquierdo-Vega, et al. (2008).

“While some studies have not found any effects of high fluoride dosages on the reproductive functions of male rats , these studies represent the distinct minority in the field. (Sprando & Collins 1996, 1997, and 1998). One possible explanation for the discrepancy in findings is the nutritional health of the tested animals. As with many other areas of fluoride research, nutritional deficiencies (e.g., protein) unequivocally exacerbate fluoride’s reproductive effects, whereas nutritional supplementation (e.g., protein or anti-oxidants such as vitamin C) can significantly prevent or ameliorate these effects.

“Consistent with the in vitro and animal research, studies of human populations have reported associations between fluoride exposure and damage to the male reproductive system. Most notably, a scientist at the Food & Drug Administration reported in 1994 that populations in the United States with more than 3 ppm fluoride in their water had lower “total fertility rates” than populations with lower fluoride levels. (Freni 1994). While 3 ppm is a higher concentration than used in water fluoridation programs (0.7 to 1.2 ppm), it is still considered a “safe” level by the EPA. To date, no U.S. health agency has attempted to replicate Freni’s findings. However, three studies of highly fluoride-exposed populations in China and India have found that high fluoride exposure is associated with reduced male fertility. (Chen 1997; Liu 1988; Neelam 1987). In addition, five studies from China, India, Mexico, and Russia.have found that high-fluoride exposure is associated with reduced male

testosterone levels. (Hao 2010; Ortiz 2003; Susheela 1996; Michael 1996; Tokar 1977).” End of FAN quote.

G. ENTEROENDOCRINE (See the Pancreas for Pancreatic enteroendocrine)

Wikipedia: Enteroendocrine cells are specialized endocrine cells of the gastrointestinal tract and pancreas. They produce gastrointestinal hormones or peptides in response to various stimuli and release them into the bloodstream for systemic effect, diffuse them as local messengers, or transmit them to the enteric nervous system to activate nervous responses.[1][2] Enteroendocrine cells of the intestine are the most numerous endocrine cells of the body.[3][4][5] In a sense they are known to act as chemoreceptors, initiating digestive actions and detecting harmful substances and initiating protective responses.[6][7] Enteroendocrine cells are located in the stomach, in the intestine and in the pancreas. Intestinal enteroendocrine cells are not clustered together but spread as single cells throughout the intestinal tract.[8]Hormones secreted include somatostatin, motilin, cholecystokinin, neurotensin, vasoactive intestinal peptide, and enteroglucagon.[9]

Searches did not readily find studies specifically evaluating the enteroendocrine cells and fluoride. We do have studies on fluoride’s effect on the gastrointestinal cells as a group. If gastrointestinal cells are being harmed with fluoride, it is reasonable to expect enteroendocrine cells to be similarly involved.

Social (2010)[257] “Results reveal that (1) the urine fluoride levels decreased in 67% and 53% of the pregnant women respectively, who attended ANCs (antenatal clinic to reduce fluoride intake and improve diet) during 1st and 2nd trimester of pregnancy. (2) An increase in Hb upon withdrawal of fluoride followed by nutritional intervention in 73% and 83% respectively has also been recorded. (3) Body mass index (BMI) also enhanced. (4) The percentage of pre-term deliveries was decreased in sample group compared to control. (5) Birth weight of babies enhanced in 80% and 77% in sample group women who attended ANC in 1st and 2nd trimester respectively as opposed to 49% and 47% respectively in the control group. (6) The number of low birth weight babies was reduced to 20% and 23% respectively in sample as opposed to 51% and 53% in control groups.”

NRC (2006)[258] “It is important to realize that GI effects depend more on the net concentration of the aqueous solution of fluoride in the stomach than on the total fluoride dose in the fluid or solid ingested. The presence of gastric fluids already in the stomach when the fluoride is ingested can affect the concentration of the fluoride to which the gut epithelium is exposed. The residual volume of stomach fluid ranges between 15 and 30 mL in people fasting overnight (Narchi et al. 1993; Naguib et al. 2001; Chang et al. 2004). Such volumes would decrease the fluoride concentration of a glass of drinking water by only about 10%. In Table 9-1, the concentrations of fluoride in the stomach were estimated from the mean reported fluoride exposures. A dilution factor was used when it was clear that the subjects already had fluid in their stomach. The results from the water fluoridation overfeed reports (concentrations of fluoride in the stomach between 20 and 250 mg/L) indicate that GI symptoms, such as nausea and vomiting, are common side effects from exposure to high concentrations of fluoride.

[257] Susheela AK et al, Effective interventional approach to control anaemia in pregnant women. Current Science, May 25, 2010. 98(10):1320-30.
[258] National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA’s Standards. National Academies Press, Washington D.C. p 229-230.

"Fluoride supplements are still routinely used today in areas where natural fluoride in the drinking water falls below 0.7 mg/L. In an early clinical trial using fluoride supplements, Feltman and Kosel (1961) administered fluoride tablets containing 1.2 mg of fluoride or placebo tablets to pregnant mothers and children up to 9 years of age. They determined that about 1% of the subjects complained of GI symptoms from the fluoride ingredient in the test tablets. If it is assumed that the stomach fluid volume after taking the fluoride supplement was approximately 250 mL, the concentration to which the stomach mucosal lining was exposed was in the neighborhood of 5 mg/L. GI effects appear to have been rarely evaluated in the fluoride supplement studies that followed the early ones in the 1950s and 1960s. Table 9-1 suggests that, as the fluoride concentration increases in drinking water, the percentage of the population with GI symptoms also increases. The table suggests that fluoride at 4 mg/L in the drinking water results in approximately 1% of the population experiencing GI symptoms."

Connett (2012) provided an overview of fluoride and gastric mucosa: "When fluoride has been used (at doses of 18-34 mg/day) as an experimental treatment for osteoporosis, gastric pain is one of the two main side effects consistently encountered. To better understand how fluoride causes this effect, researchers have sought to determine how fluoride affects the tissue that lines the gastrointestinal tract.

In a study published in the British Medical Journal, the researchers gave a *single* dose of 20 mg/F to 12 healthy volunteers and then examined, both microscopically and macroscopically, the impact on the gastric mucosa. The examination revealed that the fluoride dose caused erosions (petechiae) in the stomach of *all* the subjects tested, with six of the subjects having similar effects in the antrum as well. Other findings were as follows:

"In four subjects a layer of clotted blood was found over a large part of the gastric mucosa… Three components of the gastric mucosa were affected by fluoride: the surface epithelium, the gastric pits, and the superficial stroma. The damaged

epithelial cells were smaller than undamaged ones, and the vacuoles containing mucus were reduced in size or had disappeared. The most severely damaged epithelium was disrupted or totally lost. The most characteristic changes in the gastric pits were irregular dilation and flattening of the epithelial cells. There was also a noticeable loss of mucin."
SOURCE: Spak CJ, et al. (1989). Tissue response of gastric mucosa after ingestion of fluoride. British Medical Journal 298:1686-87. [See study]

Despite the fact that tissue damage was found in all 12 volunteers, only 4 of the volunteers experienced nausea. Thus, "using nausea as the first sign of fluoride toxicity might not be valid as all subjects showed mucosal damage."

In a follow-up study, published in 1990, the authors examined the impact of lower doses of fluoride to determine whether the use of self-applied topical gels could cause damage to children's gastric system. In the study, the volunteers ingested a single dose of just **3 to 9 mg** of fluoride, which is considerably lower than what some people ingest from higher-concentration professional fluoride gels. Despite using low doses, the authors again found significant damage to the gastric mucosa. They described this damage as follows:
"After F exposure, histopathological changes were found in nine out of ten patients. The surface epithelium of the gastric mucosa showed the greatest effects: In two cases, there was a slight dilation of the gastric pits and a focal loss of surface epithelium. In some cases, the mucus-containing intercellular vacuoles were reduced in size, and focal hemorrhages within the epithelium occurred."
SOURCE: Spak CJ, et al. (1990). Studies of human gastric mucosa after application of 0.42% fluoride gel. Journal of Dental Research 69:426-9.

Interestingly, the authors note that they "could not find any correlation between the presence of mucosal injuries and the size of the ingested F dose." Based on this, they suggest that individual variability to fluoride may be a more important predictor of fluoride-induced gastric damage when low levels of fluoride are ingested. As they

note: “The various reactions of the mucosa to F exposure are most likely due to individual variations in gastric fluid volume, gastric pH, and motility and mucosal resistance.”

Such findings emphasize the difficulty of determining a uniform “safe” fluoride dose for an entire population. Indeed, if significant variability to fluoride is observed among 10 otherwise healthy humans, the variability is likely to be quite vast when studying the population as a whole, especially when including those with diseases that render one particularly susceptible to fluoride toxicity.

EXCERPTS FROM STUDIES EXAMINING FLUORIDE’S EFFECT ON GASTRIC MUCOSA IN HUMANS

“In a prospective case controlled study, we evaluated the adverse effects of long-term fluoride ingestion on the gastrointestinal tract. Ten patients with otosclerosis who were receiving sodium fluoride 30 mg/day for a period of 3-12 months, and 10 age- and sex-matched healthy volunteers were included… Seven subjects (70%) ingesting fluoride had abdominal pain, vomiting, and nausea. Petechiae, erosions, and erythema were seen on endoscopy in all the subjects, but not in the controls. Histological examination of the gastric antral biopsy showed chronic atrophic gastritis in all the subjects but in only one (10%) healthy volunteer. Scanning electron microscopic examination showed “cracked-clay” appearance, scanty microvilli, surface abrasions, and desquamated epithelium in the subjects ingesting fluoride, but not in the controls. We conclude that long-term fluoride ingestion is associated with a high incidence of dyspeptic symptoms as well as histological and electron microscopic abnormalities.”

SOURCE: Das TK, et al. (1994). Toxic effects of chronic fluoride ingestion on the upper gastrointestinal tract. Journal of Clinical Gastroenterology 18(3):194-9.

“In a randomized double-blind study with two parallel groups of 10 male healthy volunteers each the response of gastric mucosa after a 7 days ingestion of sodium fluoride tablets (NaF) or sodium monofluorophosphate tablets (MFP) was compared. Gastroscopic evaluations were performed before treatment, day 1 and day 7… In the

MFP-group no severe gastric lesions were observed, whereas in the NaF-group in 7 of the 10 subjects significant gastric mucosal lesions including acute hemorrhages and free blood in the gastric lumen were found. The differences of the lesions scores in both groups were statistically significant (p = 0.0015)… In summary, under the experimental conditions used MFP is well tolerated by the stomach while NaF produces significant gastric mucosal lesions."

SOURCE: Muller P, et al. (1992). Sodium fluoride-induced gastric mucosal lesions: comparison with sodium monofluorophosphate. Z Gastroenterol. 30(4):252-4.

"Dental prophylaxis with APF gels (1.23%) may cause gastric distress as a side-effect. This gastric irritation is probably due to a direct toxic effect of fluoride (F), swallowed in conjunction with the treatment, on the gastric mucosa. The aim of the present study was to investigate whether–and to what extent–a dental treatment with 3 g of a 0.42%-F gel could affect the gastric mucosa due to inadvertent swallowing of the gel. Ten subjects underwent a control gastroscopy, and two weeks later, a second gastroscopy was performed two h after a F gel treatment. During the gastroscopy, the mucosa was examined and the injuries graded according to an arbitrary scale. Four biopsies of the antral and corpus regions of the stomach were taken and evaluated histologically. The mean (+/- SD) amount of F retained after the application was 5.1 +/- 2.1 mg, i.e., 40% of the applied amount of F. Petechiae and erosions were found in the mucosa in seven of the ten patients. The histopathological evaluation revealed changes in nine of ten patients, with the surface epithelium as the most affected component of the mucosa. The present study clearly shows that a treatment with a F gel of rather low F concentration may result in injuries to the gastric mucosa. The importance of current recommended guidelines so that the amount of F swallowed during a gel application can be minimized is emphasized. From a toxicological standpoint, the use of a low-F gel instead of a 1.23%-F gel in small children is recommended for avoidance of adverse gastric effects."

SOURCE: Spak CJ, et al. (1990). Studies of human gastric mucosa after application of 0.42% fluoride gel. Journal of Dental Research 69:426-9.

"We studied the response of the gastric mucosa after a single dose of fluoride. Twelve healthy volunteers (age range 22-45, four men and eight women) underwent two

endoscopies after overnight fasts. One endoscopy was a control and the other was performed two hours after subjects ingested 20 ml sodium fluoride solution containing 20 mg fluoride (53 mmol/l)… After taking fluoride all subjects had petechiae or erosions (graded 3 or 4) in the body of the stomach and six had changes (graded 1-4) in the antrum. No petechiae or erosions were recorded in the oesophagus or the duodenum. In four subjects a layer of clotted blood was found over a large part of the gastric mucosa… Three components of the gastric mucosa were affected by fluoride: the surface epithelium, the gastric pits, and the superficial stroma. The damaged epithelial cells were smaller than undamaged ones, and the vacuoles containing mucus were reduced in size or had disappeared. The most severely damaged epithelium was disrupted or totally lost. The most characteristic changes in the gastric pits were irregular dilation and flattening of the epithelial cells. There was also a noticeable loss of mucin. Our study showed that one ingestion of fluoride at a dose used to treat osteoporosis affects the gastric mucosa… Symptoms like nausea and vomiting are not unusual when fluoride is used to treat osteoporosis. They also occur occasionally when high doses are used for dental prophylaxis. In our study only four subjects developed nausea, which suggests that using nausea as the first sign of fluoride toxicity might not be valid as all our subjects showed mucosal damage."
SOURCE: Spak CJ, et al. (1989). Tissue response of gastric mucosa after ingestion of fluoride. British Medical Journal 298:1686-87.

H. Paraganglia

"Paranganglia," refers to the groups of chromaffin cells associated with the sympathetic system. "Paraganglia are neuroendocrine organs mainly comprising cells that take their origin in the neural crest. They secrete catecholamines or indolamines and peptides. They are divided into two groups, associated with the sympathetic or parasympathetic nervous systems."[259]

[259] Endocrine Pathology:: Differential diagnosis and Molecular Advances. Lloyd RV Editor. Chapter 12, Adrenal Medulla and Paraganglia by McNicol AM.

Research specifically evaluating fluoride's effect on paraganglial tissues is not readily available at this time from our search.

I. Pituitary Gland

The pituitary gland is about the size of a pea (0.018 oz) and sits at the base of the brain. The anterior pituitary regulates several physiological processes including stress, growth, reproduction, blood pressure, metabolism, salt/water regulation of kidneys, temperature, pain relief and lactation, while the intermediate lobe synthesizes and secretes melanocyte-stimulating hormone and the posterior lobe is functionally connected to the hypothalamus.

The effects of fluoride pesticides on the pituitary gland are reported at http://www.fluoridealert.org/wp-content/pesticides/effects.endocrine.pituitary.htm

J. Placenta.

The phrase "buyer beware" comes to mind (in a sad guilty way) when searching studies for the effect of fluoride on the placenta, very few exist. In our capitalistic society we expect the buyer, the patient, to be responsible for purchase, use, and safety, especially of fluoride. Apparently we adults expect the fetus to do adequate and quality research on the effects of fluoride on the placenta and themselves, because we adults sure have not. Why have we adults failed to protect the unborn?

In a 1952 issue of *Science* magazine,[260] Harold C. Hodge (chief toxicologist for the US Army's Manhattan Project) reported that women who drank artificially fluoridated water (1.0–1.2 ppm fluoride) averaged 2.09 ppm fluoride in their placentas, compared with 0.74 ppm fluoride in the placentas of women who drank nonfluoridated water (0.06 ppm fluoride). Maternal blood fluoride levels were also nearly three times higher (0.040 vs. 0.014 ppm).

[260] Gardner DE, Smith FA, Hodge HC, Overton DE, Feltman R. The fluoride concentration of placental tissue as related to fluoride content in drinking water. *Science*. 1952;115(2982):208–209.

Tskitishvili (2010)[261] “Oxidative stress with elevated intracellular Ca^{2+} concentration as well as endothelial dysfunction is a component of pre-eclampsia. Our aim was to investigate the oxidative stress-dependent expression of Endoglin and Ca^{2+}-binding S100B protein from villous and amniotic tissue cultures, and to assess sEng expression from S100B protein-stimulated endothelial cells. We initially examined Endoglin and Hydroxy-nonenal-(HNE)-modified proteins in the placentas and amnion obtained from women with pre-eclampsia (n = 8), and healthy controls (n = 8) by immunohistochemistry. To examine oxidative stress and the S100B protein effect on sEng expression from endothelial cells, normal villous and amniotic tissue cultures were stimulated by 4-HNE, sodium fluoride and xanthine/xanthine oxidase, whereas human umbilical vein endothelial cell cultures were treated with S100B protein in a dose- and time-dependent manner at 37°C in an environment of 95% air and 5% of CO_2. Culture supernatants were assessed using ELISA. Cell viability was determined using MTS assay. The concentrations of sEng and S100B protein were significantly increased in the villous and amniotic tissue culture supernatants under oxidative stress. S100B protein-stimulated endothelial cells released sEng into conditioned media with a significantly higher expression levels at a concentration of 200 pM–20 nM S100B by 2 h, whereas treated with 200 nM of S100B endothelial cells significantly expressed sEng by 12 h and stimulated the cell proliferation by the same period of time. Our findings show that oxidative stress affects sEng and S100B protein expression from villous and amniotic tissues, and picomolar and low nanomolar concentrations of S100B protein significantly up-regulate sEng release from endothelial cells leading to endothelial dysfunction.”

Dlugosz (2009) “The aim of the study was to investigate the role of oestrogens in free radical detoxication upon exposure to fluoride. Interactions between xenobiotics and

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See also: Chlubek D, Poreba R, Machalinski B. Fluoride and calcium distribution in human placenta. *Fluoride*. 1998 31(3):131–136.

Sastry GM, Mohanty S, Rao P. Role of placenta to combat fluorosis (in fetus) in endemic fluorosis area. *Natl J Integr Res Med*. 2010 Oct–Dec;1(4):16–19.

[261] E. Tskitishvili[1,3], N. Sharentuya[1], K. Temma-Asano[1], K. Mimura[1], Y. Kinugasa-Taniguchi[1], T. Kanagawa[1], H. Fukuda[1], T. Kimura[1], T. Tomimatsu[1] and K. Shimoya· Oxidative stress-induced S100B protein from placenta and amnion affects soluble Endoglin release from endothelial cells. Mol Hum Reprod. 2010 Mar;16(3):188-99. doi: 10.1093/molehr/gap104. Epub 2009 Nov 25.

oestrogens need to be investigated, especially as many chemicals interact with the oestrogen receptor. It is still unknown whether free radical-generating xenobiotics can influence the antioxidative ability of oestradiol (E(2)). In an in vitro examination of human placental mitochondria, thiobarbituric active reagent species (TBARS), hydroxyl radical ((*)OH) generation and protein thiol (-SH) groups were detected. 17beta-E(2) was examined in physiological (0.15-0.73 nM) and experimental (1-10 microM) concentrations and sodium fluoride (NaF) in concentrations of 6-24 microM. E(2) in all the concentrations significantly decreased lipid peroxidation measured as the TBARS level, in contrast to NaF, which increased lipid peroxidation. Lipid peroxidation induced by NaF was decreased by E(2). The influence of E(2) on (*)OH generation was not very significant and depended on the E(2)concentration. The main mechanism of E(2) protection in NaF exposure appeared to be connected with the influence of E(2)on thiol group levels, not (*)OH scavenging ability. The E(2) in concentrations 0.44-0.73 nM and 1-10 microM significantly increased the levels of -SH groups, in contrast to NaF, which significantly decreased them. E(2) at every concentration reversed the harmful effects of NaF on -SH group levels. No unfavourable interactions in the influence of E(2) and NaF on TBARS production, (*)OH generation, or -SH group levels were observed. The results suggest that postmenopausal women could be more sensitive to NaF-initiated oxidative stress."

Srednicka (2007)[262] "The interactions in free radicals processes between cyclosporine A (CsA) and sodium fluoride (NaF) on in vitro model human placental mitochondria were evaluated. The level of malondialdehyde, hydroxyl radical generation and concentration of sulfhydryl groups of protein was measured. The results showed that CsA with NaF did not give any toxicological interactions with NaF in the area of measured parameters.

[262] Srednicka D1, Długosz A., Interactions in free radicals processes between cyclosporine A and sodium fluoride. Acta Pol Pharm. 2007 Nov-Dec;64(6):503-8.

Hassunuma (2007)[263] Little information is available on the pathogenesis of fluorosis during the fetal and initial postnatal period. In the present study, female rats received 0 (control), 7 or 100 ppm of sodium fluoride in drinking water, one week before breeding and throughout gestation and nursing periods. The hemimandibles of the offspring were collected at 0, 7 and 14 days of postnatal life (n = 5) and processed for morphological analyses by light and electron microscopy, immunohistochemical analysis for amelogenin and morphometric study of enamel matrix and ameloblasts of incisors. The results showed a decrease in matrix production at the secretory phase at all study periods for the 100 ppm group. In this same group, the secretory ameloblasts showed reduction of enamel matrix secretion, disorganization of mitochondrial crests, large vacuoles at the apical portion of the cytoplasm, retention of intracisternal material and dilatation of some cisterns in the rough endoplasmic reticulum. In the groups of animals aged 7 and 14 days, analysis of variance showed significant reduction ($p<0.05$) in cytoplasmic volume of 23.80% and 24.75%, respectively, in relation to the control group. The smooth-ended maturation ameloblasts exhibited a large number of vacuoles with electron-dense endocytic matrix, suggesting a delay in the resorption process. Immunohistochemical analysis showed no difference in the intensity and labeling pattern of the enamel matrix in any study group. Interestingly, in offspring at the age of 14 days for the 7 ppm group, there was an increase in the matrix length at the secretory phase. Therefore, part of the excessive dose of sodium fluoride given to the mother in drinking water can reach the offspring through the placenta and mother's milk, causing morphological changes in ameloblasts and suggesting a reduction in secretion and a delay in matrix resorption.

Toyama (2001)[264] “This study sought to obtain a precise profile of fluoride concentrations at and near the neonatal line in deciduous incisors and canines from

[263] Hassunuma RM1, Zen Filho EV, Ceolin DS, Cestari TM, Taga R, de Assis GF. Ultrastructural and immunohistochemical study of the influence of fluoride excess on the development of rat incisor tooth buds. J Appl Oral Sci. 2007 Aug;15(4):292-8.

[264] Toyama Y1, Nakagaki H, Kato S, Huang S, Mizutani Y, Kojima S, Toyama A, Ohno N, Tsuchiya T, Kirkham J, Robinson C. Fluoride concentrations at and near the neonatal line in human deciduous tooth enamel obtained from a naturally fluoridated and a non-fluoridated area. Arch Oral Biol. 2001 Feb;46(2):147-53.

the naturally fluoridated area (1.0--1.3 parts/10(6) F in drinking water) of West Hartlepool and the non-fluoridated area (less than 0.1 parts/10(6) F in drinking water) of Leeds in England. An abrasive microsampling method was used to determine the distribution of fluoride and phosphorus concentrations. The profile of fluoride concentrations in 100-microm layers before and after the neonatal line, that is, in the prenatal and postnatal enamel, were significantly higher in teeth from the fluoridated than non-fluoridated areas. It was concluded that the fact that the fluoride concentrations were about the same prenatally and postnatally in deciduous enamel obtained from the fluoridated and non-fluoridated areas indicates that fluoride enters the prenatal deciduous enamel and that it is transferred through the placenta."

Li (1999)[265] "Whole embryo rotated culture technique was used to investigate the toxicity of combination of selenium, fluoride and arsenic on rat embryos at day 9.5 of gestation. The result of factorial analysis (3 x 3 x 3) showed that the main effect of combination of selenium, fluoride and arsenic on the developmental toxicity was synergistic. The mixtures with different level of these three chemicals in combination could result in different developmental toxicity. The low level combinations mainly caused teratogenic effect, and the high level combinations(selenium 2.0 micrograms + fluoride 10 micrograms + arsenic 1.0 microgram/ml culture media) caused lethal effect. The results suggested that the disorders of yolk-sac placenta in structure and function were one of teratogenic mechanisms for the combination of selenium, fluoride and arsenic."

Flores-Herrera (1999)[266] "This report describes an ATP-diphosphohydrolase activity associated with the inner membrane of human term placental mitochondria. An enriched fraction containing 30 per cent of the total protein and 80 per cent of the total ATP-diphosphohydrolase activity was obtained from submitochondrial particles. ATP-diphosphohydrolase activity was characterized in this fraction. The enzyme had

[265] Li Y1, Sun M, Wu D, Chen X. [The toxicity of combination of selenium, fluoride and arsenic on rat embryos]. Wei Sheng Yan Jiu. 1999 Mar 30;28(2):74-6.
[266] Flores-Herrera O1, Uribe A, Pardo JP, Rendón JL, Martínez F. A novel ATP-diphosphohydrolase from human term placental mitochondria. Placenta. 1999 Jul-Aug;20(5-6):475-84.

a pH optimum of 8 and catalysed the hydrolysis of triphospho- and diphosphonucleosides other than ATP or ADP. Pyrophosphate was also hydrolysed, but AMP or other monoester phosphates were not. The activity of ATP-diphosphohydrolase was dependent on Mg(2 +), Ca(2 +)or Mn(2 +)and the enzyme substrate was the cation-nucleotide complex. An excess of free cation produced inhibition.ATP-diphosphohydrolase activity was stimulated at micromolar concentrations of calcium or magnesium in the presence of La-PPi. Negative cooperativity kinetics was observed with all substrates tested. The V(max)ranged from 150 to 300nmol of Pi released/mg/min. The [S](0.5)for nucleotides was 1-10m m and 182m m for PPi. The enzyme was inhibited by orthovanadate, but not by l -phenylalanine, oligomycin, sodium azide, P(1),P(5)-di(adenosine-5')pentaphosphate or sodium fluoride.The experimental evidence showing absence of inhibition by sodium azide and sodium fluoride, hydrolysis of pyrophosphate but not of monoester phosphates, and negative cooperativity suggested that this enzyme was a novel ATP-diphosphohydrolase."

Yuan (1998)[267] "Most inhibitors of S-adenosylhomocysteine (AdoHcy) hydrolase function as substrates for the "3'-oxidative activity" of the enzyme and convert the enzyme from its active form (NAD+) to its inactive form (NADH) (Liu, S., Wolfe, M. S., and Borchardt, R. T. (1992) Antivir. Res. 19, 247-265). In this study, we describe the effects of a mechanism-based inhibitor, 6'-bromo-5', 6'-didehydro-6'-deoxy-6'-fluorohomoadenosine (BDDFHA), which functions as a substrate for the "6'-hydrolytic activity" of the enzyme with subsequent formation of a covalent linkage with the enzyme. Incubation of human placental AdoHcy hydrolase with BDDFHA results in a maximum inactivation of 83% with the remaining enzyme activity exhibiting one-third of the kcat value of the native enzyme. This partial inactivation is concomitant with the release of both Br- and F- ions and the formation of adenine

[267] Yuan CS1, Wnuk SF, Robins MJ, Borchardt RT. A novel mechanism-based inhibitor (6'-bromo-5', 6'-didehydro-6'-deoxy-6'-fluorohomoadenosine) that covalently modifies human placental S-adenosylhomocysteine hydrolase. J Biol Chem. 1998 Jul 17;273(29):18191-7.

(Ade). The enzyme can be covalently labeled with [8-3H]BDDFHA, resulting in a stoichiometry of 2 mol of BDDFHA/mol of the tetrameric enzyme. The 3H-labeled enzyme retains its original NAD+/NADH content. Tryptic digestion and subsequent protein sequencing of the [8-3H]BDDFHA-labeled enzyme revealed that Arg196 is the residue that is associated with the radiolabeled inhibitor. The partition ratio of the Ade formation (nonlethal event) to covalent acylation (lethal event) is approximately 1:1. From these experimental results, a possible mechanism by which BDDFHA inactivates AdoHcy hdyrolase is proposed: enzyme-mediated water addition at the C-6' position of BDDFHA followed by elimination of Br- ion results in the formation of homoAdo 6'-carboxyl fluoride (HACF). HACF then partitions in two ways: (a) attack by a proximal nucleophile (Arg196) to form an amide bond after expulsion of F- ion (lethal event) or (b) depurination to form Ade and hexose-derived 6-carboxyl fluoride (HDCF), which is further hydrolyzed to hexose-derived 6-carboxylic acid (HDCA) and F- ion (nonlethal event). . . . Pharmacological modulation of intracellular methylation can be achieved through feedback inhibition of methyltransferase activity by AdoHcy (2). Intracellular AdoHcy concentrations can be elevated by decreasing AdoHcy hydrolase activity (27). Numerous nucleoside analogs capable of reversibly or irreversibly inhibiting AdoHcy hydrolase have been isolated or synthesized as potential antiviral, antiparasitic, antiarthritic, immunosuppresive, and antitumor agents (3-10). More recently, AdoHcy hydrolase inhibitors have been reported to be specially effective against fliovirus such as Ebola virus (28).

Tertrin-Clary (1998)[268] "1. Introduction: Protein kinase C (PKC) plays a fundamental role in the regulation of many signal transduction mechanisms activated in response to a variety of stimuli (hormones, growth factors, neurotransmitters). Molecular cloning and biochemical studies have revealed that this kinase consists of a family of at least 12 closely related isoforms classified into four groups based on their primary structure and cofactor requirements. . . . PKC appears to perform a variety of functions in vascular smooth muscle. Many studies have reported that the activation of PKC is associated with vascular smooth muscle contractility and plays a major role in growth-related signal transduction [2]. The feto-placental circulation provides for the metabolic needs of the fetus, and regulation of blood flow in this system is critical for fetal well-being and normal development. Stem villi vessels are considered to be the major sites of fetal placenta vascular resistance [3]. Since the placental vessels lack autonomic innervation, vascular tone is regulated by locally or humorally delivered vasoactive substances [4]. Endothelin-1 (ET-1), a 21 amino acid peptide, is a potent vasoactive agent that acts on the contractility of placental vessels [5]. Several studies have reported that activation of PKC may be a component of the signal cascade resulting in the effects of this peptide on contractility and cell division in vascular smooth muscles, such as rat cardiomyocytes [6-8], bovine cerebral arteries [9], human and rat renal artery [10,11], rat aorta [12] and the rat portal vein [13]. Specific high affinity binding sites for ET-1 have been described in the muscular layer of stem villi vessels [14], and Mondon et al. [15] demonstrated that these ET-1 vascular binding sites are coupled to a phosphoinositide-specific phospholipase C pathway that generates two intracellular messengers, DAG and CaP^{2+}, that are activators of PKC.

The objective of this study was to examine the presence of PKC activity in the muscular layer of human placental stem villi vessels. . . .

[268] Tertrin-Clary C, Fournier T., Ferreè F. Regulation of protein kinase C in the muscular layer of human placental stem villi vessels. FEBS Lett. 1998 Jan 23;422(1):123-8.

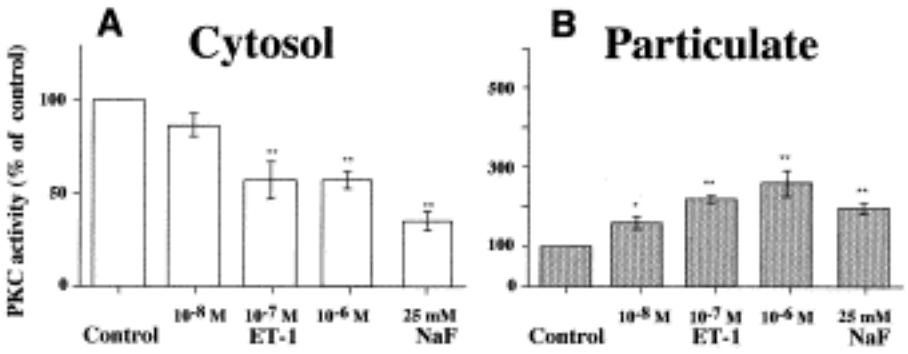

Fig. 1.

Chromatography of cytosolic and particulate-associated protein kinase C from human placental stem villi vessels on a DEAE-cellulose column. PKC activity in the eluted fractions was assayed as described in Section 2and is expressed cpm: (•) in the presence of Ca^{2+}, phosphatidylserine and diolein, (○) in the presence of EGTA, without phosphatidylserine or diolein. Results are representative of three experiments."

Montherrat-Carret (1996)[269] "To evaluate the beneficial effect of prenatal fluoride supplementation, the presence of fluoride in hard tissues in two populations of human foetuses coming from fluoridated (> or = 0.7 parts/10(6) F in drinking water) and non-fluoridated areas (< or = 0.1 parts/10(6) F in drinking water) were compared by chemical analysis and X-ray microanalysis. The fluoride concentrations measured in maternal and venous cord blood confirmed that placental transfer of fluoride was passive when fluoride intake was low. Total fluoride contents of tooth germs and mandibular bone appeared to increase with fluoride level in drinking water. However, these concentrations were too low to be detected by X-ray microanalysis. Phosphorus and calcium total contents were identical in mandibular and femoral bone of both populations. In incisor germs, phosphorus and calcium concentrations in enamel and dentine close to the amelodentinal junction did not differ significantly between the two populations. It is suggested that the low fluoride concentrations in enamel and dentine formed in utero would not have a significant effect on acid solubility."

[269]Montherrat-Carret L1, Perrat-Mabilon B, Barbey E, Bouloc R, Boivin G, Michelet A, Magloire H. Chemical and X-ray analysis of fluoride, phosphorus, and calcium in human foetal blood and hard tissues. Arch Oral Biol. 1996 Dec;41(12):1169-78.

Anand (1996)[270] “Active glycine transport was demonstrated in microvillous (maternal-facing, BBM) and basal (fetal-facing, BCM) plasma membranes of the human term placental syncytiotrophoblast. . . Nicotine, insulin, sodium fluoride and sodium arsenate were inhibitors for both the vesicles.”

Gupta (1993)[271] “Transplacental passage of fluorides was studied in 25 randomly selected neonates. Blood samples collected simultaneously from the mother and the umbilical cord showed that average fluoride concentration in the cord blood was 60% of that in mother's blood. When concentration in the mother's blood exceeded 0.4 ppm, the placenta acted as a selective barrier.

Malhotra (1993)[272] “The study was conducted on 25 healthy women residing in optimum fluoride areas, who were to deliver normally through vaginal route, to correlate the maternal and cord plasma fluoride levels and evaluate the placental transfer of fluoride. A wide variation was found in the maternal and cord plasma fluoride levels. In only 8 percent of the cases the fluoride levels in cord plasma were higher than maternal plasma. It was deduced that the placenta allows passive diffusion of fluoride from mother to foetus and does not act as a barrier.”

Vinals (1993)[273] “Fluoride is a nucleophilic reagent which has been reported to inhibit a variety of different enzymes such as esterases, asymmetrical hydrolases and phosphatases. In this report, we demonstrate that fluoride inhibits tyrosine kinase activity of insulin receptors partially purified from rat skeletal muscle and human placenta. . . . These data suggest: (i) that fluoride interacts directly and slowly with

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[270] Anand RJ1, Kanwar U, Sanyal SN. Transport of glycine in the brush border and basal cell membrane vesicles of the human term placenta. Biochem Mol Biol Int. 1996 Feb;38(1):21-30.

[271] Gupta S1, Seth AK, Gupta A, Gavane AG. Transplacental passage of fluorides. J Pediatr. 1993 Jul;123(1):139-41.

[272] Malhotra A1, Tewari A, Chawla HS, Gauba K, Dhall K. Placental transfer of fluoride in pregnant women consuming optimum fluoride in drinking water. J Indian Soc Pedod Prev Dent. 1993 Mar;11(1):1-3.

[273] Viñals F1, Testar X, Palacín M, Zorzano A. Inhibitory effect of fluoride on insulin receptor autophosphorylation and tyrosine kinase activity. Biochem J. 1993 Apr 15;291 (Pt 2):615-22.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1132568/

the insulin receptor, which causes inhibition of its phosphotransferase activity; (ii) that the binding site of fluoride is not structurally modified by receptor phosphorylation; and (iii) based on the fact that fluoride inhibits phosphotransferase activity in the absence of alterations in the binding of ATP, Mn2+ or insulin, we speculate that fluoride binding might affect the transfer of phosphate from ATP to the tyrosine residues of the beta-subunit of the insulin receptor and to the tyrosine residues of exogenous substrates."

The NRC (2006)[274] concluded in part: "The effects of fluoride on various aspects of endocrine function should be examined further, particularly with respect to a possible role in the development of several diseases or mental states in the United States. Major areas for investigation include the following: . . . thyroid disease (especially in light of decreasing iodine intake by the U.S. population). . . ."

[274] "Fluoride in Drinking Water: A Scientific Review of EPA's Standards." http://www.nap.edu/catalog/11571/fluoride-in-drinking-water-a-scientific-review-of-epas-standards

IV. NRC (2006) REPORT ON THE ENDOCRINE SYSTEM

The graph below needs no explanation.

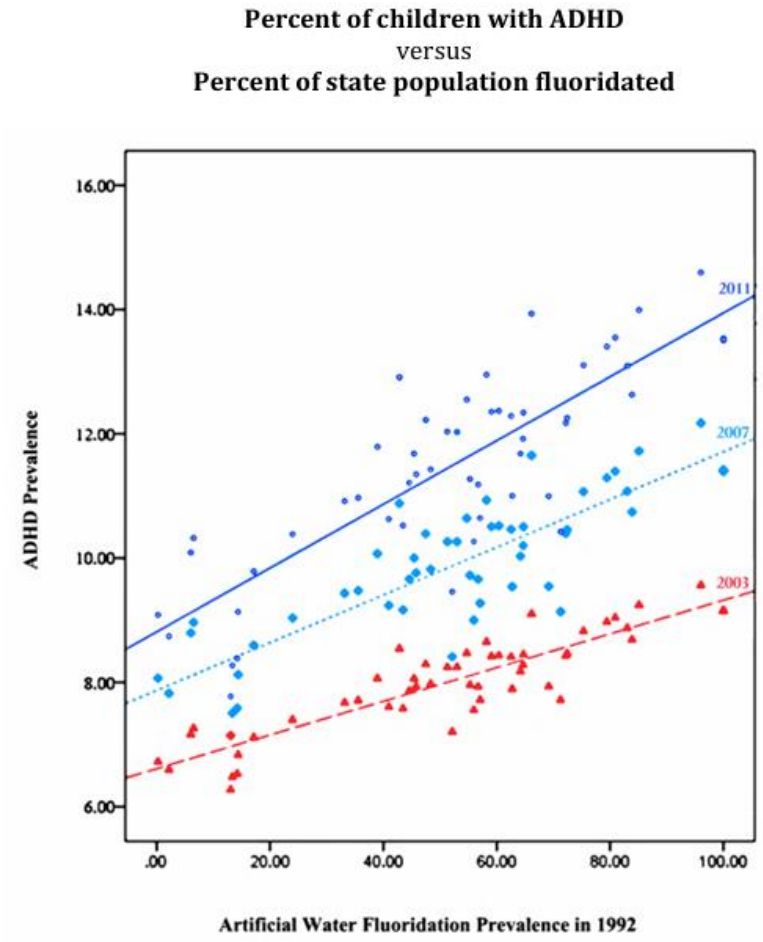

Figure 1. Artificial fluoridation prevalence predicting ADHD prevalence after adjusting for 1992 median household income, by state. Each color is for a different year of ADHD prevalence data: 2003, 2007, and 2011.

The following 9 pages are directly from pages 224-236 of the NRC's report's "Fluoride in Drinking Water: A Scientific Review of EPA's Standards."

"Effects on the Endocrine System

The endocrine system, apart from reproductive aspects, was not considered in detail in recent major reviews of the health effects of fluoride (PHS 1991; NRC 1993; Locker 1999; McDonagh et al. 2000a; WHO 2002; ATSDR 2003). Both the Public Health Service (PHS 1991) and the World Health Organization (WHO 2002) mentioned secondary hyperparathyroidism in connection with discussions of skeletal fluorosis, but neither report examined endocrine effects any further. The Agency for Toxic Substances and Disease Registry (ATSDR 2003) discussed four papers on thyroid effects and two papers on parathyroid effects and concluded that "there are some data to suggest that fluoride does adversely affect some endocrine glands." McDonagh et al. (2000a) reviewed a number of human studies of fluoride effects, including three that dealt with goiter and one that dealt with age at menarche. The following section reviews material on the effects of fluoride on the endocrine system—in particular, the thyroid (both follicular cells and parafollicular cells), parathyroid, and pineal glands. Each of these sections has its own discussion section. Detailed information about study designs, exposure conditions, and results is provided in Appendix E.

The follicular cells of the thyroid gland produce the classic thyroid hormones thyroxine (T4) and triiodothyronine (T3); these hormones modulate a variety of physiological

processes, including but not limited to normal growth and development (Larsen et al. 2002; Larsen and Davies 2002; Goodman 2003). Between 4% and 5% of the U.S. population may be affected by deranged thyroid function (Goodman 2003), making it among the most prevalent of endocrine diseases (Larsen et al. 2002). The prevalence of subclinical thyroid dysfunction in various populations is 1.3-17.5% for subclinical hypothyroidism and 0.6-16% for subclinical hyperthyroidism; the reported rates depend on age, sex, iodine intake, sensitivity of measurements, and definition used (Biondi et al. 2002). Normal thyroid function requires sufficient intake of iodine (at least 100 micrograms/day [µg/d]), and areas of endemic iodine deficiency are associated with disorders such as endemic goiter and cretinism (Larsen et al. 2002; Larsen and Davies 2002; Goodman 2003). Iodine intake in the United States (where iodine is added to table salt) is decreasing (CDC 2002d; Larsen et al. 2002), and an estimated 12% of the population has low concentrations of urinary iodine (Larsen et al. 2002).

The principal regulator of thyroid function is the pituitary hormone thyroid-stimulating hormone (TSH), which in turn is controlled by positive input from the hypothalamic hormone thyrotropin-releasing hormone (TRH) and by negative input from T4 and T3. TSH binds to G-protein-coupled receptors in the surface membranes of thyroid follicular cells (Goodman 2003), which leads to increases in both the cyclic adenosine monophosphate (cAMP) and diacylglycerol/inositol trisphosphate second messenger pathways (Goodman 2003). T3, rather than T4, probably is responsible for the feedback response for TSH production (Schneider et al. 2001). Some T3, the active form of thyroid hormone, is secreted directly by the thyroid along with T4, but most T3 is produced from T4 by one of two deiodinases (Types I and II1) in the peripheral tissue (Schneider et al. 2001; Larsen et al. 2002; Goodman 2003). T3 enters the nucleus of the target cells and binds to specific receptors, which activate specific genes.

Background

An effect of fluoride exposure on the thyroid was first reported approximately 150 years ago (Maumené 1854, 1866; as cited in various reports). In 1923, the director of the Idaho Public Health Service, in a letter to the Surgeon General, reported enlarged thyroids in many children between the ages of 12 and 15 using city water in the village

of Oakley, Idaho (Almond 1923); in addition, the children using city water had severe enamel deficiencies in their permanent teeth. The dental problems were eventually attributed to the presence in the city water of 6 mg/L fluoride, and children born after a change in water supply (to water with <0.5 mg/L fluoride) were not so affected (McKay 1933); however, there seems to have been no further report on thyroid conditions in the village.

More recently, Demole (1970) argued that a specific toxicity of fluoride for the thyroid gland does not exist, because (1) fluoride does not accumulate in the thyroid; (2) fluoride does not affect the uptake of iodine by thyroid tissue; (3) pathologic changes in the thyroid show no increased frequency in regions where water is fluoridated (naturally or artificially); (4) administration of fluoride does not interfere with the prophylactic action of iodine on endemic goiter; and (5) the beneficial effect of iodine in threshold dosage to experimental animals is not inhibited by administration of fluoride, even in excessive amounts. Bürgi et al. (1984) also stated that fluoride does not potentiate the consequences of iodine deficiency in populations with a borderline or low iodine intake and that published data fail to support the hypothesis that fluoride has adverse effects on the thyroid (at doses recommended for caries prevention). McLaren (1976), however, pointed out the complexity of the system, the difficulties in making adequate comparisons of the various studies of fluoride and the thyroid, and evidence for fluoride accumulation in the thyroid and morphological and functional changes (e.g., changes in activity of adenylyl cyclase), suggesting that analytical methods could have limited the definitiveness of the data to date. His review suggested that physiological or functional changes might occur at fluoride intakes of 5 mg/day.

Although fluoride does not accumulate significantly in most soft tissue (as compared to bones and teeth), several older studies found that fluoride concentrations in thyroid tissue generally exceed those in most other tissue except kidney (e.g., Chang et al. 1934; Hein et al. 1954, 1956); more recent information with improved analytic methods for fluoride was not located. Several studies have reported no effect of fluoride treatment on thyroid weight or morphology (Gedalia et al. 1960; Stolc and Podoba 1960; Saka et al. 1965; Bobek et al. 1976; Hara 1980), while others have reported such morphological changes as mild atrophy of the follicular epithelium (Ogilvie 1953),

distended endoplasmic reticulum in follicular cells (Sundström 1971), and "morphological changes suggesting hormonal hypofunction" (Jonderko et al. 1983).

Fluoride was once thought to compete with iodide for transport into the thyroid, but several studies have demonstrated that this does not occur (Harris and Hayes 1955; Levi and Silberstein 1955; Anbar et al. 1959; Saka et al. 1965). The iodide transporter accepts other negatively charged ions besides iodide (e.g., perchlorate), but they are about the same size as iodide (Anbar et al. 1959); fluoride ion is considerably smaller and does not appear to displace iodide in the transporter.

Animal Studies

A number of studies have examined the effects of fluoride on thyroid function in experimental animals or livestock (for details, see Appendix E, Tables E-1, E-2, and E-3). Of these, the most informative are those that have considered both the fluoride and iodine intakes.

Guan et al. (1988) found that a fluoride intake of 10 mg/L in drinking water had little apparent effect on Wistar rats with sufficient iodine intake, but a fluoride intake of 30 mg/L in drinking water resulted in significant decreases in thyroid function (decreases in T4, T3, thyroid peroxidase, and 3H-leucine), as well as a decrease in thyroid weight and effects on thyroid morphology (Table E-2). In iodine-deficient rats, fluoride intake of 10 mg/L in drinking water produced abnormalities in thyroid function beyond that attributable to low iodine, including decreased thyroid peroxidase, and low T4 without compensatory transformation of T4 to T3.

Zhao et al. (1998), using male Kunmin mice, found that both iodine-deficient and iodine-excess conditions produced goiters, but, under iodine-deficient conditions, the goiter incidence at 100 days increased with increased intake of fluoride. At 100 days, the high-fluoride groups had elevated serum T4 at all concentrations of iodine intake and elevated T3 in iodine-deficient animals. High fluoride intake significantly inhibited the radioiodine uptake in the low- and normal-iodine groups.

Stolc and Podoba (1960) found a decrease in protein-bound iodine in blood in fluoride-treated female rats (3-4 mg/kg/day) fed a low-iodine diet but not in corresponding rats fed a larger amount of iodine. Both groups (low- and high-iodine) of fluoride-treated rats showed a reduced rate of biogenesis of T3 and T4 after administration of 131I compared with controls (Stolc and Podoba 1960).

Bobek et al. (1976) found decreases in plasma T4 and T3 as well as a decrease in free T4 index and an increase in T3-resin uptake in male rats given 0.1 or 1 mg of fluoride per day (0.4-0.6 or 4-6 mg/kg/day) in drinking water for 60 days.2 The authors suggested the possibility of decreased binding capabilities and altered thyroid hormone transport in blood.

Decreases in T4 and T3 concentrations have been reported in dairy cows at estimated fluoride doses up to 0.7 mg/kg/day with possible iodine deficiency (Hillman et al. 1979; Table E-3). Reduced T3 (Swarup et al. 1998) and reduced T3, T4, and protein-bound iodine (Cinar and Selcuk 2005) have also been reported in cows diagnosed with chronic fluorosis in India and Turkey, respectively.

Hara (1980) found elevated T3 and T4 at the lowest dose (approximately 0.1 mg/kg/day), decreased T3 and normal T4 at intermediate doses (3-4 mg/kg/day), and decreased TSH and growth hormone (indicating possible effects on pituitary function) at the highest doses (10-20 mg/kg/day). This was the only animal study of fluoride effects on thyroid function to measure TSH concentrations; however, full details (e.g., iodine intake) are not available in English.

Other studies have shown no effect of fluoride on the end points examined (Gedalia et al. 1960; Siebenhüner et al. 1984; Clay and Suttie 1987; Choubisa 1999; Table E-1). Choubisa (1999) looked only for clinical evidence of goiter in domestic animals (cattle and buffaloes) showing signs of enamel or skeletal fluorosis; no hormone parameters (e.g., T4, T3, TSH) were measured. Gedalia et al. (1960) also did not measure T4, T3, or TSH; radioiodine uptake, protein-bound iodine, and total blood iodine were all normal in rats receiving fluoride doses up to approximately 1 milligram per kilogram of body weight per day (mg/kg/day). Clay and Suttie (1987) reported no significant differences from control values for T4 concentration and T3 uptake in heifers fed up to 1.4

mg/kg/day; iodine intake is not stated but probably was adequate, and TSH was not measured.

Siebenhüner et al. (1984) carried out a special experiment involving iodine depletion of the thyroid before 6 days of fluoride treatment. No effects were seen on the parameters measured, including T3 and T4 concentrations; however, TSH was not measured. In addition, propylthiouracil (PTU), the agent used to deplete the thyroid of iodine, also has an inhibitory effect on deiodinases (Larsen et al. 2002; Larsen and Davies 2002); Siebenhüner et al. (1984) did not mention this second action of PTU and its relevance to the interpretation of the experimental results, and there was no control group without the PTU treatment.

Human Studies

Several authors have reported an association between endemic goiter and fluoride exposure or enamel fluorosis in human populations in India (Wilson 1941; Siddiqui 1960; Desai et al. 1993), Nepal (Day and Powell-Jackson 1972), England (Wilson 1941; Murray et al. 1948), South Africa (Steyn 1948; Steyn et al. 1955; Jooste et al. 1999), and Kenya (Obel 1982). Although endemic goiter is now generally attributed to iodine deficiency (Murray et al. 1948; Obel 1982; Larsen et al. 2002; Belchetz and Hammond 2003), some of the goitrogenic areas associated with fluoride exposure were not considered to be iodine deficient (Steyn 1948; Steyn et al. 1955; Obel 1982; Jooste et al. 1999). Obel (1982) indicated that many cases of fluorosis in Kenya occur concurrently with goiter. Several authors raise the possibility that the goitrous effect, if not due to fluoride, is due to some other substance in the water (e.g., calcium or water hardness) that was associated with the fluoride concentration (Murray et al. 1948; Day and Powell-Jackson 1972) or that enhanced the effect of fluoride (Steyn 1948; Steyn et al. 1955). Dietary selenium deficiencies (e.g., endemic in parts of China and Africa or due to protein-restricted diets) can also affect normal thyroid function3 (Larsen et al. 2002); no information on dietary selenium is available in any of the fluoride studies. Appendix E summarizes a number of studies of the effects of fluoride on thyroid function in humans (see Table E-4).

Three studies illustrated the range of results that have been reported: (1) Gedalia and Brand (1963) found an association between endemic goiter in Israeli girls and iodine concentrations in water but found no association with fluoride concentrations (<0.1-0.9 mg/L). (2) Siddiqui (1960) found goiters only in persons aged 14-17 years; the goiters, which became less visible or invisible after puberty, were associated with mean fluorine content of the water (5.4-10.7 mg/L) and were inversely associated with mean iodine content of the water. (3) Desai et al. (1993) found a positive correlation ($P < 0.001$) between prevalence of goiter (9.5-37.5%) and enamel fluorosis (6.0-59.0%), but no correlation between prevalence of goiter and water iodine concentration ($P > 0.05$).

Day and Powell Jackson (1972) surveyed 13 villages in Nepal where the water supply was uniformly low in iodine (?1 µg/L; see Figure 8-1). Here the goiter prevalence (5-69%, all age groups) was directly associated with the fluoride concentration (<0.1 to 0.36 mg/L; $P < 0.01$) or with hardness, calcium concentration, or magnesium concentration of the water (all $P < 0.01$). Goiter prevalence of at least 20% was associated with all fluoride concentrations ? 0.19 mg/L, suggesting that fluoride might influence the prevalence of goiter in an area where goiter is endemic because of low iodine intake. The possibility of a nutritional component (undernutrition or protein deficiency) to the development of goiter was also suggested.

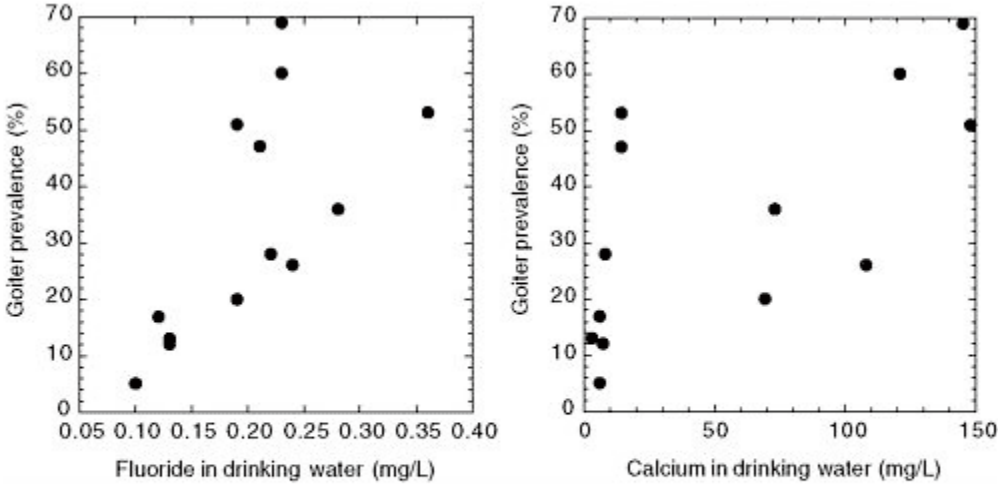

FIGURE 8-1 Goiter prevalence versus fluoride (left) and calcium (right) concentration in drinking water for 13 villages in Nepal with very low iodine concentrations.
SOURCE: Day and Powell-Jackson 1972.

Jooste et al. (1999) examined children (ages 6, 12, and 15) who had spent their entire lives in one of six towns in South Africa where iodine concentrations in drinking water were considered adequate (median urinary iodine concentration exceeding 201 µg/L [1.58 µmol/L]; see Appendix E, Tables E-4 and E-5; Figure 8-2). For towns with low (0.3-0.5 mg/L) or near "optimal" (0.9-1.1 mg/L) fluoride concentrations in water, no relationship between fluoride and prevalence of mild goiter was found (5-18%); for the other two towns (1.7 and 2.6 mg/L fluoride), however, goiter prevalences were 28% and 29%, respectively, and most children had severe enamel mottling. These two towns (and one low-fluoride town) had very low proportions (0-2.2%) of children with iodine deficiency, defined as urinary iodine concentrations <100 µg/L (<0.79 µmol/L). The town with the lowest prevalence of goiter also had the lowest prevalence of under-nutrition; the two towns with the highest prevalence of goiter (and highest fluoride concentrations) did not differ greatly from the remaining three towns with respect to prevalence of under-nutrition. The authors suggested that fluoride or an associated goitrogen might be responsible for the goiters seen in the two towns with the highest fluoride concentrations but that some other factor(s) was involved in development of goiter in the other towns.

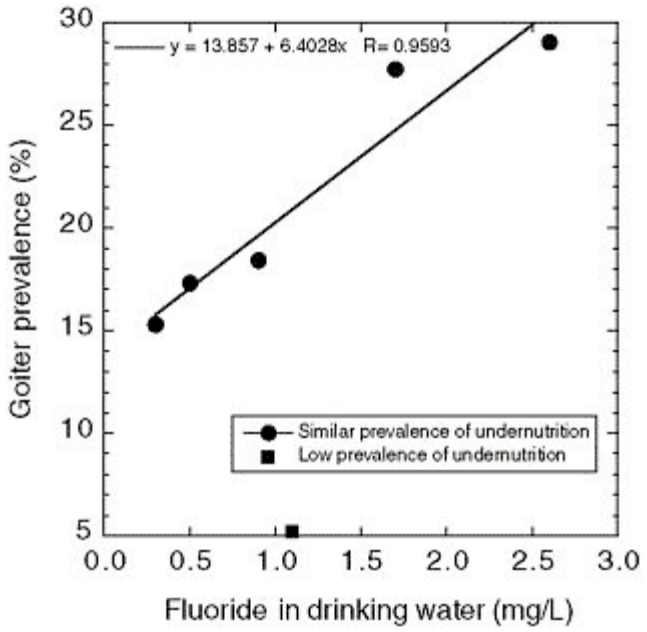

FIGURE 8-2 Goiter prevalence versus drinking water fluoride concentrations in six South African towns with adequate iodine concentrations. One town had a significantly lower prevalence of undernutrition than the other five towns and is not included in the line fitting. SOURCE: Jooste et al. 1999.

Several studies have compared various aspects of thyroid status in populations with different fluoride intakes (for details, see Appendix E, Table E-4). Leone et al. (1964) and Baum et al. (1981) reported no significant differences in thyroid status between populations with low (0.09-0.2 mg/L) and high (3-3.5 mg/L) fluoride concentrations in the drinking water. Leone et al. (1964) looked only at protein-bound iodine and physical examination of the thyroid in adults; Baum et al. (1981) measured a number of parameters in teenagers, including T4, T3, and TSH. Neither study reported iodine status of the groups. Baum et al. (1981) showed but did not explain a decrease in thyroglobulin in girls in the high-fluoride group.

Bachinskii et al. (1985) examined 47 healthy persons, 43 persons with hyperthyroidism, and 33 persons with hypothyroidism. Prolonged consumption of “high-fluoride” drinking water (2.3 mg/L, as opposed to “normal” concentrations of 1 mg/L) by healthy persons was associated with statistically significant changes in TSH concentrations (increased), T3 concentrations (decreased), and uptake of radioiodine (increased), although the mean values for TSH and T3 were still within normal ranges (see Appendix E, Table E-6). The mean value of TSH for the healthy group (4.3 ± 0.6 milliunits/L; Table E-6) is high enough that one expects a few individuals to have been above the normal range (typically 0.5-5 milliunits/L; Larsen et al. 2002). These results were interpreted as indicating disruption of iodine metabolism, stress in the pituitary-thyroid system, and increased risk of developing thyroidopathy (Bachinskii et al. 1985).

Lin et al. (1991) examined 769 children (7-14 years old) for mental retardation in three areas of China, including an area with “high” fluoride (0.88 mg/L) and low iodine, an area with “normal” fluoride (0.34 mg/L) and low iodine, and an area where iodine supplementation was routine (fluoride concentration not stated). Ten to twelve children in each area received detailed examinations, including measuring thyroid 131I uptake and thyroid hormone concentrations. Children in the first area had higher TSH, slightly higher 131I uptake, and lower mean IQ than children in the second area. Children in the first area also had reduced T3 and elevated reverse T3, compared with children in the second area. The authors suggested that high fluoride might exacerbate the effects of iodine deficiency. In addition, the authors reported a difference in T3/rT3 (T3/reverse-T3) ratios between high- and low-fluoride areas and suggested that excess fluoride ion affects normal deiodination.

A recent study by Susheela et al. (2005) compared thyroid hormone status (free T4, free T3, and TSH) of 90 children with enamel fluorosis (drinking water fluoride ranging from 1.1 to 14.3 mg/L) and 21 children without enamel fluorosis (0.14-0.81 mg/L fluoride in drinking water) in areas where iodine supplementation was considered adequate.4 Forty-nine children (54.4%) in the sample group had “well-defined hormonal derangements”; findings were borderline in the remaining 41 children. The types of hormonal derangements included elevated TSH and normal T4 and T3 (subclinical hypothyroidism); low T3 and normal T4 and TSH (“low T3 syndrome”); elevated T3 and TSH and normal T4 (possible T3 toxicosis); elevated TSH, low T4, and normal T3 (usually indicative of primary hypothyroidism and iodine deficiency); and low T3, high TSH, and normal T4. All but the first category are considered to be associated with or potentially caused by abnormal activity of deiodinases. The authors concluded that fluoride in excess may be inducing diseases that have usually been attributed to iodine deficiency and that iodine supplementation may not be adequate when excess fluoride is being consumed.

Thyroid hormone disturbances were also noted in the control children, and urine and fluoride concentrations in the control children reflect higher fluoride intake than can be accounted for by the drinking water alone (Susheela et al. 2005). Thus, the authors recommend that end points such as hormone concentrations should be examined with

respect to serum or urinary fluoride concentrations, not just drinking water fluoride concentrations. In addition, they note that all hormone endpoints (T3, T4, and TSH) should be examined, lest some of the abnormalities be missed.

Mikhailets et al. (1996) detected thyroid abnormalities (moderate reduction of iodine uptake, low T3, normal T4, and increased TSH) in 165 aluminum workers with signs of chronic fluorosis and an estimated average fluoride intake of 10 mg/working day. A tendency toward increased TSH was observed with increased exposure time and with more severe fluorosis. Workers with more than 10 years of service had a significant decrease in T3 concentration in comparison to controls. The frequency of individuals with low concentrations of T3 (corresponding to hypothyroidism) was 65% among workers with more than 10 years of service and 54% among workers with Stage 2 fluorosis. The highest frequency of occurrence of low T3 (76%) was observed in people with chronic fluoride intoxication including liver damage (moderate cytolysis), suggesting a disorder in peripheral conversion of T4 to T3 (deiodination). The possibility of indirect effects of fluorine on enzymatic deiodination was also suggested.

Tokar? et al. (1989) and Balabolkin et al. (1995) have also reported thyroid effects in fluoride- or fluorine-exposed workers; full details of these studies are not available in English. Balabolkin et al. (1995) found that 51% of the workers examined had subclinical hypothyroidism with reduced T3.

No changes in thyroid function were detected in two studies of osteoporosis patients treated with NaF for 6 months or several years (Eichner et al. 1981; Hasling et al. 1987; for details, see Appendix E, Table E-7). These study populations are not necessarily representative of the general population, especially with respect to age and the fact that they usually receive calcium supplements. In an earlier clinical study to examine the reported effects of fluoride on individuals with hyperthyroidism, Galletti and Joyet (1958) found that, in 6 of 15 patients, both basal metabolic rate and protein-bound iodine fell to normal concentrations, and the symptoms of hyperthyroidism were relieved after fluoride treatment. Fluoride was considered clinically ineffective in the other 9 patients, although improvement in basal metabolic rate or protein-bound iodine was observed in some of them. In the 6 patients for whom fluoride was effective, tachycardia and tremor

disappeared within 4-8 weeks, and weight loss was stopped. The greatest clinical improvement was observed in women between 40 and 60 years old with a moderate degree of thyrotoxicosis; young patients with the classic symptoms of Graves' disease did not respond to fluoride therapy. Radioiodine uptake tests were performed on 10 of the patients, 7 of whom showed an inhibitory effect on initial 131I uptake by the thyroid.

Discussion (Effects on Thyroid Function)

In studies of animals with dietary iodine sufficiency, effects on thyroid function were seen at fluoride doses of 3-6 mg/kg/day (Stolc and Podoba 1960; Bobek et al. 1976; Guan et al. 1988; Zhao et al. 1998); in one study, effects were seen at doses as low as 0.4-0.6 mg/kg/day (Bobek et al. 1976). In low-iodine situations, more severe effects on thyroid function were seen at these doses (Stolc and Podoba 1960; Guan et al. 1988; Zhao et al. 1998). Effects on thyroid function in low-iodine situations have also been noted at fluoride doses as low as 0.06 mg/kg/day (Zhao et al. 1998), ?0.7 mg/kg/day (Hillman et al. 1979), and 1 mg/kg/day (Guan et al. 1988). Studies showing no effect of fluoride on thyroid function did not measure actual hormone concentrations (Gedalia et al. 1960; Choubisa 1999), did not report iodine intakes (Gedalia et al. 1960; Clay and Suttie 1987; Choubisa 1999), used fluoride doses (<1.5 mg/kg/day) below those (3-6 mg/kg/day) associated with effects in other studies (Gedalia et al. 1960; Clay and Suttie 1987), or did not discuss a possibly complicating factor of the experimental procedure used (Siebenhüner et al. 1984). Only one animal study (Hara 1980) measured TSH concentrations, although that is considered a "precise and specific barometer" of thyroid status in most situations (Larsen et al. 2002). Full details of Hara's report are not available in English.

Goiter prevalence of at least 20% has been reported in humans exposed to water fluoride concentrations ? 0.2 mg/L (low-iodine situation; Day and Powell-Jackson 1972) or 1.5-3 mg/L (undernutrition, but adequate iodine; Jooste et al. 1999); however, other causes of goiter have not been ruled out. Bachinskii et al. (1985) showed increased TSH concentrations and reduced T3 concentrations in a population with a fluoride concentration of 2.3 mg/L in their drinking water (in comparison to a group with 1.0 mg/L), and Lin et al. (1991) showed similar results for a population with 0.88 mg/L

fluoride in the drinking water (in comparison to a group with 0.34 mg/L); another study showed no effect at 3 mg/L (Baum et al. 1981). Among children considered to have adequate iodine supplementation, Susheela et al. (2005) found derangements of thyroid hormones in 54% of children with enamel fluorosis (1.1-14.3 mg/L fluoride in drinking water), and in 45-50% of "control" children without enamel fluorosis but with elevated serum fluoride concentrations. Mikhailets et al. (1996) observed an increase in TSH in workers with increased exposure time and with more severe fluorosis; low T3 was found in 65% of workers with more than 10 years of service and in 54% of workers with Stage 2 fluorosis. Several studies do not include measurements of T4, T3, or TSH (Siddiqui 1960; Gedalia and Brand 1963; Leone et al. 1964; Day and Powell-Jackson 1972; Teotia et al. 1978; Desai et al. 1993; Jooste et al. 1999).

Nutritional information (especially the adequacy of iodine and selenium intake) is lacking for many (iodine) or all (selenium) of the available studies on humans. As with the animal studies, high fluoride intake appears to exacerbate the effects of low iodine concentrations (Day and Powell-Jackson 1972; Lin et al. 1991). Uncertainty about total fluoride exposures based on water fluoride concentrations, variability in exposures within population groups, and variability in response among individuals generally have not been addressed. Although no thyroid effects were reported in studies using controlled doses of fluoride for osteoporosis therapy, the study populations are not necessarily representative of the general population with respect to age, calcium intake, and the presence of metabolic bone disease.

Thus, several lines of information indicate an effect of fluoride exposure on thyroid function. However, because of the complexity of interpretation of various parameters of thyroid function (Larsen et al. 2002), the possibility of peripheral effects on thyroid function instead of or in addition to direct effects on the thyroid, the absence of TSH measurements in most of the animal studies, the difficulties of exposure estimation in human studies, and the lack of information in most studies on nutritional factors (iodine, selenium) that are known to affect thyroid function, it is difficult to predict exactly what effects on thyroid function are likely at what concentration of fluoride exposure and under what circumstances.

Suggested mechanisms of action for the results reported to date include decreased production of thyroid hormone, effects on thyroid hormone transport in blood, and effects on peripheral conversion of T4 to T3 or on normal deiodination processes, but details remain uncertain. Both peripheral conversion of T4 to T3 and normal deiodination (deactivation) processes require the deiodinases (Types I and II for converting T4 to T3 and Types I and III for deactivation; Schneider et al. 2001; Larsen et al. 2002; Goodman 2003). Several sets of reported results are consistent with an inhibiting effect of fluoride on deiodinase activity; these effects include decreased plasma T3 with normal or elevated T4 and TSH and normal T3 with elevated T4 (Bachinskii et al. 1985; Guan et al. 1988; Lin et al. 1991; Balabolkin et al. 1995; Michael et al. 1996; Mikhailets et al. 1996; Susheela et al. 2005). The antihyperthyroid effect that Galletti and Joyet (1958) observed in some patients is also consistent with an inhibition of deiodinase activity in those individuals.

The available studies have generally dealt with mean values of various parameters for the study groups, rather than with indications of the clinical significance, such as the fraction of individuals with a value (e.g., TSH concentration) outside the normal range or with clinical thyroid disease. For example, in the two populations of asymptomatic individuals compared by Bachinskii et al. (1985), the elevated mean TSH value in the higher-fluoride group is still within the normal range, but the number of individuals in that group with TSH values above the normal range is not given.

In the absence of specific information in the reports, it cannot be assumed that all individuals with elevated TSH or altered thyroid hormone concentrations were asymptomatic, although many might have been. For asymptomatic individuals, the significance of elevated TSH or altered thyroid hormone concentrations is not clear. Belchetz and Hammond (2003) point out that the population-derived reference standards (e.g., for T4 and TSH) reflect the mean plus or minus two standard deviations, meaning that 5% of normal people have results outside a given range. At the same time, healthy individuals might regulate plasma T4 within a “personal band” that could be much more narrow than the reference range; this brings up the question of whether a disorder shifting hormone values outside the personal band but within the population reference range requires treatment (Davies and Larsen 2002; Belchetz and

Hammond 2003). For example, early hypothyroidism can present with symptoms and raised TSH but with T4 concentrations still within the reference range (Larsen et al. 2002; Belchetz and Hammond 2003).

Subclinical hypothyroidism is considered a strong risk factor for later development of overt hypothyroidism (Weetman 1997; Helfand 2004). Biondi et al. (2002) associate subclinical thyroid dysfunction (either hypo or hyperthyroidism) with changes in cardiac function and corresponding increased risks of heart disease. Subclinical hyperthyroidism can cause bone demineralization, especially in postmenopausal women, while subclinical hypothyroidism is associated with increased cholesterol concentrations, increased incidence of depression, diminished response to standard psychiatric treatment, cognitive dysfunction, and, in pregnant women, decreased IQ of their offspring (Gold et al. 1981; Brucker-Davis et al. 2001). Klein et al. (2001) report an inverse correlation between severity of maternal hypothyroidism (subclinical or asymptomatic) and the IQ of the offspring (see also Chapter 7).

A number of authors have reported delayed eruption of teeth, enamel defects, or both, in cases of congenital or juvenile hypothyroidism (Hinrichs 1966; Silverman 1971; Biggerstaff and Rose 1979; Noren and Alm 1983; Loevy et al. 1987; Bhat and Nelson 1989; Mg'ang'a and Chindia 1990; Pirinen 1995; Larsen and Davies 2002; Hirayama et al. 2003; Ionescu et al. 2004). No information was located on enamel defects or effects on eruption of teeth in children with either mild or subclinical hypothyroidism. The possibility that either dental fluorosis (Chapter 4) or the delayed tooth eruption noted with high fluoride intake (Chapter 4; see also Short 1944) may be attributable at least in part to an effect of fluoride on thyroid function has not been studied." (End quote of NRC)

VI. FLUORIDE, IODINE AND GOITER[275]

A reasonably consistent body of animal and human research shows that fluoride exposure worsens the impact of iodine deficiency. (Gas'kov 2005; Hong 2001; Wang 2001; Zhao 1998; Xu 1994; Lin 1991; Ren 1989; Guan 1988).[276] Iodine is needed for T3 and T4 hormone production and thus an adequate iodine intake is considered important for the proper thyroid function.

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275 Additional References

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Researchers report an iodine deficiency coupled with fluoride exposure produces a more damaging effect on neurological development than iodine deficiency alone. (Hong 2001; Xu 1994; Lin 1991; Ren 1989).[277] The studies, which utilize childhood intelligence as the metric for assessing neurological health, have found that fluoride levels in water as low as 0.9 ppm can worsen the IQ effect of iodine deficiency. (Lin 1991).[278] Studies have reported an association between fluoride and reduced IQ among children with adequate iodine intake, (Choi 2012),[279] and iodine deficiency appears to lower the threshold at which fluoride damages the brain, (Xu 1994; Guan 1988).[280] and dental fluorosis. (Zhao 1998; see also Pontigo-Loyola 2008).[281]

Iodine deficiency is still a public health concern in the United States. (CDC 1998). More than 11% of all Americans, and more than 15% of American women of child-bearing age, presently have urine iodine levels less than 50 mcg/L (Caldwell et al., 2008),[282] indicating moderate to severe iodine deficiency. An additional 36% of reproductive-aged women in the U.S. are considered mildly iodine deficient (<100 mcg/L urinary iodine). Without success, the National Research Council has therefore called for studies investigating the interactive effects of fluoride and iodine on US populations.

The Fluoride Goiter Iodine Connection

Studies dating back to the 19th century have implicated fluoride as a possible cause of goitre. Goitre (aka goiter) is an enlargement of the thyroid gland that in some cases can produce visible swelling in the neck. Although the main cause of goitre is iodine deficiency, it can also be caused by other things, including hypothyroidism and

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[277] Ibid #6.

[278] Ibid #6

[279] Choi AL, et al. (2012). Developmental Fluoride Neurotoxicity: A Systematic Review and Meta-Analysis. *Environmental Health Perspectives* 2012 Jul 20. [Epub ahead of print]

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goitrogens (substances that cause goitre). Studies that have examined human populations with adequate intake of iodine have reported mixed results about fluoride's ability to produce goitre. (NRC 2006; Burgi 1984; McLaren 1969).[283] The research has been more consistent, however, where the examined populations had either excessive iodine intakes, or deficient iodine intakes. (Gas'kov 2005; Hong 2001; Wang 2001; Xu 1994; Yang 1994; Lin 1986).[284] Most of this latter research was initially published in either Russian or Chinese and was only recently translated into English by the Fluoride Action Network. Accordingly, previous reviews of fluoride/goitre research (e.g., NRC 2006) were not able to take these studies into account. As such, the evidence linking fluoride to goitre for populations with excessive, or deficient, iodine exposure is stronger than previously recognized.

Dogs have been found to suffer a high incidence of hypothyroidism, the relationship between fluoride contamination and thyroid disease in pets deserves further attention, particularly since it was fluoride's production of goiter in dogs that first prompted the idea that fluoride could be an anti-thyroid agent. (Maumene 1854).[285]

A consistent body of animal and human research shows that fluoride exposure worsens the impact of an iodine deficiency. Iodine is the basic building block of the T3 and T4 hormones and thus an adequate iodine intake is essential for the proper functioning of the thyroid gland. When iodine intake is inadequate during infancy and early childhood, the child's brain can suffer permanent damage, including mental retardation.[286]

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[284] See Footnote #6
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[286] See previous Nomination to OHAT for Fluoride and Neurological development.
See also

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In China, researchers have repeatedly found that an iodine deficiency coupled with fluoride exposure produces a significantly more damaging effect on neurological development than iodine deficiency alone. In the first study to investigate the issue,

Ren (1989) "From the results it is evident that disrupted child intellectual development is among the effects on the human body from a harmful environment containing both high fluoride and low iodine, and this disruption is clearly much more serious than the effects of iodine deficiency alone."[287]

In 1991, a UNICEF-funded study concluded that fluoride levels of just 0.9 ppm (less than the level added to many water supplies for fluoridation) were sufficient to worsen the effects of iodine deficiency. The authors found that, when compared to children with iodine deficiency in a low-fluoride area, the children with iodine deficiency in the 0.9 ppm area had increased TSH levels, reduced T3, reduced intelligence, retarded bone development, and reduced hearing. According to the authors:

"Statistically significant differences existed between these areas, suggesting that a low iodine intake coupled with high fluoride intake exacerbates the central nervous lesions and the somatic developmental disturbance of iodine deficiency."[288]

In 1994, Xu and colleagues measured the IQ rates of children living in 8 areas with differing levels of both iodine and fluoride in exposure. Of all the areas studied, the region with the high fluoride/low iodine content had the lowest IQ. In addition, when

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- Shen X, Zhang Z, Xu X. (2004). [Influence of combined iodine and fluoride on phospholipid and fatty acid composition in brain cells of rats] Wei Sheng Yan Jiu. 33(2):158-61.
- Wang J, Ge Y, Ning H, Wang S. (2004). Effects of high fluoride and low iodine on biochemical indexes of the brain and learning-memory of offspring rats. Fluoride 37(4): 201-208.

[287] Ren D, et al. (1989). A study of the intellectual ability of 8-14 year-old children in high fluoride, low iodine areas. Chinese Journal of Control of Endemic Diseases 4(4):251 (republished in Fluoride 2008; 41:319-20).

[288] SOURCE: Lin Fa-Fu; et al (1991). The relationship of a low-iodine and high-fluoride environment to subclinical cretinism in Xinjiang. Endemic Disease Bulletin 6(2):62-67 (republished in Iodine Deficiency Disorder Newsletter Vol. 7(3):24-25).

compared against the low-iodine area, the high fluoride/low iodine area had a significantly higher rate of thyroid swelling. According to the authors:
"A higher chance of one being affected by thyroid swelling is likewise more prevalent in regions containing a high amount of fluoride but low amount of iodine, and regions where a relatively lower amount of iodine is detected. We believe that in a region where the level of iodine is low, but fluoride is significantly elevated, the level of toxicity in thyroid swelling could increase."[289]

Wang (2004) "In comparison with control rats, the learning and memory ability of the offspring rats was depressed by high fluoride, low iodine, or the combination of high fluoride and low iodine. Brain protein was decreased by low iodine and even more by the combined interaction of high fluoride and low iodine. The activity of cholinesterase (ChE) in the brain was affected to some extent by high fluoride and low iodine but was especially affected by high fluoride and low iodine together."[290]

Hong (2001) "The IQ results of this study show no significant difference between the average IQs of those children from the high fluoride only areas and the high fluoride/high iodine areas, however the result from the high fluoride/low iodine group show statistically significant differences as compared to that of the low fluoride/low iodine group."[291]

The interactive effects of fluoride and low iodine on neurological health is consistent with other research showing that fluoride intensifies the anti-thyroid effects of iodine deficiency, and vice versa.

Guan (1988) "This study reveals that the degree of impairment of thyroid morphology and function is related with the amount of fluorine taken by rats. Goiter occurs in rats

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[289] Xu Y, et al. (1994). The effect of fluorine on the level of intelligence in children. *Endemic Disease Bulletin* 9(2):83-84.
[290] Wang J, et al. (2004). Effects of high fluoride and low iodine on biochemical indexes of the brain and learning-memory of offspring rats. Fluoride 37(4): 201-208.
[291] Hong F, et al. (2001). Research on the effects of fluoride on child intellectual development under different environments. Chinese Primary Health Care 15(3):56-57 (republished in Fluoride 2008; 41(2):156–60).

with iodine deficiency. Damage to the thyroid is observed in rats on iodine deficient diet and highly fluorinated water [30 ppm]. These changes are much more severe than in rats on a normal level iodine diet and highly fluorinated water. This seems to suggest that competitive antagonistic action exists between fluorine and iodine in the thyroid gland."[292]

An animal study by Zhao et al (1998) found that fluoride and low iodine have "mutually interacting effects" on the thyroid gland, as evident by changes in thyroid weight, time-specific alterations in thyroid hormone levels, increased bone fluoride content, and increased severity of dental fluorosis. As with other studies, Zhao found that fluoride has interactive effects with iodine excess as well. [See study]

More recently, a team of Russian researchers studied a population with iodine deficiency that was exposed to varying levels of fluoride air pollution. The team found that indices of thyroid disease, including stunted growth and thyroid swelling, were more severe, and prophylactic measures less effective, in the population with heavier exposure to fluoride pollution. According to the authors:
"Natural iodine deficiency and ambient air pollution with fluorine compounds were examined for their combined influence on the prevalence and severity of iodine-deficiency disorders. The excess intake of fluorine was shown to increase the incidence of thyroid diseases and to lower anthropometric indices in children. The preventive measures performed to eliminate iodine-deficiency disorders under intensive ambient air pollution with fluorine compounds were found to be insufficiently effective."[293]

Fluoride, Low Iodine, and Dental Fluorosis

[292] Guan ZZ, et al. (1988). Synergistic action of iodine-deficiency and fluorine-intoxication on rat thyroid. Chinese Medical Journal 101(9):679-84.
[293] Gas'kov AIu, et al. (2005). [The specific features of the development of iodine deficiencies in children living under environmental pollution with fluorine compounds]. [Article in Russian] Gig Sanit. 2005 Nov-Dec;(6):53-5.

As noted above, the animal study by Zhao (1998) found that iodine deficiency worsened the severity of dental fluorosis in the fluoride-treated rats. Xu (1994) found far higher rates of dental fluorosis in a population with low iodine exposure, than a similar population with adequate iodine exposure. Although both communities had 0.8 ppm fluoride in the water, the rate of dental fluorosis was 89% in the low-iodine area, which was more than double the fluorosis rate (40%) in the area with adequate iodine. (Similar to dental fluorosis in the USA).

More recently, a research team in Mexico reported a high rate of fluorosis in an area known for iodine deficiency. (Pontigo-Loyola 2008). Since the rate of fluorosis was higher than would be expected under normal circumstances, the authors suggested that iodine deficiency could be one of the factors contributing to the high rate. According to the authors,

"The hypothesized relationship between iodine deficiency and increased prevalence of fluorosis appears to be relevant to Hidalgo."[294]

Iodine Deficiency in the United States

Over the past few decades, the rate of iodine deficiency has increased in the United States. According to the National Research Council (NRC), "Iodine intake in the United States (where iodine is added to table salt) is decreasing, and an estimated 12% of the population has low concentrations of urinary iodine." (NRC 2006). In light of this trend, the NRC has called upon researchers to begin studying the endocrine and neurological effects that fluoride exposures may be having on the health of people with low iodine intake. As the NRC stated in 2006:

"The effects of fluoride on various aspects of endocrine function should be examined further, particularly with respect to a possible role in the development of several diseases or mental states in the United States. Major areas for investigation include the

[294]Pontigo-Loyola AP, et al. (2008). Dental fluorosis in 12- and 15-year-olds at high altitudes in above-optimal fluoridated communities in Mexico. Journal of Public Health Dentistry 68(3):163-6.

following: thyroid disease (especially in light of decreasing iodine intake by the U.S. population)."

GOITER HISTORY

Goitre (goiter) is an enlargement of the thyroid gland that in some cases can produce visible swelling in the neck. The suggested main deficiency cause of goitre is iodine. Goitre can also be caused by other things, including hypothyroidism and substances that cause goitre (goitrogens).

Since as far back as the 19th century, fluoride has been identified as a possible goitrogen. In the research to date, studies that have examined human populations with adequate intake of iodine have reported mixed results about fluoride's ability to produce goitre. (NRC 2006; Burgi 1984; McLaren 1969). Where, however, the examined populations had either excessive iodine intakes, or deficient iodine intakes, the research has been more consistent in finding a goitrogenic effect from fluoride. (Gas'kov 2005; Hong 2001; Wang 2001; Xu 1994; Yang 1994; Lin 1986). Since most of this latter research was initially published in either Russian or Chinese and was only recently translated into English by the Fluoride Action Network, the NRC's review of fluoride's goitrogenic potential (e.g, NRC 2006) was not able to take this evidence into account. As such, the evidence linking fluoride to goitre is stronger than previously determined, at least for populations with excessive, or deficient, exposure to iodine.

Origins of the Fluoride/Goitre Connection:

Fluoride was first suspected to be a goitrogen in 1854, when Maumeme reported producing goitre in a dog after 4 months of daily fluoride exposure (9 to 55 mg/day). Based on this and subsequent research in the early 20th century, doctors in Europe and South America began using fluoride as a medical treatment for hyperthyroidism (over-active thyroids). (McLaren 1969). As a goitrogen, doctors believed fluoride could suppress the thyroid's function and thereby alleviate symptoms in people with overly active thyroids. Subsequent clinical research found merit in this idea, as a daily fluoride

treatment of just 2 to 5 mg/day was found capable of reducing thyroid function in a group of hyperthyroid patients. (Galletti & Joyet 1958). Ultimately, however, more effective treatments were discovered and the use of fluoride was phased out by the 1960s. (Merck Index 1968).

Fluoride & Goitre in Humans:

Note: the NRC (2006) review did not include the last decade of research and more studies have been translated.

NRC (2006):

“Three studies illustrated the range of results that have been reported: (1) Gedalia and Brand (1963) found an association between endemic goiter in Israeli girls and iodine concentrations in water but found no association with fluoride concentrations (<0.1-0.9 mg/L). (2) Siddiqui (1960) found goiters only in persons aged 14-17 years; the goiters, which became less visible or invisible after puberty, were associated with mean fluorine content of the water (5.4-10.7 mg/L) and were inversely associated with mean iodine content of the water. (3) Desai et al. (1993) found a positive correlation ($P < 0.001$) between prevalence of goiter (9.5-37.5%) and enamel fluorosis (6.0-59.0%), but no correlation between prevalence of goiter and water iodine concentration ($P > 0.05$).”

The NRC did not have access to a series of Chinese studies that FAN[295] has subsequently translated that provide data on the relationship between fluoride and goitre in communities with either iodine excess, or iodine deficiency. In these studies, fluoride’s capacity to increase the goitre rate has been consistently demonstrated, suggesting that the relationship between fluoride and goitre is stronger and more easily detected in populations (and individuals) with sub-optimal iodine intakes.

[295] FAN, Fluoride Action Network. www.fluoridealert.org

Meng (2013)“ Fluoride, a goitrogenic substance in drinking water, is another contributing factor to high GP. The fluoride concentration of drinking water was as high as 1.00 mg/kg in Chongqing municipality, which led Chongqing to have the highest GP (18.37%, 18 of 98) amongst all study areas.”[296]

Gas’kov (2005)“ Analysis of the simultaneous action of factors of the environment (iodine deficits and fluorosis) has shown that the basic cause of enlargement of the thyroid in children is an excessive intake of fluorine. Increasing the amount of iodine absorbed under conditions of excessive intake of fluorine cannot be an effective prophylactic measure directed at the elimination of iodine deficiency states.”[297]

Hong F (2001) “In endemic areas with high fluoride and high iodine, there was greater prevalence of both fluorosis and goiter than in the areas with only one of these two factors. . . . The high fluoride/low iodine group had an increased rate of goiter as compared to low fluoride/low iodine group, possibly stemming from the toxic effects of fluoride interacting with and aggravating the damage caused by a low iodine environment.”[298]

Wang X (2001) “In high iodine and high fluorine areas, the goiter and dental fluorosis rates of children aged from 8 to 12 were clearly higher than the control point, indicating that high iodine and high fluorosis have worse effects on children’s thyroid and teeth.”[299]

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[296] Meng F, et al. (2013). Assessment of iodine status in children, adults, pregnant women and lactating women in iodine-replete areas of China. PLoS One 8(11):e81294.
[297] Gas’kov A, et al. (2005). The specific features of the development of iodine deficiencies in children living under environmental pollution with fluorine compounds. *Gig Sanit.* Nov-Dec;(6):53-5.
[298] Hong F, et al. (2001). Research on the effects of fluoride on child intellectual development under different environments. Chinese Primary Health Care 15(3):56-57 (republished in Fluoride 2008; 41(2):156–60).
[299] Wang X, et al. (2001). Effects of high iodine and high fluorine on children’s intelligence and thyroid function. Chinese Journal of Endemiology 20(4):288-90.

Yang (1994) “For children 15 or younger, the rate of thyroid swelling was 29.8% (96/322), and the rate of dental fluorosis reached 72.98% (235/322). In the control group, the rates were 16.13% (15/93) and 18.28 (17/93), respectively, with P<0.01 in all cases, indicating that the harm caused by a high fluoride-high iodine environment is particularly serious in the case of children.”[300]

Lin F (1986) “In the lower alluvial plains, endemic goiter occurred concomitantly with endemic fluorosis and the contents of iodine in both water and urine were higher, but did not reach the level found in countries where goiter could be attributed to excess intake of iodine.The fact that in the circumstances of the lower uptake of I in thyroid for 24 hours and normal values of T3, T4, TSH, endemic goiter still was slightly prevalent indicated that fluoride also was a factor responsible for goiter.”[301]

Jooste (1999) “OBJECTIVE: The study was undertaken to investigate whether endemic goitre still exists in the Northern Cape Province of South Africa more than 55 years after it was reported and, if so, whether iodine deficiency, or fluoride in the drinking water, is linked to the goitres. DESIGN: Cross-sectional study of children in three pairs of towns. SUBJECTS: The 6-, 12- and 15-year-old children (n = 671) who had been lifetime residents in two Northern Cape towns with low levels, two towns with near optimal levels and two towns with high levels of fluoride in the drinking water were recruited through the schools as study participants. RESULTS: Endemic goitre was found in all the towns except one, ranging from 5% to 29%. Iodine deficiency did not prevail in the study area because the median urinary iodine concentration, exceeding 1.58 micromol/l in all but one of the towns, indicated a more than adequate iodine consumption. The drinking water and, to a lesser extent, iodised

[300] Yang Y, et al. (1994). The effects of high levels of fluoride and iodine on intellectual ability and the metabolism of fluoride and iodine. Chinese Journal of Epidemiology 15(4):296-98 (republished in Fluoride 2008; 41:336-339).
[301] Lin F, et al. (1986). A preliminary approach to the relationship of both endemic goiter and fluorosis in the valley of Manasi River, Xin-Jiang to environmental geochemistry. Chinese Journal of Endemiology 5(1):53-55.

salt were important sources of iodine. No relationship was found between fluoride in the water and the mild goitre prevalence (5% to 18%) in the four towns with either a low or near optimal fluoride content in the water. The causal factor(s) responsible for the goitres in these four towns were not clear from our data. However, the prevalence of goitre was higher (28% and 29%) in the two towns with high levels of fluoride in the water. CONCLUSION: These results indicate that either a high fluoride level in the water or another associated goitrogen, other than iodine deficiency, may have been responsible for these goitres."[302]

Desai (1993) "We examined 22,276 individuals for presence of goitre and dental fluorosis and estimated the fluoride and iodine content of their drinking water. Overall goitre and dental fluorosis prevalences were 14.0% and 12.2%, respectively, and were significantly and positively correlated. No significant relationship was observed between water iodine level and goitre. In the study area only 0.3% of cases were visible goitre (Grade-II and above) and all goitre cases were euthyroid. This suggests that fluoride-induced goitres are brought about by anatomical or structural changes rather than functional changes."[303]

Obel (1982)" Areas which have endemic goitre in Kenya are highlands in the central parts of the country where there are no lakes from which iodide-rich foodstuffs, such as fish, could be found. Iodized salt has been mandatorily available in Kenya for many years. Indeed, most of the cases of goitre from these areas do not show iodide deficiency on biochemical evaluation. Many of these patients manifest clinical and laboratory findings of simple goitre (normal plasma levels of thyroxine, triiodothyronin, thyroid stimulating hormone, and normal iodine uptake values). It therefore would appear unlikely that absolute iodide deficiency per se would account for endemic goitre in Kenya. . . . It is interesting that the same areas which suffer

[302] Jooste PL, et al. (1999). Endemic goitre in the absence of iodine deficiency in schoolchildren of the Northern Cape Province of South Africa. European Journal of Clinical Nutrition 53(1):8-12.
[303] Desai VK, et al. (1993). Epidemiological study of goitre in endemic fluorosis district of Gujarat. Fluoride. 26(3):187-90.

from endemic goitre in Kenya also have the highest prevalence of fluorosis in the country. Indeed, many cases of fluorosis in Kenya have concurrent fluorosis."[304]

Day (1972). "The prevalence of goitre in 17 Himalayan villages has been estimated. Water-samples from each village were taken, and levels of iodine, fluoride, and hardness determined. In 13 villages wide variations in goitre prevalence were not attributable to differences in iodine intake, which remained constant within a narrow range. Instead, variations in goitre prevalence were found to correlate closely with the fluoride content (p=0-74; P<0-01) and with the hardness (p=0.77; P<0-01) of the water in each village. The effects of fluoride and water hardness seem to be independent."[305]

Siddiqui (1969) "With regard to the slight and temporary enlargement of the thyroid encountered in the age group 14-17 (type b), detailed scrutiny of the data . . . reveals that with a fall in mean fluorine content of the water from 10.7 mg/l in Kamaguda to 5.4 mg/l in Yellareddyguda, there was a corresponding progressive fall in the incidence of pubertal goiters from 40% in Kamaguda to 9% in Yellareddyguda, However, associated with the fall in fluorine content there was also a rise in mean iodine of the water. The figures can be interpreted to indicate that, so far as type b goiters are concerned, (1) fluorine may be actually goitrogenic, and (2) high concentrations of iodine may have a goiter-preventing effect. Investigations in other areas, where the variations in fluorine content are not associated with variations in iodine content of the type encountered here, may throw light on this particular problem."[306]

Steyn DG, et al. 1955. In 1936 while on an investigation into poisoning of man and animal by subterranean waters in the North-Western Cape Province, one of us

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[304] Obel AO. (1982). Goitre and fluorosis in Kenya. East African Medical Journal 59:363-365.
[305] Day TK, Powell-Jackson PR. (1972). Fluoride, water hardness, and endemic goitre. Lancet 1:1135-1138.
[306] Siddiqui AH. (1969). Incidence of simple goiter in areas of endemic fluorosis in Nalgonda district, Andhra Pradesh, India. Fluoride 2(2): 200-05.

[D.G.S. (126-129)] encountered several cases of goitre in European women living on farms. Enquiries made, revealed that a fair percentage of people, especially women, settling in this part of the country developed enlargement of the thyroid gland within 10 to 15 years after having entered the area. This was a puzzling phenomenon as the North Western Cape Province is known to be rich in iodine. It was realized that endemic goitre in this area could not possibly be the result of primary iodine deficiency in the soil, food and water. It was thought that the cause must be sought in the drinking water. The area is semi-arid and all drinking water, except that of towns and farms situated on the Orange River, is drawn from wells and boreholes. It was also known that the subterranean waters in the North-Western Cape Province generally contain harmful quantities of fluorine. It was considered that there was a possibility that fluorine has an antithyroid (goitrogenic) action. After having consulted the literature and conducting some experiments upon rats, it was realized that fluorine is a goitrogenic agent and that endemic goitre in the North-Western Cape Province is due not to an inherent primary iodine deficiency but chiefly to the general presence of harmful quantities of fluorine in the drinking-water. It is possible that the large quantities of calcium generally present in the subterranean waters in that area, enhances the goitrogenic effect of fluorine. Generally speaking the diet of the people is very satisfactory as it included a good percentage of meat with vegetables, fruit and bread. A large percentage of the vegetables and fruit is imported."[307]

Wilson (1941) "The distribution of endemic goitre in the Punjab and in England is related to the geological distribution of fluorine and to the distribution of human dental fluorosis (mottled enamel). Inquiry showed the presence of dental fluorosis among school-children in two areas of Somerset where two previous observers had recorded a high incidence of goitre, and the absence of dental fluorosis in an adjoining area selected as control where endemic goitre was absent."[308]

[307] Steyn DG, et al. 1955. Endemic goitre in the Union of South Africa and some neighbouring territories. Union of South Africa. Department of Nutrition.
[308] Wilson DC. (1941). Fluorine in the aetiology of endemic goitre. The Lancet 15(6129): 212-213.

Liu H (2013) “Excessive iodide and fluoride coexist in the groundwater in many regions, causing a potential risk to the human thyroid. To investigate the mechanism of iodide- and fluoride-induced thyroid cytotoxicity, human thyroid follicular epithelial cells (Nthy-ori 3-1) were treated with different concentrations of potassium iodide (KI), with or without sodium fluoride (NaF). . . . Collectively, excessive iodide and/or fluoride is cytotoxic to the human thyroid. Although these data do not manifest iodide could induce the IRE1 pathway, the cytotoxicity followed by exposure to fluoride alone or in combination with iodide may be related to IRE1 pathway-induced apoptosis. Furthermore, exposure to the combination of excessive iodide and fluoride may cause interactive effects on thyroid cytotoxicity.”[309]

Liu (2012) “Endemic fluorosis is a serious problem in public health. Previous studies have indicated that patients with thyroid goiters usually live in fluoride-affected areas. However, the mechanism of goitrogenesis caused independently by fluoride is still unclear. The principle objective of this study was to investigate the possible roles of nitric oxide (NO) and vascular endothelial growth factor (VEGF) in the genesis of fluoride-induced nodular goiters. . . . The results showed that the average relative weight of the thyroid glands of rats in the fluoride-treated groups was significantly higher than that in control rats ($p<0.05$). The proliferation and dilatation of capillary blood vessels, enlarged follicles with excessive colloid, and obvious nodules were found in the thyroid glands of fluoride-treated rats. Compared to the control group, the expression of VEGF mRNA in the thyroid gland and the serum NO levels in the fluoride-treated groups were significantly increased ($p<0.05$). Furthermore, the deposition of VEGF in epithelial and follicular cells of the thyroid gland was significantly higher in fluoride-treated groups than in the control group. These results suggested that abnormal expression of VEGF induced by fluoride can lead to the proliferation of vascular endothelial cells in the thyroid gland. Accordingly, VEGF oversecreted locally by vascular endothelial cells might contribute to the proliferation of epithelial and follicular cells, resulting in the formation of hyperplastic

[309]Liu H et al, The role of the IRE1 pathway in excessive iodide- and/or fluoride-induced apoptosis in Nthy-ori 3-1 cells in vitro. Toxicol Lett. 2014 Jan 30;224(3):341-8. doi: 10.1016/j.toxlet.2013.11.001. Epub 2013 Nov 11.

nodules and enlargement of the thyroid gland. Furthermore, we proposed that there might be a positive feedback mechanism between NO and VEGF expression in fluoride-induced goiter formation. It was concluded that angiogenic and vasodilative factors such as VEGF and NO must be involved in fluoride-induced thyroid goitrogenesis."[310]

Zeng Q (2012) "To explore the toxic effect of fluoride on the human thyroid cells (Nthy-ori 3-1) and its mechanism. . . . To Nthy-ori 3-1 cells, fluoride under experimental concentrations decreases cell viability, improve the LDH leakage rate, and ROS level. It blocks the cells in S phase and induce cell apoptosis."[311]

Liu (2012) "Endemic fluorosis is a serious problem in public health. Previous studies have indicated that patients with thyroid goiters usually live in fluoride-affected areas. . . It was concluded that angiogenic and vasodilative factors such as VEGF and NO must be involved in fluoride-induced thyroid goitrogenesis."[312]

Bashar (2011) "High-fluoride (100 and 200 ppm) water was administered to rats orally to study the fluoride-induced changes on the thyroid hormone status, the histopathology of discrete brain regions, the acetylcholine esterase activity, and the learning and memory abilities in multigeneration rats. Significant decrease in the serum-free thyroxine (FT4) and free triiodothyronine (FT3) levels and decrease in acetylcholine esterase activity in fluoride-treated group were observed. Presence of eosinophilic Purkinje cells, degenerating neurons, decreased granular cells, and vacuolations were noted in discrete brain regions of the fluoride-treated group. In the T-maze experiments, the fluoride-treated group showed poor acquisition and

[310] Liu G[1], Zhang W, Jiang P, Li X, Liu C, Chai C. Role of nitric oxide and vascular endothelial growth factor in fluoride-induced goitrogenesis in rats. Environ Toxicol Pharmacol. 2012 Sep;34(2):209-17. doi: 10.1016/j.etap.2012.04.003. Epub 2012 Apr 10.

[311] Zeng Q et al. [Studies of fluoride on the thyroid cell apoptosis and mechanism]. [Article in Chinese] Journal; Zhonghua Yu Fang Yi Xue Za Zhi. 2012 Mar;46(3):233-6.

[312] Liu G, Zhang W, Jiang P, Li X, Liu C, Chai C. Role of nitric oxide and vascular endothelial growth factor in fluoride-induced goitrogenesis in rats. Environ Toxicol Pharmacol. 2012 Sep;34(2):209-17. doi: 10.1016/j.etap.2012.04.003. Epub 2012 Apr 10.

retention and higher latency when compared with the control. The alterations were more profound in the third generation when compared with the first- and second-generation fluoride-treated group. Changes in the thyroid hormone levels in the present study might have imbalanced the oxidant/antioxidant system, which further led to a reduction in learning memory ability. Hence, presence of generational or cumulative effects of fluoride on the development of the offspring when it is ingested continuously through multiple generations is evident from the present study."[313]

Cai (2009) "Objective: To observe the effects of fluoride on thyroid morphology, thyroid peroxidase and serum thyroid hormones. Methods: One-month ablactating SD rats were randomly divided into groups: the control group low-fluoride group, middle-fluoride group, high-fluoride group; fed with water containing different fluoride concentration by adding NaF respectively. Rats were sacrificed after being fed for six months. The morphology of thyroid was observed through light microscope. The TPO activity was measured with upgrade guaiacol method. Radio-immunoassay was used to detect serum thyroid hormones. Results: The major changes included increased follicles with colloid accumulation in high fluoride groups. With the dose of fluoride increasing, TPO activity significantly decreased as compared with the control group (P0.05). FT4 levels of the high-fluoride were significantly lower compared with the control group (P0.05). Conclusions: Chronic fluoride excess leads to definite histological changes in rat thyroid, inhibiting TPO activity so that level of thyroid hormone is decreased,which shows that fluoride can cause goiter, and cause abnormal changes of thyroid metabolism function."[314]

Zang (2008) "To investigate the mechanism of goiter caused by fluoride, goiter model of SD rats was produced by administering sodium fluoride in drinking water.

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[313] Basha PM[1], Rai P, Begum S. Fluoride toxicity and status of serum thyroid hormones, brain histopathology, and learning memory in rats: a multigenerational assessment. Biol Trace Elem Res. 2011 Dec;144(1-3):1083-94. doi: 10.1007/s12011-011-9137-3. Epub 2011 Jul 14.

[314] Cai Q, Li Hong. (2009). Effects of Fluoride on the Thyroid Morphology and Thyroid Peroxidase and Serum Thyroid Hormones. Journal of Liaoning Medical University.

Histological section of thyroid gland was made, and inducible nitric oxide synthase (iNOS) and vessel endothelial growth factor (VEGF) were determined by RT-PCR. Results showed that the capillary vessels in thyroid glands of the rats treated with fluoride proliferated and an obvious nodular goiter occurred in the fluoride-treated rats. Compared with the control, the contents of iNOS and VEGF in the thyroid glands of the rats with fluorosis was increased significantly (P0.05).It was concluded from the results that the mechanism of goiter caused by fluoride was that fluoride induced the over-expressions of iNOS and VEGF mRNAs in thyroid gland, which caused hyperplasia of capillary vessels."[315]

Shen (2004) "OBJECTIVE: Investigating the influence of combined iodine and fluoride on phospholipid and fatty acid composition in brain cells of rats. METHODS: Five groups of rats were provided with deionized drinking water containing 0 and 150 mg/L NaF, and containing both 150 mg/L NaF and 0.003, 0.03 or 3 mg/L KI respectively for 5 months. Then phospholipid and fatty acid composition were determined using liquid chromatography. RESULTS: The phospholipid composition had no obvious change. The high concentration fluoride (150 mg/L) and high concentration Iodine (3 mg/L) with high concentration fluoride could cause significant changes of the fatty acid composition in brain cells of rats, the proportion of unsaturated fatty acid (C18:2) was significantly decreased and the saturated fatty acid (C12:0) increased obviously. The antagonistic action of 0.03 mg/L KI drinking water on this kind of influence induced by 150 mg/L NaF was the most evident, whereas that of 3 mg/L KI was action of synergetic toxicity. CONCLUSION: Fluorosis had obvious influence on phospholipid and fatty acid composition in brain cells of rats, and its mechanism might be associated with action of lipid peroxidation, and 0.03 mg/L KI is the optimal concentration for the antagonistic action with this influence from fluorosis."[316]

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[315] Zhang W, et al. (2008). Expressions of iNOS and VEGF mRNAs in thyroid gland of rat with goiter induced by fluoride. Chinese Veterinary Science.

[316] Shen X, et al. (2004). [Influence of combined iodine and fluoride on phospholipid and fatty acid composition in brain cells of rats]. Wei Sheng Yan Jiu 33(2):158-61. [Article in Chinese]

Zhao (1998) “fluorine also affected the thyroid changes induced by ID [iodine deficiency] or IE [iodine excess]. After 100 days of treatment, fluorine showed some stimulatory effect on the thyroid in ID conditions and inhibitory effect in IE conditions. After 150 days, however, the effects of fluorine on the thyroid reversed as compared with that of 100 days. On the other hand, difference of iodide intake could also increase the toxic effects of FE on the incisors and bones.”[317]

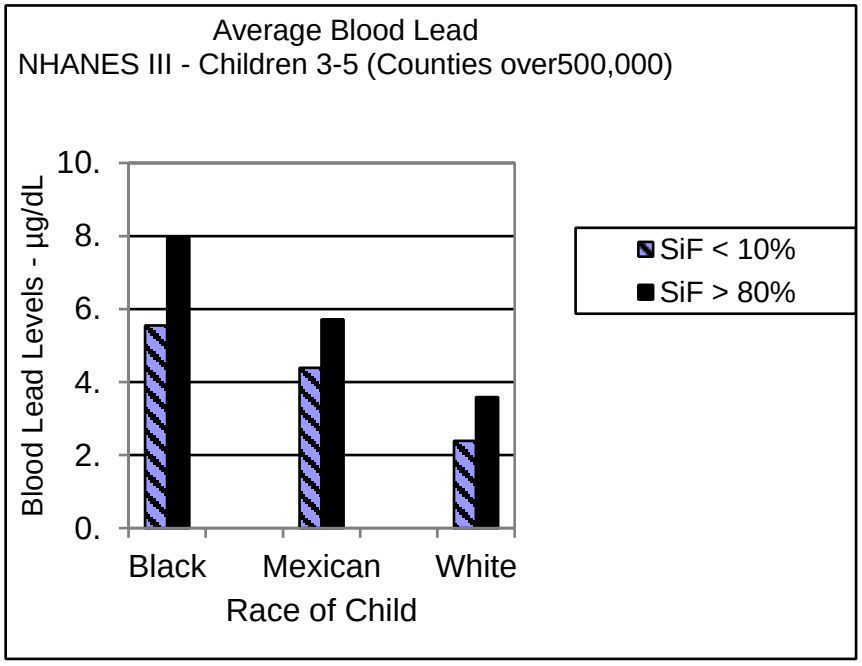
Burg (1984)[318] Burgi and colleagues published a critique of then-existing research linking fluoride to thyroid dysfunction, including goitre and included studies which failed to find a relationship between fluoride and goiters.

[317] Zhao W, et al. (1998). Long-term effects of various iodine and fluorine doses on the thyroid and fluorosis in mice. Endocrine Regulation 32(2):63-70.
Environ Toxicol Pharmacol. 2014 Jul;38(1):332-40. doi: 10.1016/j.etap.2014.06.008. Epub 2014 Jun 27.

[318] Burgi H, et al. (1984): Fluorine and the Thyroid Gland: A Review of the Literature. *Klin Wochenschr*. 1984 Jun 15;62(12):564-9.

Blood **Lead** levels in Fluoridated areas 2X higher for Whites and 6X higher for Blacks[319]

Prevalence of children with elevated blood lead (PbB>10mug/dL) is about double that in non-fluoridated communities. When FSA was added "lead concentrations spiked to over 900 ppb. Effects of fluoridation and disinfection agent combinations on lead leaching from leaded-brass parts.[320]



Fluoridation is in a regulatory vacuum, no authority appears willing to buck the fluoridation lobby and protect the public.

This addendum is by no means complete or definitive. I have simply run out of energy, time and money to be complete.

The Board should dig deeper into all streams of evidence for themselves. Having the evidence handed to you condensed on a silver platter does not provide a full comprehension as digging out the information yourself.

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[319] Confirmation of and explanations for elevated blood lead and other disorders in children exposed to water disinfection and fluoridation chemicals. Coplan MJ, Patch SC, Masters RD, Bachman MS. Neurotoxicology. 2007 Sep;28(5):1032-42. Epub 2007 Mar 1.
See also: Masters RD, Coplan M. 1999 International Journal of Environmental Science 56: 435-449.
And: Masters RD, Coplan MJ, Hone BT, Dykes JF. 2000 Neurotoxicology 21(6): 1091-1100.

[320] Maas RP, Patch SC, Christian AM, Coplan MJ. Neurotoxicology. 2007 Sep;28(5):1023-31. Epub 2007 Jun 30
See also: Blood lead concentrations in children and method of water fluoridation in the United States, 1988-1994. Macek MD, Matte TD, Sinks T, Malvitz DM. Environ Health Perspect. 2006 Jan;114(1):130-4.

In addition, more streams of evidence must be included, such as harm to the mitochondria – powerhouse of each cell. Good Manufacturing Practices (GMP) for drugs, harm to kidneys having to excrete the highly reactive toxin, GI tract at each level, pineal gland which has the highest concentration of fluoride of an organ in the body, along with various methods to measure harm, the synergistic effects of other chemicals with fluoride, age, race and gender variations along with uncertainty factors, margin of error, intraspecific factors and product assay should be reviewed and carefully considered.

However, we have given the Board adequate evidence to simply remove your endorsement of fluoridation.

Thank you for your consideration of this nomination.

Sincerely,

Bill Osmunson DDS, MPH
Audrey Adams
Washington Action for Safe Water

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
GENERAL COUNSEL

February 14, 2013

Gerald Steel, PE
7303 Young Road NW
Olympia, WA 98502

Dear Mr. Steel:

This is in response to your letter of December 28, 2012 to EPA Administrator Lisa Jackson in which you asked several questions about the status of an MOU between EPA and the Federal Drug Administration (FDA) published in 1979. I am replying on behalf of her.

Your first question is whether, from the viewpoint of EPA, the purpose of a 1979 Memorandum of Understanding (MOU) between EPA and the Federal Drug Administration (FDA) was "to take away from FDA, and give to EPA, responsibility for regulating public drinking water additives intended for preventative health care purposes and unrelated to contamination of public drinking water?" Your second question is whether, if that was the purpose of the 1979 MOU, the MOU was terminated through a subsequent Federal Register notice.

The answer to your first question is no, so there is no need to address your second question. The purpose of the MOU was not to shift any responsibilities between the Agencies. Rather, it was to help facilitate effective coordination of our respective legal authorities. Under the Safe Drinking Water Act (SDWA), EPA is the lead federal agency with responsibility to regulate the safety of public water supplies. EPA does not have responsibility for substances added to water solely for preventative health care purposes, such as fluoride, other than to limit the addition of such substances to protect public health or to prevent such substances from interfering with the effectiveness of any required treatment techniques. SDWA Section 1412(b)(11); see also A Legislative History of the Safe Drinking Water Act, Committee Print, 97th Cong, 2d Session (February 1982) at 547. The Department of Health and Human Services (HHS), acting through the FDA, remains responsible for regulating the addition of drugs to water supplies for health care purposes.

The 1979 MOU was intended to address contamination of drinking water supplies as a result of direct or indirect additives to drinking water, not to address the addition of substances solely for preventative health purposes. 44 Fed. Reg. 42775 (July 20, 1979) ("EPA and FDA agree: (1) that *contamination* of drinking water from the use and application of direct and indirect additives and other substances poses a potential public health problem...")(emphasis added). It was intended to avoid potentially duplicative regulation of "food", which FDA had, in the past, considered to include drinking water. 44 Fed. Reg. 42775 (July 20, 1979). The MOU did not address drugs or other substances added to water for health care purposes.

I hope that this has adequately answered your inquiry. Please do not hesitate to contact Carrie Wehling of my staff (202-564-5492) if you have further questions about this.

Sincerely,

Steven M. Neugeboren
Associate General Counsel
Water Law Office

WASHINGTON ACTION FOR SAFE WATER

Washington Action for Safe Water
Bill Osmunson DDS, MPH President
1418 – 112th Ave NE #200
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May 22, 2011

Washington State Board of Health
Craig McLaughlin, Executive Director
Craig.McLaughlin@DOH.WA.GOV

PETITION FOR RULE MAKING (#11) WAC 246-290-460
FLUORIDE SERUM CONCENTRATION
CENTERS FOR DISEASE CONTROL

RCW 43.20.50(2) MANDATES THE BOARD TO ASSURE SAFETY OF WATER.

Ten rule change petitions for water safety have been made over the last year to the Board of Health, this is the eleventh. Evidence presented in the first ten should be reviewed and included in this petition. The twelfth petition will cover the proposed EPA RfD. The Board of Health appears to have jurisdiction over the concentration of fluoride in public water[1] for ensuring safety of the public health. Although neither the EPA nor CDC have jurisdiction over the safety or efficacy of the addition of fluoride to public water with the intent to prevent disease and more than one national standard for fluoride exposure and safety are provided by the EPA and CDC, the Washington State Board of Health appears to defer to the EPA Office of Water and CDC Oral Health Division for one of their opinions.

The Board should be inclusive of all national standards for fluoride and for the protection of the public ensure all safety standards are met. For many people there is no reasonable alternative source of water than public water. A lack of water safety with too much fluoride can cause many thousands of dollars in health damage and life long disability. We are all concerned about dental caries, the pain, loss of function, and costs for treatment. However, public health intervention should be measured in the community at large and when evidence of lack of efficacy is found, rather than adding more money and time to an intervention which is not working, effort should be made to focus on those methods which are working to reduce the disease. Many are ingesting too much fluoride from several sources, the evidence of efficacy is incomplete, and the known risks can be serious. It is time for the Board to support other methods of dental caries reduction such as diet and hygiene rather than chemotherapy.

Fluoride is regulated by Federal and Washington State laws as a poison and exempt from poison laws when regulated as a prescription drug.[2] Authorization by the Legislature to fluoridate water did not exempt fluoride from other general laws such as

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[1] The AGO 1992 No.17,

> "2. The Legislature has authorized the Board of Health to establish, and the Department of Health to enforce, a comprehensive regulatory scheme for public water systems."

The Board of Health stated:

> "The Board does not appear to have authority to adopt rules related to a water district deciding whether to fluoridate. The Board's authority is to regulate allowable concentration levels and method of approval of water additives." (June 9, 2010 Board Meeting Handout, page 2, emphasis added).

[2] Appendix 1 Washington Board of Pharmacy. See also FDA FOI response previous Petitions.

FDA CDER approval, label, good manufacturing practices, safety determined by the Board, CDC ATSDR (Agency for Toxic Substances & Disease Registry) or the EPA.

For example, the Legislature has recommended vaccinations. The Legislature's recommendation of vaccinations does not exempt vaccinations from FDA CDER approval. In other words, vaccinations must also be FDA CDER approved, manufactured, labeled and dispensed according to legend drug laws. Likewise, the Legislature may permit, recommend or require fluoridation, but that does not exempt fluoridation from other general laws regulating drugs and/or highly toxic substances.

The CDC Oral Health Division should not be significantly relied on for national standards of fluoride safety and efficacy.

*The CDC Oral Health Division has no jurisdiction over public water safety.
*The CDC Oral Health Division has no jurisdiction over appropriate label of caution, dosage, drug interactions, or good drug manufacturing practices.
*The CDC Oral Health Division simply markets their bias without evaluating medical safety.
*The CDC Oral Health Division has no liability for harm caused by their errors.
*The CDC Oral Health Division is made up primarily of dental experts lacking in legal, toxicological or pharmaceutical training, and without medical diagnostic training. A medical diagnosis of brain, thyroid or skeletal damage is outside the purview of the dental profession and not appropriately considered by the CDC Oral Health Division.
*The CDC Oral Health Division cherry picks their evidence and reviewers from like minded believers to support tradition and existing bias.
*The CDC Oral Health Division has failed to determine an optimal tooth fluoride concentration for the prevention of dental caries because studies do not find a significant difference in tooth fluoride concentration between healthy and carious teeth.[3]
*The CDC Oral Health Division has failed to determine an optimal serum fluoride concentration for the prevention of dental caries.
*The CDC Oral Health Division has failed to determine an optimal urine fluoride concentration for the prevention of dental caries.
*The CDC Oral Health Division bases their optimal fluoride concentration on estimates, assumptions, tradition, low quality studies lacking in controls, any margin of safety from unknowns, and is without one single randomized controlled trial for efficacy or safety.
*The CDC Oral Health Division does not include infants or high risk subpopulations.
*The CDC Oral Health Division is a mirror, loyal soldiers, of the American Dental Association which has represented in court that it owes no duty to protect the health of the public.
*The CDC Oral Health Division has refused to permit a live presentation by scientists opposed to fluoridation. The CDC should not be scared of reviewing scientific evidence.

The Board relies on the CDC Oral Health Division for guidance to ensure the Board's rules are consistent with national standards.[4] However, the Board has limited

[3] The outer few microns of enamel do show a difference in fluoride concentration depending on topical use of fluoride. See CDC ATSDR www.atsdr.cdc.gov/ToxProfiles/tp11-c6.pdf Accessed 5/17/11
[4] October 14, 2010 WBOH petition denial for rule change: concentration of fluoride in water.

their consideration to the CDC's Oral Health Division and failed to consider other CDC national standards such as for serum fluoride concentration (SFC) or total fluoride exposure maximums.

Measuring individual serum fluoride concentrations (SFC) is superior for determining individual fluoride exposure than assuming/estimating individual fluoride exposure based on water fluoride concentration, in part because fluoride exposure is from many sources and each person's ability to excrete excess fluoride is different. Measuring serum fluoride concentrations will be more precise and protective of subpopulations especially infants. Measurements are better than estimates.

The CDC advises, "Normal serum fluoride levels are <20 mcg/L (0.02 ppm) but varies substantially on the basis of dietary intake and environmental levels."[5] The Legislature mandates the Board of Health to ensure safe water. If fluoride concentrations in water raise serum fluoride concentrations above CDC "normal" concentrations <0.02 ppm, the Board will have evidence that the fluoridated water concentration is not safe and a reduction of fluoride concentration is appropriate. This petition provides the water districts with the opportunity to adjust fluoride water concentration to ensure serum fluoride concentrations do not exceed 0.02 ppm a national standard as recommended by the CDC. This petition is a reasonable step in protecting the public.

> "The NRC (2006) concluded that lifetime exposure to fluoride at an estimated average daily intake of 0.08 mg/kg/day (average adult fluoride intake with water at 4 mg/L and equal to EPA's new RfD) is likely to result in higher bone fracture rates, and the available information suggests an increased likelihood of bone fracture for daily fluoride intakes of 0.05 mg/kg/day (average adult fluoride intake at 2 mg/L and equal to IOM's recommended intake). The Agency for Toxic Substances and Disease Registry (ATSDR) has identified a chronic-duration Minimal Risk Level(MRL) for oral exposure to fluoride of 0.05 mg/kg/day, based on an increased risk of bone fracture (ATSDR 2003)."[6]

For example, a 3 kg infant should not ingest more than 0.15 mg F/day (3 kg X 0.05 mg F/day = 0.15 mg F/day). If the infant drinks one liter of milk made with fluoridated water, the fluoride concentration of the water should not exceed 0.15 ppm. To protect infants, public water should not exceed 0.15 ppm. For a 6 kg infant 0.3 ppm water fluoridation would be maximum. Although this petition does not set the fluoride concentration in public water somewhere around 0.15 ppm to 0.3 ppm to protect infants, the data collected by this petition will in time either bring fluoridation concentrations into compliance with the CDC's national standard of less than 0.05 mg F/kg/day or have scientific measured evidence to support a higher fluoride exposure level.

The CDC Oral Health Division/HHS has indirectly acknowledged their previous recommendation of fluoridation level at 1 ppm has not been protective. Many are ingesting too much fluoride. The evidence of excess exposure did not just hit the CDC Oral Health Division in the last few months. Most of the evidence used by the CDC Oral Health Division has been around for several decades and the primary research is over

[5] http://www.bt.cdc.gov/agent/hydrofluoricacid/pdf/hydrofluoriccasedef.pdf Accessed 5/17/11

[6] Appendix 2 Thiessen p 5. The entire Thiessen document is material to this petition and should be carefully reviewed and included in consideration.

half a century old. In other words, for decades the CDC Oral Health Division has failed to protect the public from excess fluoride ingestion, in part because of a flawed assumption of efficacy. For fluoridation safety, the Board of Health cannot rely exclusively on one side of CDC guidance and must include the CDC ASTDR guidance. The evidence of excess fluoride exposure is not unknown to the Board of Health.

US HEALTH AND HUMAN SERVICES PROPOSE LOWER FLUORIDE CONCENTRATION IN WATER.

January 7, 2011, the HHS cautiously evaded the thorny problem of FDA jurisdiction over drugs and announced in a press release, "HHS' proposed recommendation of 0.7 milligrams of fluoride per liter of water replaces the current recommended range of 0.7 to 1.2 milligrams."

WAC 246-290-460 (DOH) currently specifies a range of 0.8 to 1.3 ppm (mg/L) fluoride in water which is less protective than 0.7 ppm suggested by the CDC Oral Health Division and significantly higher concentrations than the CDC national health standard of 0.05 mg F/kg/day. Washington public water systems are unable to reasonably comply with both concentrations and CDC national standard and the WAC needs to be reconsidered.

The Board has a choice to follow the proposed CDC Oral Health Division's 0.7 ppm fluoride in water, follow the CDC <0.02 ppm fluoride in serum, follow the CDC 0.05 mg F/kg/day, or be inclusive of all three CDC national standards. By including all CDC national standards, the Board will be sensitive to stakeholders on both sides of this controversial issue and of most importance will protect the public.

In an attempt to combine all three CDC national standards, our proposed rule change for WAC 246-290-460 is in italics and red (the last part of the WAC omitted here is without change):

"Fluoridation of drinking water.

(1) Purveyors shall obtain written department approval of fluoridation treatment facilities before placing them in service.

(2) Where fluoridation is practiced, purveyors shall maintain fluoride concentrations ~~in the range 0.8 through 1.3 mg/L~~ *below 0.7 mg/L* throughout the distribution system *and human serum fluoride levels below 0.02 ppm whichever is lower.*

(3) Where fluoridation is practiced, purveyors shall take the following actions to ensure that concentrations remain at optimal levels and that fluoridation facilities and monitoring equipment are operating properly:

(a) Daily *water* monitoring.

(i) Take daily monitoring samples for each point of fluoride addition and analyze the fluoride concentration. Samples must be taken downstream from each fluoride injection point at the first sample tap where adequate mixing has occurred.

(ii) Record the results of daily analyses in a monthly report format acceptable to the department. A report must be made for each point of fluoride addition.

(iii) Submit monthly monitoring reports to the department within the first ten days of the month following the month in which the samples were collected.

(b) *Monthly serum monitoring for public water systems serving over 50,000 customers.*
Fluoride serum concentration will be measured on a minimum of 5 randomly selected serum samples of residents' drinking primarily water from the water system, either tested in house or through a state or private medical laboratory. The serum fluoride results shall be submitted to the department within the first ten days of the month following the month in which the sample results were reported.
If twenty percent of the serum samples taken result in serum fluoride concentrations at or greater than 0.02 mg/L, the purveyor shall reduce the fluoride concentration in water by 0.1 mg/L each month until serum fluoride concentrations are less than 0.01 mg/L for 80% of samples or no additional fluoride is being added to the public water system.
An appeal for exemptions from monthly serum fluoride testing converting to quarterly testing can be made to the department after serum fluoride concentrations are stabilized.
(c) Monthly *water* split sampling.
(i) Take a monthly split sample at the same location where routine daily monitoring samples are taken. A monthly split sample must be taken for each point of fluoride addition.
(ii) Analyze a portion of the sample and record the results on the lab sample submittal form and on the monthly report form.
(iii) Forward the remainder of the sample, along with the completed sample form to the state public health laboratory, or other state-certified laboratory, for fluoride analysis.
(iv) If a split sample is found by the certified lab to be:
(A) Not within the range of 0.8 to 1.3 mg/l below 0.7 mg/L, the purveyor's fluoridation process shall be considered out of compliance. . . ."

Our proposal to randomly measure fluoride serum concentrations is a reasonable scientific assessment. Gathering actual measured data will eventually achieve CDC compliance with serum fluoride concentrations. WASW expects the Board's compliance with CDC recommendations (<0.02 mg serum F/kg/day) will also reasonably bring the Board into compliance with the EPA RfD (see petition 12), although the water fluoride concentration may still not be safe for a few high risk individuals.

The economic impact of measured fluoride serum concentrations should be less than $200 per test (probably contracted for less than $100) or $1,000 per month or $12,000 per year paid for by the large public water systems. Current fluoridation chemical costs are about $1.00/person/year for large systems. A 30% reduction (1 ppm to 0.7 ppm) in fluoridation chemical costs for 50,000 people would be about $15,000/year. Our estimate of about $12,000 is offset by the $15,000 reduction in fluoridation concentration and will probably be offset further by additional reductions in fluoride concentration. When the testing shows serum is consistently within national standards, the testing could be reduced to a quarterly report. The Board and Department would receive information from several water districts for a glimpse of statewide fluoride exposure.

Finding serum for testing would require a lab to ask existing patients whether they predominantly drank fluoridated water and permission to test their blood. The patient would not incur any additional charge and not need to have an additional needle

used to collect the sample because the patient is already getting blood drawn. As an alternative, the water district could ask for volunteers from the water users. Some people would like to know their serum fluoride levels and would volunteer or be referred by their doctors and dentists.

The ultimate fluoride concentration goal for the Board of Health should be to determine the optimal fluoride concentration within teeth for effectiveness of tooth decay reduction and fluoride within serum for safety. Unfortunately, dental caries are not lower in teeth with higher concentrations of fluoride so an optimal concentration of fluoride in teeth has not been determined or estimated. However, to achieve that unknown ultimate theoretical goal of increased tooth fluoride concentration, the Board in keeping with the Legislature's mandate for safety should start by focusing on serum fluoride concentrations. After all, systemic fluoride goes through the serum to reach the tooth.[8]

FLUORIDE SERUM LEVELS

The NRC (2006) report for the EPA presented fluoride serum levels over 300 times in their report and serum fluoride concentrations must be considered by the Board;

Fluoride concentrations in bodily fluids (e.g., urine, plasma, serum, saliva) are probably most suitable for evaluating recent or current fluoride exposures or fluoride balance (intake minus excretion), although some sources indicate that samples obtained from fasting persons may be useful for estimating chronic fluoride intake or bone fluoride concentrations (e.g., Ericsson et al. 1973; Waterhouse et al. 1980).

The Legislature mandated the Board of Health to ensure "safety" of water, not "efficacy" of contaminants/additives/drugs.

It should be no surprise researchers are focusing on the more accurate serum fluoride concentration than the imprecise estimate of fluoride exposure and the relative source contribution of fluoridated water. FDA approval would appropriately require studies proving safety and efficacy and target organ concentrations along with drug interactions. Because fluoridation is neither safe nor effective, it is not a surprise that the FDA advised the Board that fluoridation would probably not be approved. The FDA advises:

> "Drug companies seeking to sell a drug in the United States must first test it. The company then sends CDER the evidence from these tests to prove the drug is safe and effective for its intended use. A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the company's data and proposed labeling. If this independent and unbiased review establishes that a drug's health benefits outweigh its known risks, the drug is approved for sale. The center doesn't actually test drugs itself, although it does

[8] The outer few microns of enamel are affected by topical fluoride applications such as toothpaste at 1,000 ppm and evidence is growing that the increased fluoride in the outer few microns of enamel may reduce dental caries.

conduct limited research in the areas of drug quality, safety, and effectiveness standards.

> Before a drug can be tested in people, the drug company or sponsor performs laboratory and animal tests to discover how the drug works and whether it's likely to be safe and work well in humans. Next, a series of tests in people is begun to determine whether the drug is safe when used to treat a disease and whether it provides a real health benefit."
> www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm Accessed 10/26/10

The wise use of drugs by doctors, patients, and the Board of Health includes an approved drug label and the Board must provide a label for fluoridation. The intent of some of our petitions is to be part of an appropriate label, moving the Board into greater compliance with what the FDA CDER would require to protect the public.
For decades, the regulation and control of new drugs to protect the public in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S.

> "Title 21: Food and Drugs§ 314.50 Content and format of an application. (d)(1)(i) Drug substance . A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls."

If the Washington Board of Health disagrees with the Washington Board of Pharmacy, FDA CDER, RCW, and FFDCA that fluoride is a drug, then fluoride is a poison and must be regulated as a poison under poison laws. The Board has chosen a path outside those laws and is assuming legal jurisdiction. Therefore, to protect the public, the Board must substantially comply with the intent of Federal and state poison and drug laws.

This petition is in agreement with the protective intent of Federal and state regulatory agencies and laws even though it will not bring the Board and Public Water Systems into compliance with Federal and state laws. This petition is expected to eventually bring the fluoride concentration in water into compliance with the EPA's RfD.

Sincerely yours,

Bill Osmunson DDS, MPH President
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Bellevue, WA 98004 bill@teachingsmiles.com

Comments on
EPA's Fluoride Risk Assessment and
Relative Source Contribution
Documents

Prepared for the
U.S. Environmental Protection Agency

April 19, 2011

Submitted at the request of the
International Academy of Oral Medicine and Toxicology (IAOMT)
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These comments on recent reports from the U.S. Environmental Protection Agency's Office of Water (EPA 2010a,b) are submitted to the Environmental Protection Agency (EPA) in response to their January 7, 2011, announcements (EPA 2011a,b) and January 2011 fact sheet (EPA 2011c). These comments are not to be considered a comprehensive review of the EPA reports or of fluoride exposure or toxicity.

The author of these comments is a professional in the field of risk analysis, including exposure assessment, toxicity evaluation, and risk assessment. She has recently served on two subcommittees of the National Research Council's Committee on Toxicology that dealt with fluoride exposure and toxicity, including the NRC's Committee on Fluoride in Drinking Water. She has also authored an Environmental Protection Agency report on fluoride toxicity.

These comments are submitted at the request of the International Academy of Oral Medicine and Toxicology (IAOMT), and their preparation was supported in part by the IAOMT. Opinions and conclusions expressed herein are those of the author.

Summary

The comments below pertain primarily to EPA's recent reports on exposure and relative source contribution (EPA 2010a) and non-cancer risk assessment (EPA 2010b) for fluoride. The goal of these two reports is the derivation of a new Reference Dose (RfD) for fluoride. The RfD is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (EPA 2009). However, EPA's new RfD for fluoride is not protective for a number of adverse health effects. EPA inappropriately includes an estimate of benefit in its assessment of the risk of adverse effects; the assumed benefit is not supported by available data. The exposure estimate does not include some important subsets of the population. The uncertainty factor of 1 selected by EPA does not reflect limitations of the data used (EPA 2011d) and will not lead to protection of the U.S. population from deleterious effects. Thus, EPA's new Reference Dose for fluoride, 0.08 mg/kg/day, fails to meet the standards of a Reference Dose as defined by EPA.

(1) Evaluation of safety

EPA should be reminded of its definitions for the Maximum Contaminant Level Goal (MCLG) and the Reference Dose (RfD):

> **MCLG:** Maximum Contaminant Level Goal. A non-enforceable health goal which is set at a level at which no known or anticipated adverse effect on the health of persons occurs and which allows an adequate margin of safety. (EPA 2009)
>
> **RfD:** Reference Dose. An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. (EPA 2009)

> **Reference Dose (RfD):** An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments. (EPA 2011d)

EPA's recent risk assessment for fluoride (EPA 2010b) is based on protection of the population from severe dental fluorosis. Dental fluorosis, including severe dental fluorosis, is a well-known effect from overexposure to fluoride during the early years of life. The National Research Council (NRC 2006) concluded that severe dental fluorosis is an adverse health effect, not merely a cosmetic effect as EPA had previously determined for "objectionable" dental fluorosis (EPA 1989). It is certainly appropriate to protect the population from severe dental fluorosis. However, there are a number of other "known or anticipated adverse" or "deleterious" effects that should also be protected against. EPA's new RfD for fluoride of 0.08 mg/kg/day (EPA 2010b) is not adequately protective.

The NRC (2006) concluded that EPA's MCLG for fluoride (4 mg/L) was not protective, based on severe dental fluorosis, stage II skeletal fluorosis, and increased risk of bone fracture. These are adverse effects for which there is sufficient information in the literature to consider them to be "known." However, the NRC also described a number of other adverse health effects which can reasonably be "anticipated" from fluoride exposure, but for which the information base is much less complete. While the NRC did not need these additional adverse health effects or deleterious effects to conclude that the MCLG was inadequately protective, EPA should consider them in setting a new RfD or a new MCLG, in keeping with its definitions for the MCLG and the RfD.

A revised RfD and MCLG should continue to protect against "objectionable" dental fluorosis (defined as moderate or severe; EPA 1989), not just severe dental fluorosis. Raising the RfD to 0.08 mg/kg/day (EPA 2010b) from the previous value of 0.06 mg/kg/day (EPA 1989) will not be protective for "objectionable" dental fluorosis. Severe dental fluorosis is obviously an adverse health effect, given the increased risk for dental caries (NRC 2006; EPA 2010b); Health Canada (2009) considers moderate dental fluorosis to be an adverse effect, and the NRC (2006) reports the general consensus in the literature that both severe and moderate dental fluorosis should be prevented. The psychological and social ramifications of "objectionable" dental fluorosis are not well characterized, but it should be intuitive that "objectionable" dental fluorosis can be deleterious (causing harm or damage; New Oxford American Dictionary) to an individual's social or emotional well-being, whether or not EPA considers it to be an "adverse health effect." In addition, the cost to repair objectionable dental fluorosis can be considerable.

EPA has not considered the association of dental fluorosis with increased risk of other adverse health effects, including thyroid disease, lowered IQ, and bone fracture (Alarcón-Herrera et al. 2001; Zhao et al. 1996; Li et al. 1995; Lin et al. 1991; Desai et al. 1993; Yang et al. 1994; Jooste et al. 1999; Susheela et al. 2005). For instance, data reported by Alarcón-Herrera et al. (2001) show a clear relationship between severity of dental fluorosis and increased likelihood of having had a bone fracture (Fig. 1). To the best of my knowledge, no studies in the U.S. or Canada have looked for associations between dental fluorosis and risk of other adverse effects. However, the

failure to look for adverse health effects does not demonstrate the absence of adverse health effects. The available information indicates that an association between dental fluorosis and other adverse health effects can reasonably be "anticipated," supporting a need for EPA to protect against most or all dental fluorosis, not just severe dental fluorosis.

In addition to the "known" adverse health effects of dental fluorosis, skeletal fluorosis, and increased risk of bone fracture, "anticipated" adverse health effects from fluoride exposure or community water fluoridation include (but are not limited to) carcinogenicity, genotoxicity, endocrine effects, increased blood lead levels, and hypersensitivity (reduced tolerance) to fluoride. These effects (described in more detail below) are not as well studied as the dental and skeletal effects, which should indicate that a greater margin of safety is necessary to ensure protection of the population—"in the face of uncertain evidence it is important to act in a manner that protects public health" (Tickner and Coffin 2006). The incompleteness of the information base is not a justification to ignore these effects in setting a new RfD or MCLG. In addition, it should be noted that some of these effects may occur at lower fluoride exposures than those typically associated with dental or skeletal effects, such that protection against the dental or skeletal effects does not necessarily ensure protection against other anticipated adverse health effects.

A few comments regarding the interpretation of the available fluoride studies may be helpful. As Cheng et al. (2007) have described, a "negative" study may simply mean that the study was not sufficiently sensitive to demonstrate a moderate (as opposed to large) effect. This is often due to use of too small a sample size. In addition, study populations are often grouped by community, water source, or fluoride concentration in the water, rather than by individual intake. Due to the wide variation in drinking water intake, this approach results in study groups with overlapping intakes and makes it difficult to detect dose-response relationships that do in fact exist.

The few studies that have looked at age-dependent exposure to fluoride have found increased risks of adverse effects (e.g., Bassin et al. 2006 for osteosarcoma; Danielson et al. 1992 for hip fracture risk); studies that have not looked at age-dependent exposure cannot be assumed to provide evidence of no effect. Similarly, studies that have used a measure of current exposure where a cumulative measure would be more appropriate, or vice versa, cannot be assumed to demonstrate lack of an effect.

Studies of fluoride toxicity in laboratory animals are sometimes dismissed as irrelevant because the exposures or fluoride concentrations used were higher than those expected for humans drinking fluoridated tap water. It is important to know that animals require much higher exposures (5-20 times higher, or more; see NRC 2006; 2009) than humans to achieve the same effects or similar fluoride concentrations in bone or serum. In other words, humans are considerably more sensitive to fluoride than are most animal species that have been studied.

EPA based its new RfD only on severe dental fluorosis in part because adequate dose-response information was available for severe dental fluorosis but not for skeletal effects. While it would be nice to have good dose-response information for various adverse health effects, the lack of it should not be a justification to eliminate a "known" or "anticipated" effect from being considered in setting an RfD or MCLG. As described in the IRIS Glossary's definition (EPA 2011d), an RfD can be set from a NOAEL (no observed adverse effect level) or LOAEL (lowest observed adverse effect level) in the absence of dose-response information.

In fact, a number of adverse health effects can be expected to occur in at least some individuals when estimated average intakes of fluoride are around 0.05 mg/kg/day or higher (NRC 2006; 2009); in other words, a LOAEL for some adverse health effects is lower than EPA's new RfD, which is supposed to protect the population, including sensitive subgroups, from deleterious effects during a lifetime (EPA 2009; 2011d). For persons with iodine deficiency (one example of a sensitive subgroup), average intakes as low as 0.01-0.03 mg/kg/day could produce effects (NRC 2006). The remainder of this section briefly summarizes some (not all) of the adverse health effects, known and anticipated, that should be considered in EPA's reevaluation of the drinking water standards for fluoride. Most of these effects have been reviewed in detail by the NRC (2006), although the NRC did not specifically evaluate health risks over the whole range of fluoride intakes or attempt to identify a "safe" level of fluoride exposure. Consideration of carcinogenicity and genotoxicity do not belong in a non-cancer risk assessment, of course, but they should be part of EPA's reevaluation of the drinking water standards and so are included here.

Skeletal fluorosis

Bone fluoride concentrations in the ranges reported for stage II and III skeletal fluorosis will be reached by long-term fluoride exposures of 0.05 mg/kg/day or higher (estimated from NRC 2006). Chachra et al. (2010) have recently reported bone fluoride content for residents of Toronto (fluoridated for 32-36 years at the time of the study) and Montreal (not fluoridated) who were undergoing total hip replacement surgery; most of the individuals had a diagnosis of osteoarthritis. Two of the 53 individuals in Toronto had bone fluoride concentrations in the range reported for skeletal fluorosis (NRC 2006), although both individuals would have been well into adulthood when exposure to fluoridated water began. The study did not include exposure histories; nevertheless, it does indicate that bone fluoride concentrations in fluoridated North American cities can be in the range reported for skeletal fluorosis.

Bone fluoride concentrations, radiologic changes, and symptoms are not clearly correlated (Franke et al. 1975). Most of the literature addresses high fluoride exposures over a few years; there has been essentially no investigation of effects of low exposures over many years and no effort to identify fluorosis of any stage in the U.S. "Arthritis" (defined as painful inflammation and stiffness of the joints) is the leading cause of disability in the U.S., currently affects at least 46 million adults in the U.S. (including 50% of the population > 65 years old), and is expected to affect 67 million adults in the U.S. by 2030 (CDC 2006). The possibility that a sizeable fraction of "bone and joint pain" or "arthritis" in U.S. adults is attributable to fluoride exposure has not been addressed, although it is plausible, given what is known about fluoride intakes.

Increased risk of bone fractures

The NRC (2006) concluded that lifetime exposure to fluoride at an estimated average daily intake of 0.08 mg/kg/day (average adult fluoride intake with water at 4 mg/L and equal to EPA's new RfD) is likely to result in higher bone fracture rates, and the available information suggests an increased likelihood of bone fracture for daily fluoride intakes of 0.05 mg/kg/day (average adult fluoride intake at 2 mg/L and equal to IOM's recommended intake). The Agency for Toxic Substances and Disease Registry (ATSDR) has identified a chronic-duration Minimal Risk Level

(MRL) for oral exposure to fluoride of 0.05 mg/kg/day, based on an increased risk of bone fracture (ATSDR 2003). The NRC's findings (NRC 2006) indicate that the ATSDR's MRL is not protective enough, and thus EPA's RfD is even less protective. The available studies consider fluoride intake only in terms of the concentration in the local drinking water, and most use fluoridated water (1 mg/L, corresponding to an average daily intake of 0.03 mg/kg/day for adults) as a control. Thus there is probably considerable overlap in exposures between groups, making effects more difficult to distinguish, and the entire dose response range of interest has not been well studied. The findings in humans are consistent with animal studies that have found increased brittleness of bones with increased fluoride exposure (Clark and Mann 1938; Turner et al. 1997; 2001).

Danielson et al. (1992) reported an increased relative risk for hip fracture in a fluoridated area of 1.27 (95% CI 1.08-1.46) for women and 1.41 (95% CI 1.00-1.81) for men. These authors reported a difference between women exposed to fluoride prior to menopause and those exposed afterwards. For women exposed prior to menopause, the fracture risk was considerably higher than for those not exposed to fluoride. Many studies of fracture risk have not looked at age-specific exposure, or have involved women exposed only after menopause, when fluoride uptake into bone is probably substantially lower. EPA (2010b, p. 85) includes the Danielson et al. study in a table of bone fracture studies but does not include the finding for men and does not discuss the issue of timing of fluoride exposure with respect to menopause.

The Iowa study reported effects on bone mineral concentration and bone mineral density with average childhood fluoride intakes of 0.02-0.05 mg/kg/day (Levy et al. 2009). Linear correlation between dental fluorosis and risk of bone fracture has been reported for children and adults (Alarcón-Herrera et al. 2001; Fig. 1). Bone fracture rates in children in the U.S. may be increasing (e.g., Khosla et al. 2003), but fluoride exposure has not been examined as a possible cause or contributor.

Carcinogenicity

Three U.S. courts have found water fluoridation to be injurious to human health, specifically that it may cause or contribute to the cause of cancer and genetic damage (described in detail by Graham and Morin 1999). The NRC's committee on fluoride toxicology unanimously concluded that "Fluoride appears to have the potential to initiate or promote cancers," even though the overall evidence is "mixed" (NRC 2006). Referring to the animal studies, the committee also said that "the nature of uncertainties in the existing data could also be viewed as supporting a greater precaution regarding the potential risk to humans." The committee discussed the limitations of epidemiologic studies, especially ecologic studies (those in which group, rather than individual, measures of exposure and outcome are used), in detecting small increases in risk—in other words, the studies are not sensitive enough to identify small increases in cancer risk; therefore a "negative" study does not necessarily mean that there is no risk (see also Cheng et al. 2007).

While the NRC did not assign fluoride to a specific category of carcinogenicity (i.e., known, probable, or possible), the committee did not consider either "insufficient information" or "clearly not carcinogenic" to be applicable. The committee report (NRC 2006) includes a discussion of how EPA establishes drinking water standards for known, probable, or possible

carcinogens; such a discussion would not have been relevant had the committee not considered fluoride to be carcinogenic. The question becomes one of how strongly carcinogenic fluoride is, and under what circumstances.

The case-control study by Bassin et al. (2006) is the only published study thus far to have looked at age-dependent exposure to fluoride. This study reported a significantly elevated risk of osteosarcoma in boys as a function of estimated age-specific fluoride intake. Osteosarcoma is a bone cancer that commonly results in amputation of an affected limb and may result in death. At the very least, this study indicates that similar studies of pediatric osteosarcoma that have not looked at age-dependent intake cannot be considered to show "no effect."

While a few other studies (e.g., Gelberg et al. 1995) have looked at individual fluoride exposure (as opposed to group or ecologic measures of exposure), these have looked at total fluoride exposure until time of diagnosis or treatment. Given that there is a "lag time" of a few years between onset of a cancer and its diagnosis, use of cumulative fluoride exposure until time of diagnosis is potentially misleading, as fluoride exposure during the last several years (during the "lag time") cannot have contributed to the initiation of a cancer but could have a significant effect on the estimate of cumulative fluoride exposure.

The 1990 National Toxicology Program (NTP) study on sodium fluoride officially concluded that "there was *equivocal evidence of carcinogenic activity* of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas in dosed animals" (NTP 1990; italics in the original). According to the published report, a "small number of osteosarcomas occurred in mid- and high-dose male rats. These neoplasms occurred with a significant dose response trend, but at a rate within the upper range of incidences previously seen in control male rats in NTP studies" (NTP 1990). It is important to realize that the historic controls from previous studies had not had the special low-fluoride diet used for this study, and therefore more properly constitute a low- to mid-range exposed group rather than a control group. This and other concerns were described in a memo within the Environmental Protection Agency (Marcus 1990) and reported in the press (Hileman 1990). These concerns and the testimony before the U.S. Senate of the union representing EPA scientists (Hirzy 2000) should be taken seriously by the EPA.

In humans, osteosarcomas tend to occur most commonly in young people (pediatric cases) or the very old (adult or geriatric cases), with a higher incidence in males than in females (Bassin et al. 2006). Sergi and Zwerschke (2008) indicate that 60-75% of cases are in patients between 15 and 25 years old. In the NTP 2-year study, fluoride exposure was begun when the animals were 6 weeks old, as is typical for NTP and similar studies (Hattis et al. 2004). Puberty in the rat typically occurs at about 32 days of age in females and 42 days in males (e.g., Gray et al., 2004; Evans 1986). Thus, the age of 6 weeks in the NTP study probably corresponds to pubertal or post-pubertal animals. The cases of osteosarcoma in the rats were reported in the late stages of the test, and probably corresponded to geriatric osteosarcomas in humans. In Bassin's study, the age range for which the fluoride-osteosarcoma association was most apparent was for exposures at ages 4-12 years, with a peak for exposures at age 6-8 years (Bassin et al. 2006). Very likely, the fluoride exposures in most of the animal studies have started after the age corresponding to the apparent most susceptible age in humans, and thus these animal studies may have completely missed the most important exposure period with respect to initiation of the majority of human osteosarcomas. Therefore, this animal study cannot be interpreted as showing no evidence of

causation for pediatric osteosarcoma, although, properly interpreted, it does show evidence for causation of geriatric osteosarcoma.

Genotoxicity

Genotoxicity, or the ability to damage the genetic material (genes and chromosomes) of cells, is considered indicative of potential carcinogenicity. A number of mammalian *in vitro* systems have shown dose-dependent cytogenetic or cell transformational effects from fluoride exposure (reviewed by NRC 2009). Several reports suggest an indirect or promotional mechanism, e.g., inhibition of DNA synthesis or repair enzymes, rather than a direct mutagenic effect (Lasne et al. 1988; Aardema et al. 1989; Aardema and Tsutsui 1995; Meng and Zhang 1997). Human cells seem to be much more susceptible to chromosome damage from fluoride than are rodent cells (Kishi and Ishida 1993).

A recent paper by Zhang et al. (2009) describes a new testing system for potential carcinogens, based on induction of a DNA-damage response gene in a human cell line. Sodium fluoride tests positive in this system, as do a number of other known carcinogens, representing a variety of genotoxic and nongenotoxic carcinogenic mechanisms. Known noncarcinogens—chemicals not associated with carcinogenicity—did not test positive. The system described by Zhang et al. (2009) is considerably more sensitive than the older systems for most chemicals examined; a positive effect was seen at a fluoride concentration of about 0.5 mg/L, or a factor of 10 lower than in other systems.

A fluoride concentration of 0.5 mg/L in urine will routinely be exceeded by many people consuming fluoridated water (NRC 2006); for people with substantial fluoride intake, serum fluoride concentrations may also reach or exceed 0.5 mg/L. Acute fluoride exposures (e.g., accidental poisoning, fluoride overfeeds in drinking water systems) have resulted in fluoride concentrations in urine well in excess of 5 mg/L in a number of cases (e.g., Penman et al. 1997; Björnhagen et al. 2003; Vohra et al. 2008). Urine fluoride concentrations can also exceed 5 mg/L if chronic fluoride intake is above about 5-6 mg/day (0.07-0.09 mg/kg/day for an adult; based on NRC 2006), right at the intake expected with EPA's new RfD of 0.08 mg/kg/day. Thus, at EPA's RfD, kidney and bladder cells are probably exposed to fluoride concentrations in the ranges at which genotoxic effects have been reported *in vitro*, especially when the more sensitive system of Zhang et al. (2009) is considered. Based on the results of Zhang et al. (2009), most tissues of the body are potentially at risk if serum fluoride concentrations reach or exceed 0.5 mg/L. In addition, cells in the vicinity of resorption sites in fluoride-containing bone are potentially exposed to very high fluoride concentrations in extracellular fluid (NRC 2006) and thus are also at risk for genotoxic effects.

Endocrine effects

The NRC (2006) concluded that fluoride is an endocrine disruptor. Endocrine effects include altered thyroid function or increased goiter prevalence (at fluoride intakes of 0.05-0.1 mg/kg/day, or 0.01-0.03 mg/kg/day with iodine deficiency), impaired glucose tolerance (at fluoride intakes above 0.07 mg/kg/day), a decrease in age at menarche in girls in fluoridated towns, and disruptions in calcium metabolism (calcitonin and parathyroid function, at fluoride intakes of

0.06-0.15 mg/kg/day or higher). ATSDR's toxicological profile for fluoride (ATSDR 2003) refers to an animal study of thyroid function that would give a lower MRL (value not given) than the MRL derived for bone fracture risk (0.05 mg/kg/day).

Thyroid dysfunction and Type II diabetes presently pose substantial health concerns in the U.S. (NRC 2006). Of particular concern is an inverse correlation between maternal subclinical hypothyroidism and the IQ of the offspring. In addition, maternal subclinical hypothyroidism has been proposed as a cause of or contributor to development of autism in the child (Román 2007; Sullivan 2009). Calcium deficiency induced or exacerbated by fluoride exposure may contribute to a variety of other health effects (NRC 2006).

Steingraber (2007) has described the decrease in age at puberty of U.S. girls and the associated increased risk of breast cancer and other problems. EPA (2010b, pp. 13, 87; 2010c, pp. 9-10) mentions that hormonal changes over recent decades, evidenced by earlier puberty (decreasing age of menarche) now in comparison with the 1940s, may affect the applicability of the study used to derive the RfD to today's population. EPA fails to consider the possibility that some of these hormonal changes may actually have been induced by fluoride exposure (reviewed by NRC 2006).

With respect specifically to thyroid effects, EPA should compare its approach for fluoride with that for perchlorate. EPA's recent press release on perchlorate (EPA 2011e) indicates that the regulation to be pursued for perchlorate is intended "to protect Americans from any potential health impacts." Perchlorate "may impact the normal function of the thyroid." "Thyroid hormones are critical to the normal development and growth of fetuses, infants and children." Perchlorate "may disrupt the thyroid's ability to produce hormones that are critical to developing fetuses and infants." As reviewed by NRC (2006), fluoride also "may impact the normal function of the thyroid" and "may disrupt the thyroid's ability to produce hormones that are critical to developing fetuses and infants." In addition, EPA (2011e) indicates that 5-17 million people may have perchlorate in their drinking water, due largely to unintentional contamination. In contrast, more than 184 million people, or more than 60% of the U.S. population (CDC 2009), have fluoride in their drinking water due to deliberate addition of the chemical.

Increased blood lead levels

An increased likelihood of elevated blood lead levels is associated with use of silicofluorides (usually H_2SiF_6 or Na_2SiF_6) as the fluoridating agent (NRC 2006; Coplan et al. 2007). Approximately 90% of people on fluoridated water in the U.S. are on systems using silicofluorides (NRC 2006). The chemistry and toxicology of these agents, especially at low pH (e.g., use of fluoridated water in beverages such as tea, soft drinks, or reconstituted fruit juices), have not been adequately studied (NRC 2006). Associations between silicofluoride use and biological effects in humans have been reported, in particular, elevated levels of blood lead in children and inhibition of acetylcholinesterase activity (reviewed by Coplan et al. 2007). A recent study in rats found significantly higher concentrations of lead in both blood and calcified tissues of animals exposed to both silicofluorides and lead (Sawan et al. 2010).

In addition to biological effects of silicofluorides, the interaction of silicofluorides (as the fluoridating agent) and disinfection agents (specifically, chloramines) increases the leaching of lead from plumbing fixtures into drinking water (Maas et al. 2005; 2007). A recent

Congressional investigation discussed the failure of the CDC to publicize information about high lead levels in drinking water and children's blood in Washington, D.C. (Leonnig 2010). The interaction of silicofluorides and chloramines is the probable explanation for the high lead levels (Maas et al. 2005; 2007). EPA considers lead to be a probable human carcinogen and to have no practical threshold with respect to neurotoxicity (EPA 2004b)—in other words, there is considered to be no safe level of lead exposure, and the MCLG for lead is zero (EPA 2009).

Additional adverse health effects

Fluoride intake is likely to affect the male reproductive-hormone environment, beginning at intakes of around 0.05 mg/kg/day (reviewed by NRC 2009). A "safe" intake with respect to male reproductive effects is probably somewhere below 0.03 mg/kg/day.

Grandjean and Landrigan (2006) list fluoride as an "emerging neurotoxic substance" that needs further in-depth studies. The major concern is neurotoxic effects during human development.

The NRC has reviewed the possible association between exposure to fluoridated water (approximately 0.02 mg/kg/day for adults) and increased risk of Down syndrome (trisomy 21) in children of young mothers, discussed a possible mechanism, and recommended further study (NRC 2006). Fetuses with Down syndrome are less likely to survive to birth, due both to higher natural fetal loss and to a high rate of pregnancy termination (Buckley and Buckley 2008; Forrester and Merz 1999; Siffel et al. 2004; Biggio et al. 2004).

Hypersensitivity or reduced tolerance to fluoride has been reported for exposure to fluoridated water (approximately 0.02 mg/kg/day for adults) or use of fluoride tablets (approximately 1 mg/day). Symptoms include skin irritation, gastrointestinal pain and symptoms (nausea, vomiting, diarrhea, constipation), urticaria, pruritus, stomatitis, chronic fatigue, joint pains, polydipsia, headaches, and other complaints (Waldbott 1956; 1958; Feltman and Kosel 1961; Grimbergen 1974; Petraborg 1977; Spittle 2008; reviewed by NRC 2006). Patients were often unaware that their drinking water contained fluoride. Symptoms improved with avoidance of fluoridated water and recurred with consumption of fluoridated water or with experimental challenge with sodium fluoride. Double-blind tests of patients have confirmed hypersensitivity to fluoride (Grimbergen 1974; Waldbott 1956; 1958). Many of the observed symptoms represent true allergic phenomena, while others (e.g., gastrointestinal symptoms) could be due to a lower level of tolerance for fluoride (intoxication at lower exposure; Waldbott 1956; 1958).

(2) Inclusion of benefit

The EPA has included an assumption of benefit in its risk assessment for fluoride, including the preservation of an intake of 0.05 mg/kg/day as desirable (based on IOM 1997) and exclusion of possible adverse health effects (in this case, with only severe dental fluorosis being considered) below an intake of 0.07 mg/kg/day (EPA 2010b). IOM (1997) based its recommended intake on an assumed cariostatic effect of ingested fluoride. A number of sources (reviewed by NRC 2006), including the CDC (2001), now indicate that any beneficial effect of fluoride on teeth is topical (e.g., from toothpaste), not from ingestion. Featherstone (2000) describes mechanisms by which topical fluoride has an anti-caries effect and states that "[f]luoride incorporated during tooth development [i.e., from ingested fluoride] is insufficient to play a significant role in caries

protection." "The fluoride incorporated developmentally—that is, systemically into the normal tooth mineral—is insufficient to have a measureable effect on acid solubility" (Featherstone 2000). "The prevalence of dental caries in a population is not inversely related to the concentration of fluoride in enamel, and a higher concentration of enamel fluoride is not necessarily more efficacious in preventing dental caries" (CDC 2001). Fluoride concentrations in drinking water or saliva are too low to be contributing significantly to a topical anti-caries effect, especially since most drinking water is not "swished" around the teeth before being swallowed. CDC (2001) states that "The concentration of fluoride in ductal saliva, as it is secreted from salivary glands, is low—approximately 0.016 parts per million (ppm) in areas where drinking water is fluoridated and 0.006 ppm in nonfluoridated areas. This concentration of fluoride is not likely to affect cariogenic activity." Thus, as pointed out by one of the reviewers of EPA's recent risk assessment (EPA 2010c), it is not correct to treat fluoride as a "nutrient" with a recommended intake.

The same reviewer (EPA 2010c) also pointed out that a risk assessment for adverse health effects should be separated from any assessment of benefits or recommended intake. The reasonable approach would be to set an RfD and MCLG based solely on the risks of adverse health effects, with an adequate margin of safety (EPA 2009) or an uncertainty factor that adequately reflects limitations of the data used (EPA 2011d). Then if EPA is required to consider presumed benefits, that requirement can be taken into account, together with the health risks, in setting an enforceable level (i.e., the Maximum Contaminant Level). However, before compromising its mission of protecting the public from adverse health effects due to contaminants in drinking water, EPA should critically review the available data (described below), which do not support a benefit from fluoride in drinking water.

EPA no doubt is aware that the U.S. Food and Drug Administration (FDA) considers fluoride in toothpaste to be a non-prescription drug (e.g., FDA undated-a; undated-b) and fluoride “supplements” (usually tablets or lozenges) to be prescription drugs (e.g., Medline Plus 2008). The goal of community water fluoridation is to provide a dental health benefit to individuals and to the population generally (Federal Register 2010), as acknowledged by EPA's recent reference (Federal Register 2010) to a "treated population" and by the present effort to include a recommended intake in the risk assessment for fluoride (EPA 2010b). This in effect puts local governments and water treatment personnel in charge of administering a chemical (i.e., a drug) to the population in an effort to improve individual and population health (Cross and Carton 2003; Cheng et al. 2007). EPA's own exposure assessment (EPA 2010a) demonstrates that fluoride from tap water exceeds that from either non-prescription (toothpaste) or prescription (tablets or lozenges) fluoride sources, yet this exposure occurs without any monitoring for either efficacy or side effects, without the “drug information” or warning labels generally provided for drugs, and without any semblance of informed consent.

The University of York has carried out perhaps the most thorough review to date of human studies on effects of fluoridation. Their work (McDonagh et al. 2000) is often cited as showing the safety and efficacy of water fluoridation, but it actually does neither (Wilson and Sheldon 2006; Cheng et al. 2007). The report mentions a surprising lack of high quality studies demonstrating benefits, and also finds little evidence that water fluoridation reduces socioeconomic disparities:

> Given the level of interest surrounding the issue of public water fluoridation, it is

> surprising to find that little high quality research has been undertaken. (McDonagh et al. 2000)
>
> Water fluoridation aims to reduce social inequalities in dental health, but few relevant studies exist. The quality of research was even lower than that assessing overall effects of fluoridation. (Cheng et al. 2007)
>
> Evidence relating to reducing inequalities in dental health was both scanty and unreliable. (Wilson and Sheldon 2006)

The apparent benefit is modest, about a 15% difference in the proportion of caries-free children (McDonagh et al. 2000). The American Dental Association (2005) states that "water fluoridation continues to be effective in reducing dental decay by 20-40%," which would translate to less than 1 decayed, missing, or filled permanent tooth (DMFT) in older children and adolescents (based on U.S. data from CDC 2005).

Neither McDonagh et al. (2000) nor the ADA (2005) mentions that fluoride exposure appears to delay the eruption of permanent teeth, although this has been known since the 1940s (Short 1944; NRC 2006). A delay in tooth eruption alters the curve of caries rates with respect to age and complicates the analysis of age-specific caries rates (Psoter et al. 2005; Alvarez 1995; Alvarez and Navia 1989). Komárek et al. (2005) have calculated that the delay in tooth eruption due to fluoride intake may explain the apparent reduction in caries rates observed when comparisons are made at a given age, as is usually done—in other words, the apparent dental benefit from fluoride intake shown in some studies is simply an artifact of fluoride-induced delay in tooth eruption. EPA should not consider benefit of fluoride intake without properly accounting for delayed tooth eruption.

Most studies of benefits of fluoride intake or fluoridation have failed to account for a number of important variables, including individual fluoride intakes (as opposed to fluoride concentrations in the local water supplies), sugar intake, socioeconomic variables, and the general decline in caries rates over the last several decades, independent of water fluoridation status. When World Health Organization data on oral health of children in various countries are compared, similar declines in caries over time are seen in all developed countries, regardless of fluoridation status (Cheng et al. 2007; Neurath 2005).

The only peer-reviewed paper to be published from California's major oral health survey in the 1990s reported no association between fluoridation status and risk of early childhood caries (Shiboski et al. 2003). The paper did not address other types of caries.

The single study that has examined caries experience in relation to individual fluoride intakes at various ages during childhood (the Iowa study) has found no association between fluoride intake and caries experience; caries rates (% of children with or without caries) at ages 5 and 9 were similar for all levels of fluoride intake (Warren et al. 2009). The authors state that "the benefits of fluoride are mostly topical" and that their "findings suggest that achieving a caries-free status may have relatively little to do with fluoride *intake*" (emphasis in the original). Most of the children with caries had "relatively few decayed or filled surfaces" (Warren et al. 2009). The authors' main conclusion:

> Given the overlap among caries/fluorosis groups in mean fluoride intake and extreme variability in individual fluoride intakes, firmly recommending an "optimal" fluoride intake is problematic. (Warren et al. 2009)

The national data set collected in the U.S. in 1986-1987 (more than 16,000 children, ages 7-17, with a history of a single continuous residence) shows essentially no difference in caries rates in the permanent teeth of children with different water fluoride levels (Table 1; Fig. 2; data obtained from Heller et al. 1997; similar data can be obtained from Iida and Kumar 2009). Analysis in terms of mean DMFS (decayed, missing, or filled tooth surfaces) for the group (Fig. 3), as opposed to caries prevalence, shows an apparent 18% decrease between the low-fluoride (< 0.3 mg/L) and fluoridated (0.7-1.2 mg/L) groups. In absolute terms, this is a decrease of about one-half (0.55) of one tooth surface per child. One possible explanation is delayed tooth eruption, which was not considered in the study. Note that the mean DMFS for the highest fluoride group is higher than for either of the two intermediate groups, also indicating that DMFS scores are not solely a function of water fluoride concentration. The increased DMFS score with the highest water fluoride concentration suggests that the increased susceptibility of fluorosed teeth to caries eventually surpasses the apparent decrease in caries attributable to fluoride-induced delay in tooth eruption. When the data are examined by the distribution of DMFS scores (Fig. 4), no real difference in caries experience with respect to water fluoride concentration is observed. In contrast, the same data set shows a clear dose response for both fluorosis prevalence and fluorosis severity with fluoride concentration (Heller et al. 1997; Table 1; Fig. 5).

The available data, responsibly interpreted, indicate little or no beneficial effect of water fluoridation on oral health. EPA should not assume or suppose beneficial effects of community water fluoridation in evaluating the health risks from fluoride in drinking water.

(3) Estimation of exposure

EPA's exposure estimate (EPA 2010a) excludes children up to 6 months old. Given that dental fluorosis is associated with exposures during the first 6 months of life (Hong et al. 2006a,b), as well as later periods, these children should also be included in the exposure estimate. EPA's risk assessment document (EPA 2010b, p. 96) indicates that "mineralization of the secondary teeth begins at about 6 ± 2 months," which should be sufficient justification to include the youngest children in the exposure estimate. For other adverse health effects such as thyroid or neurological effects, infancy could be a critical exposure period. In addition, it is important to distinguish between breast-fed and bottle-fed infants, and between bottle-fed infants fed ready-to-feed formula and those fed formula prepared with tap water. These constitute readily identifiable subgroups; considering them in one group could lead to underestimates of exposure for infants fed formula prepared with tap water.

EPA's exposure estimate (EPA 2010a) does not include sensitive population subgroups, although these are to be protected in setting an RfD or MCLG (see definitions above). Groups known to be at risk of high fluoride intake include those with high water intake (e.g., outdoor workers, athletes, and individuals with diabetes insipidus or other medical conditions) or exposure to other sources of fluoride intake (NRC 2006). In addition, people with impaired renal function are at

higher risk of adverse effects per unit intake of fluoride, due to impaired excretion of fluoride and consequent higher fluoride concentrations in the body.

(4) Characterization of uncertainty

EPA (2010b, p. 105) has used an uncertainty factor of 1 in establishing its new oral RfD for fluoride, based on defining a level of intake "that provides anticaries protection without causing severe dental fluorosis." A value of 1 for the uncertainty factor is inappropriate for a number of reasons.

First, as described above, severe dental fluorosis is not the most sensitive or even the most deleterious adverse health effect reported for fluoride exposure, merely one for which a good dose-response curve can be generated and which leads to an RfD high enough to "protect" the alleged benefits of fluoride intake. EPA surmises, but cannot demonstrate, that the RfD will also be protective for skeletal effects and for severe dental fluorosis in primary teeth. As described above, available information for a number of other adverse health effects or deleterious effects indicates that an intake of 0.08 mg/kg/day will not be protective.

Second, it is inappropriate to consider possible benefits in deriving a level of intake that will be protective for adverse effects. For one thing, the benefits, if real, might not involve the same individuals as those at risk for the adverse effects. More importantly, as described above, the benefits at best are small and are probably an artifact of a fluoride-induced delay in tooth eruption. Any benefit from fluoride exposure is from topical exposure, not systemic ingestion.

Third, EPA (2010b, p. 106) claims that its toxicity database for fluoride is complete. Given that the same report describes weaknesses in the database for skeletal effects, how can the database be considered complete? In addition, EPA has not considered a number of other health effects considered plausible by NRC (2006), many of which would occur at lower exposures than those required for severe dental fluorosis. The database on these "anticipated" effects is incomplete, as evidenced by the number of recommendations for further research listed by the NRC (2006). Again, how can EPA consider its database to be complete?

Fourth, the exposure assessment does not include the youngest age group, although this age is probably important for several adverse health effects (including severe dental fluorosis) and can include some of the highest exposures (due to use of fluoridated tap water in preparation of formula).

Fifth, the risk assessment and exposure assessment do not include known population subgroups that could be more sensitive to the effects of fluoride or that could have high fluoride exposures. The data set used to derive the RfD does not include individuals living in hot areas and does include only whites (EPA 2010b). The Centers for Disease Control and Prevention (CDC) has reported that the black population in the U.S. has higher rates of dental fluorosis than whites, including higher rates of moderate and severe dental fluorosis (CDC 2005). EPA (2010b) describes at least two studies reporting higher dental fluorosis rates in blacks than in whites. How can an uncertainty factor of 1 provide adequate protection for the black population? What about other minority populations? Economically disadvantaged populations?

Sixth, the definition for the MCLG (given above) includes allowing for an adequate margin of safety. How can there be an adequate margin of safety when EPA assumes both a recommended

intake of 0.05 mg/kg/day and a lower limit of harm at 0.08 mg/kg/day (0.07 from water, 0.01 from other sources)? Where is the adequate margin of safety? This is especially important since drinking water intake can vary by more than a factor of 10, depending on age, activity level, and the presence of certain health conditions such as diabetes insipidus (NRC 2006; EPA 2004a).

Seventh, EPA is basing its risk assessment on a decades-old study of drinking water containing natural fluoride. Close to two-thirds of the U.S. population is supplied with drinking water artificially fluoridated with silicofluorides. As discussed above, there is still too much unknown about the chemistry of silicofluorides in plumbing systems and about the differences in physiological or toxicological effects in people depending on the type of fluoridation chemical used. Is EPA confident that a risk assessment based on natural fluoride in water is adequately protective for populations whose water is treated with silicofluorides?

EPA needs a serious reevaluation of its uncertainty factor, in order to provide adequate protection against "known and anticipated adverse health effects" to all members of the U.S. population.

(5) Other comments

EPA's fact sheet (EPA 2011c) is misleading when it says "The NRC report does not question the beneficial effects for fluoride at levels practiced for fluoridation programs." The NRC report (NRC 2006) actually says "Assessing the efficacy of fluoride in preventing dental caries is not covered in this report" (p. 14) and "As noted earlier, this report does not evaluate nor make judgments about the benefits, safety, or efficacy of artificial water fluoridation" (p. 16). While several (at least) individual committee members do question the benefits, safety, and efficacy of artificial water fluoridation, the committee as a whole did not address the issue, as it was not part of our charge. In fact, information in the NRC report indicates that some adverse health effects can reasonably be expected at exposure levels anticipated for people drinking artificially fluoridated water. The NRC report also brings up the largely unstudied hazards that are associated with use of silicofluorides for fluoridation of drinking water.

The descriptions of the stages of skeletal fluorosis (EPA 2010b, pp. 64, 70-71) are incorrect. These descriptions should correspond to the description on pp. 170-171 of NRC (2006), which was taken from p. 46 of a Public Health Service report (PHS 1991). EPA appears to have copied the description from the prepublication version of the NRC report (p. 139 of the prepublication version). The description was corrected in the final published version of the NRC report. EPA should be certain that it is referring throughout to the final version of the NRC report.

EPA should also be careful that it is accurately reporting what the NRC report has said. For example, in one place EPA (2010b, p. 72) refers to an individual with skeletal fluorosis as having "excessive" water intake, citing the NRC report. The NRC report, citing the original paper, simply says that water intake may have been "increased." "Increased" water consumption in a hot area simply means higher than expected for moderate climates; it could be totally appropriate for the hot climate and not at all excessive. In the peer review document for the risk assessment, EPA (2010c, p. 8) refers to NRC having identified a water fluoride level of 4 mg/L as being the potential threshold for skeletal effects. In fact, the NRC report said that a water fluoride level of 4 mg/L was not protective for skeletal effects and that 2 mg/L might not be either. The NRC

report did not examine the whole dose response range and did not identify a threshold for skeletal effects.

On pp. 18-19 of the peer review response document for the risk assessment (EPA 2010c), EPA indicates that they have nominated fluoride for future biomonitoring efforts at CDC. EPA should greatly encourage CDC to obtain this information, something which the NRC (2006) also recommended.

Table 1. Caries prevalence and fluorosis prevalence with water fluoride concentration.[a]

Water fluoride concentration	Children with no caries	Mean DMFS score[b]	Children with fluorosis[c]	Mean severity of fluorosis[d]
mg/L	%		%	
< 0.3	53.2	3.08	13.5	0.30
0.3 - < 0.7	57.1	2.71	21.7	0.43
0.7 - 1.2	55.2	2.53	29.9	0.58
> 1.2	52.5	2.80	41.4	0.80

[a] Data for permanent teeth of children ages 5-17 (caries experience and DMFS score) or 7-17 (dental fluorosis), with a history of a single residence, from Tables 2 and 5 of Heller et al. (1997).
[b] Decayed, missing, or filled tooth surfaces (permanent teeth).
[c] Includes very mild, mild, moderate, and severe fluorosis, but not "questionable."
[d] Dean's Community Fluorosis Index.

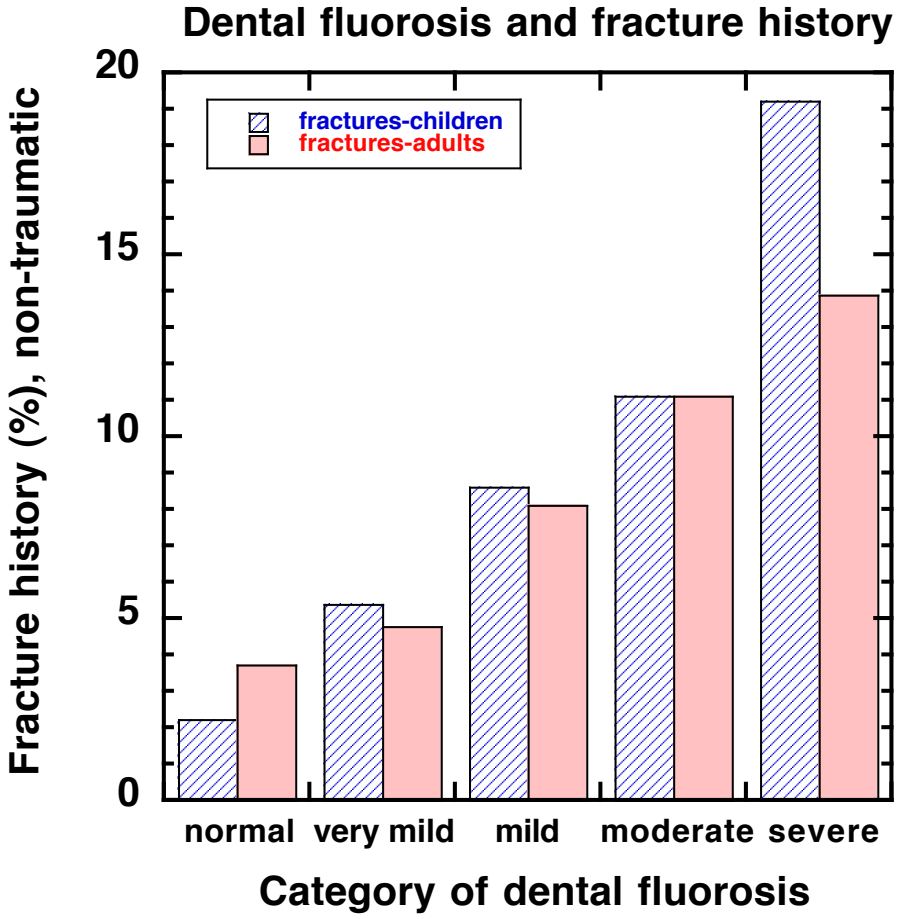

Fig. 1. Fracture history with category of dental fluorosis for children (ages 6-12) and adults (ages 13-60). Numerical values were obtained from information in Tables 5 and 6 of Alarcón-Herrera et al. (2001).

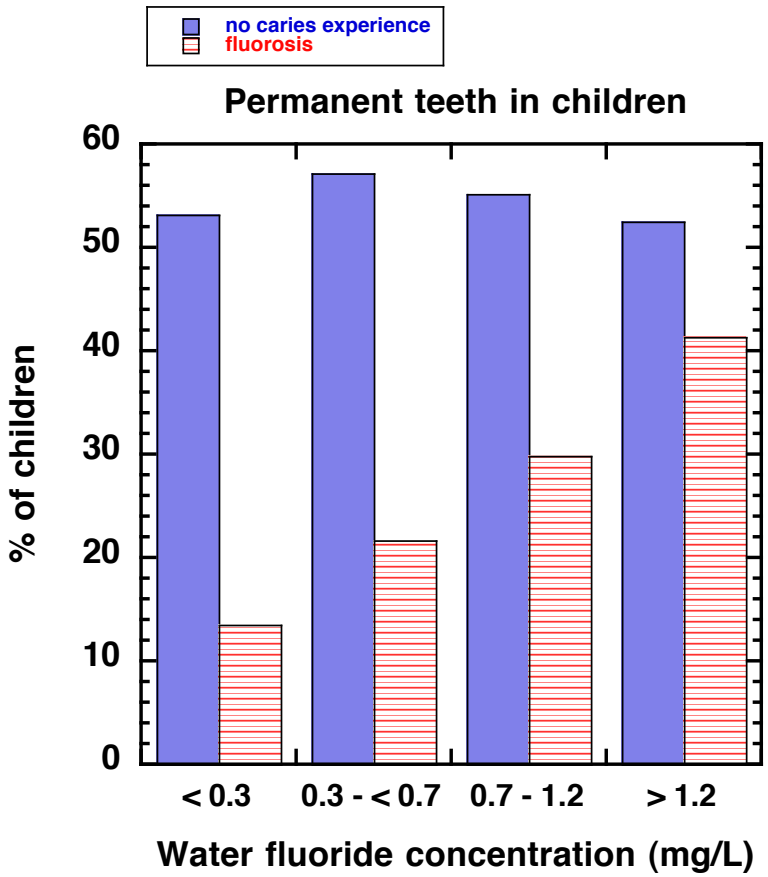

Fig. 2. Percent of children with no caries experience in the permanent teeth (DMFS = 0) and with fluorosis, with respect to water fluoride concentration. Data are shown as % of total children having no caries experience or having fluorosis (very mild, mild, moderate, or severe, but not questionable). Numerical values are provided in Table 1 of these comments and were obtained from Tables 2 and 5 of Heller et al. (1997).

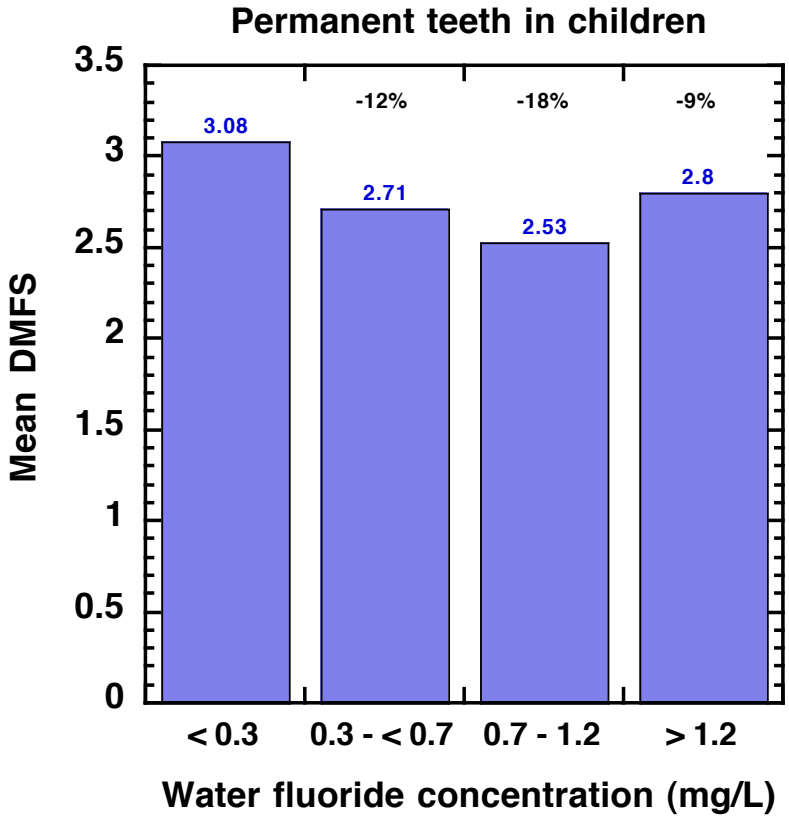

Fig. 3. Mean DMFS score (decayed, missing, or filled tooth surfaces in permanent teeth), with respect to water fluoride concentration. Numerical values are provided in Table 1 of these comments and were obtained from Table 2 of Heller et al. (1997). The percent difference with respect to the lowest fluoride group is also provided.

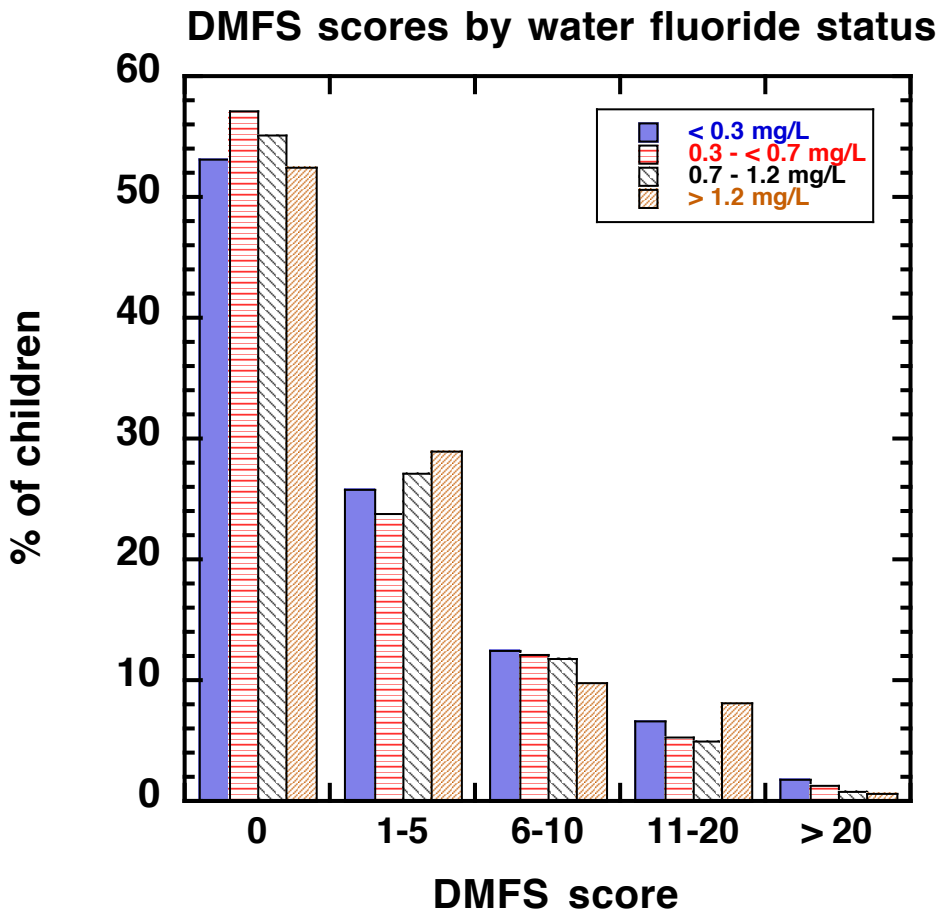

Fig. 4. Percent of children by DMFS score, with respect to water fluoride concentration. Data are shown as % of total children in a given group according to the number of decayed, missing, or filled tooth surfaces in the permanent teeth (DMFS). Data were obtained from Table 2 of Heller et al. (1997).

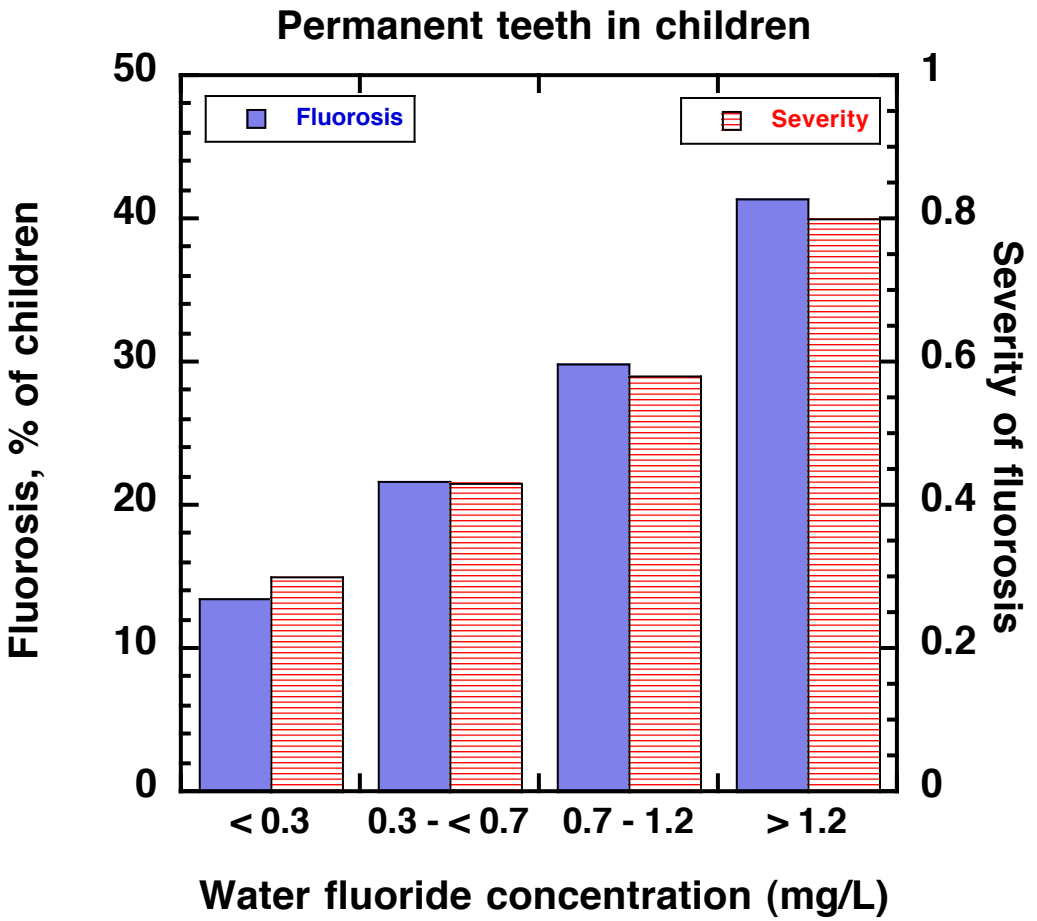

Fig. 5. Fluorosis prevalence and severity with water fluoride concentration for children ages 7-17 with a history of a single continuous residence. Data are shown as (left) % of total children having fluorosis (very mild, mild, moderate, or severe, but not questionable) or (right) severity of fluorosis by Dean's Community Fluorosis Index. Numerical values are provided in Table 1 of these comments and were obtained from Table 5 of Heller et al. (1997).

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FLUORIDE AND DENTAL CARIES: SECOND THOUGHTS IN VIEW OF RECENT EVIDENCE FROM GERMANY

SUMMARY: After seventy years of controversial discussion, the reports by Dean et al. that purported to demonstrate an inverse relationship between the prevalence of tooth decay in children and the fluoride content of drinking water are still cited as strong evidence for a significant anti-caries effect of fluoride, despite their many shortcomings. In addition, major hypotheses for possible cariostatic mechanisms of fluoride action have been found to be seriously flawed. Sociodemographic factors, as presented here from a part of Germany, appear to be better predictors of caries in children than the fluoride content of water supplies, raising the question: How much does fluoride really help to prevent or reduce tooth decay, especially among the most socially deprived and less advantaged?

Keywords: Childhood caries; Dental caries epidemiology; Fluoroapatite; Fluoride and dental caries; Mayen-Koblenz Area; Oral enzymes; Sociodemographic variables; Water fluoridation.

In 1939–1940, when organized dentistry celebrated its first centennial, H Trendley Dean of the US Public Health Service, after conducting surveys of dental fluorosis in relation to fluoride levels in drinking water, reported finding an impressive inverse relationship between the fluoride content in water supplies and the prevalence of dental caries in children. These studies, supplemented by examinations of children in 21 cities as well as reports from fluoridation trials initiated in 1945, have become the subject of controversial analysis and discussions.[1-4] Despite their weaknesses, these early studies are still widely cited to support claims for the effectiveness of water fluoridation to prevent dental caries, even though it has become increasingly difficult to attribute the almost world-wide caries decline in developed nations to the anticipated beneficial anti-caries effects of fluoridated water.[3] Similarly, there are indications that the anti-caries effectiveness of fluoridated dental products may have been overrated.[5]

The failure to find epidemiological evidence in support of any single means of fluoride application has been mainly attributed to the widespread availability of fluoride-containing products including fluoride-containing toothpastes and mouthwashes, fluoride-impregnated tooth-picks and dental floss, fluoride in tea, fluoride tablets, fluoridated table salt, and topical fluoride application by dentists.[6] There is growing evidence, however, that nonfluoride variables such as significant improvements in nutrition, health education, and socioeconomic standards may play a major role in caries prevention, along with the increased use of antibiotics and better oral hygiene.[1,6-8]

Adequate evaluation of the many possible factors is difficult because the tool often used in dental epidemiology, i.e., the mean number of decayed, missing or filled primary or permanent teeth (dmft or DMFT) or tooth surfaces involved (dmfs or DMFS) per “child” or per 100 “children” *examined*, can be misleading and is subject to serious bias for reasons such as the following:

(1) There are variable numbers of caries-free children in study groups, and the number of carious teeth in children with caries experience may or may not actually differ appreciably between groups. Thus the observation that about 75 percent of caries defects develop in about 25 percent of children at high risk[9] could obscure the presence of a *large* or a *small* number of children with caries-free teeth. For

example, a mean overall DMFT score of 2.0 per child (among 100 children examined) could mean 50 of the children are caries-free, and 50 have a mean DMFT score of 4.0 per child. It could also mean that 100 children have a mean DMFT score of 2.0 per child, and none are caries-free.

(2) The dmf and DMF scores are also influenced by the number of erupted teeth, for which there is biological, environmental, dietary, and genetic variability among children, often especially between boys and girls of the same age. Some researchers also point to evidence that excessive exposure to fluoride can cause a delay in tooth eruption.[3,4]

(3) Inter- or intra-examiner variability may also account for considerable differences in the diagnosis of actually decayed teeth in the same mouth, hence the need for "calibrated" examiners in dental surveys.

(4) Even so, the examiner calibration issue has no bearing on the number of missing or filled teeth, since a non-calibrated dental practitioner has already decided in the past – rightly or wrongly – whether or not a tooth was to be filled or extracted.

(5) As pointed out in a recent report discussed near the end of this editorial, it is also difficult to distinguish between restorative fillings for treatment of cavities and prophylactic (sealant) fillings of pits and fissures where no underlying decay was present or diagnosed.

(6) The m or M and the f or F parts of the index also reflect not only availability of dental care as judged, for example, by the dentist/population ratio, but also socioeconomic status in regard to health education, diet, personal dental care, and ability to pay for treatment. Interestingly, this view, along with a tendency of some dentists to overtreat, is now being used to explain an increased caries prevalence found in some studies.[10]

Epidemiology often shows a correlation between two variables under investigation, but in itself it cannot prove a cause-and-effect relationship. Therefore, various hypotheses have been advanced to explain possible anti-caries effects of fluoride. These include inhibition of certain cariogenic bacteria and the formation at the enamel surface of a layer of fluorapatite, claimed to offer more resistance to acids causing tooth decay than the usually prevailing hydroxyapatite mineral.

Both hypotheses have failed the test of time, yet researchers have been resourceful in coming up with new replacements, of which only a few can be discussed here. Thus, as reviewed recently by Clinch, the early-proposed questionable impact of fluoride on cariogenic oral bacteria lacks confirmation.[11] The fluoroapatite argument, since its inception in the 19th century, has undergone a number of modifications. The fluorine content of fluorapatite is about 3.8%, which roughly corresponds to the amount of fluoride found in bones and teeth by early "indirect" analytical methods. Towards the end of the 19th century, when more reliable methods of F analysis became available, fluoride was reclassified from a supposed major component of teeth to a rather small fraction amounting to 0.1% at most.[12] In 1938, Armstrong and Brekhus claimed that, even though the overall amounts are low, sound dental enamel contained more fluoride than carious

enamel (0.0111% vs. 0.0069%).[13] While it was generally taken for granted that the samples were "from the same mouths,"[14] it took 25 years before the principal author of the original report revised his previous conclusions: the difference was "due in major part to the higher mean age, amounting to 16 years, of the persons who supplied the sound teeth." This is significant because the fluoride content of hard tissues increases with age. In the follow-up investigation by the same author, enamel fluoride of sound or carious third molars was not found to be different in persons of comparable age.[15]

Still, the fluorapatite hypothesis was not discarded even after only minute amounts of fluoride were found to be present in dental enamel, but it was modified by the claim that a protective layer is formed at the surface. Another few decades had to pass until, in November of last year, a group of researchers at Saarland University, Germany, reported their discovery that such a layer is formed only on a nanometer scale and thus may not offer much protection against dental caries and may be worn off easily during normal eating while chewing food.[16] Nevertheless, convinced of a "clearly demonstrated cariostatic effect of fluoride compounds in various forms of applications" (their references again include the controversial studies of Dean et al.), the authors of this work promise further investigation of the action of fluoride on dental enamel.

How hard it is for some authors to accept negative evidence concerning Dean's early work and the paradigm resulting from it of fluoride's effectiveness to reduce tooth decay is also seen in a recent report on dental examinations of first-grade schoolchildren in Germany.[17] The drinking water of several communities in the Mayen-Koblenz-Kreis area (MYK) of West Germany's "Eifel," a landscape of low mountains, accumulates elevated natural levels of fluoride as it passes through strata of former volcanic activity. This particular geology offered an opportunity to repeat in Germany what Dean had done in the USA. In February and March 1977, Johannes Einwag, a graduate student in the dental department of the University of Bonn, examined children (ages 3 to 6, and 13 to 14 years) in seven communities in the area to relate the caries prevalence to the fluoride content of the water. Additional examinations were conducted in September of that year "in order to get statistically significant results," without any indication of how many children in which community or communities thus had the disadvantage of higher dental age.[18] The results, as presented in his doctoral thesis, indicated that the children in *one* community in the area, Polch (0.1 ppm F), had about 40 percent more decayed, missing and filled tooth surfaces (dmfs/DMFS) than children in the *six* fluoride communities in the area (0.9 to 1.6 ppm F).

This difference may or may not be due to different fluoride exposure. Especially in Polch, more primary teeth had been extracted ("m" being 19.5 or 15.9 percent of the dmfs among 5 or 6 year old children) because, according to Einwag, some dentists were apparently not inclined to treat (fill) carious primary teeth. Each extracted tooth enters the dmfs index as four or five surfaces and may thus lead to an overestimation of the caries prevalence. Similarly, the permanent teeth of 13 and 14 year-old children in Polch had received a slightly more intense dental treatment as indicated by the M + F contribution to the DMFS index: 51% as opposed to about 41% of the DMFS of the children in the other communities.

Beginning in the mid-1970s, educational efforts have been in place to reduce dental caries in the Mayen-Koblenz area. Several health insurance companies initiated dental hygiene projects in the kindergartens and distributed toothbrushes and rinsing cups. In the 1980s, dentists of the area organized an initiative and provided instructions on dental hygiene in the kindergartens. Since summer of 1985, health insurance companies and local dentists formed the *Arbeitsgemeinschaft Jugendzahnpflege* and expanded their efforts to include primary schools in their prophylaxis programs. At the end of the 1990s annual dental examinations of first-grade pupils began, and since then they have revealed a steady decline in caries prevalence among first-graders, with those of the Mayen-Koblenz-Kreis area having better teeth than the children in Koblenz, a city with many socially deprived areas.[19,20] However, this overall decline in caries was not attributed primarily to expanded dental education but rather to increased fluoride use, even though shortly after the start of the examinations, no correlation could be found between the prevalence of dental caries and the fluoride content in the water.[20]

In a recent publication, this remarkable finding was analyzed by Reinhard Steinmeyer, a dentist with the MYK Health Authority and board member of the *Arbeitsgemeinschaft Jugendzahnpflege*. According to Steinmeyer, the expected beneficial dental effects of fluoride may be semi-additive until a state of "saturation" results, at which point no further benefit from additional fluoride is obtained. Thus the question arises whether the fluoride content of the drinking water in the MYK communities can still be shown to exert some anti-caries effect. But, in fact, such a connection does not appear to exist. The caries prevalence among 9,555 first-graders, aged 6 to 7 years, in all 63 schools of 48 communities in the area failed to show any correlation with water fluoride. On the other hand, sociodemographic factors (unemployment, migration, financial aid from social care institutions, etc.) were known for families of 7,563 children and were found to serve as better predictors of caries experience. In this subgroup the mean percentage of caries-free 6- and 7-year-old children decreased from 64.5% to 58.1% and 50.9% in the order of high, middle, and low socio-economic status.

In further detail, as can be seen from the following table, the percentage of children from families in the middle socio-economic group actually increased with increasing fluoride levels in the water, while the percentage in the high socio-economic group decreased. However, at no socioeconomic level was there evidence of a consistent pattern of increasing caries-free teeth with increasing water fluoride levels. On the other hand, lower socio-economic status was associated with a decreasing percentage of caries-free children, not with less fluoride in the water. Therefore, in the light of these and earlier findings, the question must be asked: Does fluoride in drinking water actually help reduce tooth decay to any significant extent, especially in poorer children or even in all children?

As cited above,[7,8] dental comparisons of selected communities while neglecting important nonfluoride factors can be misleading. Still, such weak evidence continues to be used to support claims of the effectiveness of fluoride to prevent dental caries. This reluctance to recognize that an overall reduction in tooth decay

may not be due to fluoride in drinking water has been described as "tardive photopsia", in which those who adhere to an outdated and unverified belief are "slow to see the light."[21]

Table. Percent of children according to socioeconomic status in relation to water fluoride concentration, caries-free dentition, dmft, and DMFT of 7,563 children (data from Steinmeyer[17])

Socioeconomic status	Fluoride category				
	I (≤0.2 ppm)	I-II (ca. 0.3 ppm)	II (>0.3–<0.7 ppm)	II-III (ca. 0.7 ppm)	III (>0.7 ppm)
	Percent children by fluoride category[a]				
High		100.0	58.3	22.2	19.0
Middle	21.7		41.7	77.8	81.0
Low	78.3				
	Percent caries-free				
High		68.9	60.0	62.0	
Middle	57.9		60.6	57.8	
Low	50.9				
	dmft (only for teeth #3,4,5 in each quadrant)[b]				
High		0.90	1.22	0.94	
Middle	1.46		1.08	1.33	
Low	1.62				
	DMFT				
High		0.024	0.045	0.019	
Middle	0.097		0.028	0.048	
Low	0.053				

[a]Calculated from data of Steinmeyer.[17]

[b]Central and lateral incisors not counted as they tend to be shed in children of this age group.[17]

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WASHINGTON ACTION FOR SAFE WATER

August 16, 2010

Washington State Board of Health

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PETITION FOR RULE MAKING (#2): WATER FLUORIDATION,

WAC 246-290-460 OUTLINE

This petition relates to the concentration of fluoride, when fluoride is chosen to be added to drinking water. In response to the question of the intent for fluoridation, the Board of Health responded, "This agency, therefore, is not in possession of any records related to the Board's "purpose and intent for supporting the addition of fluoride to public drinking water."[1] If the Board has no purpose or intent for supporting the addition of fluoride to public drinking water, then the Board should support a reduction of the recommended concentration of fluoride being added to drinking water.

The Board of Health also responded that target concentrations of fluoride in water were last revised in 1999. The Board of Health also responded that "the Board complies with all state statutes" which should include statutes regarding the manufacturing of drugs added to public water.

Our June 9, 2010 petition requested the Board of Health to comply with state statues requiring manufacturers of drugs, in this case water suppliers, to be licensed and the drug approved by the Food and Drug Administration. The Board of Health denied the petition, apparently because the Board believes it lacks authority to require fluoride drugs used in Washington State be FDA approved. We disagree. This new petition, however, provides discussion and evidence for the Board of Health to make an informed decision to lower the concentration of fluoride added to water.

Dental caries is a common disease and especially problematic for the young and poor. Relying on a public health intervention which lacks efficacy, increases risks and wastes taxpayer dollars, is not good public policy.

I. PETITION TO IMPROVE AND PROTECT THE PUBLIC'S HEALTH WITH RULE MAKING ON FLUORIDATION (FLUORIDE ADDED TO PUBLIC DRINKING WATER)

This petition is made in the interest of a safer and healthier Washington.

The only intent of fluoridation is to prevent or mitigate dental caries, dental decay, and therefore fluoridation is defined as a drug by all drug regulatory agencies and laws.

In respect for the Board of Health's time, this petition does not repeat many of the citations provided by the June 9, 2010 petition. The supporting evidence for that petition which is in the Board's possession should be reviewed for this petition.

The manufacturing of a substance with the intent to prevent disease, defined as a prescription drug by the Washington State Board of Pharmacy, unapproved by the FDA (Food and Drug Administration), defined as a drug by the FD&C Act and Washington Statutes, and dispensed to everyone without

[1] July 22, 2010 letter to Bill Osmunson regarding public information disclosure request.

controlled dosage and without their consent must be closely and continuously reconsidered, controlled and monitored for safety, dosage, and efficacy.

This petition focuses on the concentration of fluoride added to public water and provides some of the evidence supporting the lowering of the current Board of Health recommended target concentrations.

II. WASHINGTON STATE BOARD OF HEALTH'S AUTHORITY TO REGULATE THE CONCENTRATION OF FLUORIDE ADDED TO PUBLIC WATER

The Washington State Board of Health should promulgate proper rules and regulations pertaining to fluoridation and should enforce such rules and regulations. The Board "shall provide a forum for the development of public health policy in Washington state" and for over 10 years the Board does not appear to have provided a forum for the development of public health policy as it relates to fluoridation or the concentration of fluoridation.

Pursuant to RCW 43.20.50 (1) "The state board of health shall provide a forum for the development of public health policy in Washington state. . . ." RCW 43.20.50 (2) "In order to protect public health, the state board of health shall: (a) Adopt rules for group A public water systems . . . necessary to assure safe and reliable public drinking water and to protect the public health. Such rules shall establish requirements regarding : . . . (ii) Drinking water quality standards . . . (b) Adopt rules as necessary for group B public water systems . . ." And further under RCW 70.142.010 to establish standards for chemical contaminants in public drinking water and "consider the best available scientific information establishing the standards."

The Board of Health responded to the June 9 petition, without confidence or citation, "The Board does not appear to have authority to adopt rules related to a water district deciding whether to fluoridate. The Board's authority is to regulate allowable concentration levels and method of approval of water additives." (June 9, 2010 Board Meeting Handout, page 2).

The Board has the duty to protect the public health and assure safe public drinking water to both group A and B public water systems. These petitioners disagree with the Board of Health's initial opinion and for the health of the public and the cost to tax payers recommends the Board of Health more seriously consider this petition. It is within the authority of the Board of Health to require water systems to obey drug laws when drugs are added to the water. If a drug is not approved by the FDA, then it should be prohibited for use in water. Certainly, a drug lacking FDA approval should not be forced on an entire public, entirely preventing a patient's freedom of choice

This petition focuses on the undisputed jurisdiction of the Washington Board of Health to work for a safer and healthier Washington and regulate allowable concentration levels of the fluoridated water drug added to water.

This petition does not relate to naturally occurring fluoride, a contaminant, which is regulated by the EPA (Environmental Protection Administration).

The Board defers to the CDC (Centers for Disease Control) without citation for support of a safe range of fluoride concentration, 0.8 ppm to 1.3 ppm in WAC 246-290-460.[2]

The CDC clearly states:

> "While it is not CDC's responsibility to determine what levels of fluoride in water are safe, ..."[3]

The Board of Health errs when it relies on the CDC to determine what levels of fluoride in water are safe when the CDC clearly states that "it does not have responsibility to determine what levels of fluoride in water are safe." Congress has not given the CDC the authorization on which the Washington Board of Health depends. Congress has given the Food and Drug Administration the responsibility to regulate the dosage of drugs.

The CDC suggests that:

> "fluoridation remains the most equitable and cost-effective method of delivering fluoride to all members of most communities, regardless of age, educational attainment, or income level."[4]

The CDC errs when suggesting fluoridation is equitable. Fluoridation is not "equitable" for those choosing not to be fluoridated and is equitable only if freedom is discarded and ignored. Equity is important for all patients, not a select subpopulation. We do not give our consent to be fluoridated.

The CDC errs when suggesting fluoridation is the most cost effective method of delivering fluoride. Delivering a pea size amount of toothpaste is more "cost-effective" than fluoridation and would provide freedom of choice for cohorts.

The CDC errs when it implies all members of a community should be targeted. People without teeth in a fluoridated community do not benefit. The potential target population for the ingestion of fluoride is ages 4 to 6. Babies and toddlers do not benefit. Older children and adults do not appear to benefit.

Forcing an unapproved drug on people does not educate them for good health habits of oral hygiene and nutrition which will mitigate dental decay and a host of other diseases.

Freedom for all should not be set aside in an attempt to treat a subpopulation with an unapproved drug, especially when it has little benefit.

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[2] Washington State Board of Health meeting handout, June 9, 2010, page 2
[3] http://www.cdc.gov/fluoridation/safety.htm
[4] CDC, MMWR October 22, 1999 Vol. 48 No.41

III. INTENT OF USE

To determine the appropriate concentration of fluoride in water, the intent of use must be considered. The intent of use determines the definition of a substance as it relates to regulatory agencies. It appears the Board has not been provided a clear understanding of the difference between treating water and treating people. If the intent of use is to treat water, the substance is regulated by the EPA. If the intent of use is to treat people, the substance is regulated by the FDA. The EPA also regulates contaminants added in excess of MCL.

If the substance is added with the intent to treat or prevent disease, the substance is defined as a drug and regulated by drug regulatory authorities for manufacturing, dispensing, administering and gaining individual consent. The evaluating of a contaminant in water is considerably different than evaluating a drug for the prevention of disease.

A. Assessment of Efficacy: Testing Water or Testing Patients

The assessment method for evaluating the success of an additive is to test or measure the water.

The assessment method for evaluating the success of a drug is to test or measure the disease in the patient.

In the case of an experimental unapproved drug such as fluoridation we must test the cohort for efficacy, reduction in dental caries, a reduction in dental treatment costs, and also test for safety with a lack of increase in adverse effects. Fluoridation fails on all counts. The current measured evidence for dental caries reduction is mixed and without confidence, measured dental treatment costs are not lower for all age groups in fluoridated communities, and measured adverse effects, such as dental fluorosis, are undisputed.

Adding a substance to water with the intent to kill pathogens in water and adding a substance to water with the intent to prevent disease in humans has different purposes, different regulatory agencies, different testing (assessment) practices, different levels of confidence for safety and efficacy, and different forms of consent. There is little in common between an additive and a drug.

1. TESTING WATER. Substances mixed with water with the **INTENT** to disinfectant water, additives such as chlorine (bleach), are regulated by the EPA under the Safe Drinking Water Act. A disinfectant is added to water at a recommended concentration and is tested by measuring the remaining pathogenic bacterial count in the water. If there is a surge of contaminated water, additional chlorine maybe added to the system to ensure an adequate reduction in the bacteria and the water may be tested to ensure efficacy. Knowing the substance can be toxic to both pathogens and humans, judgment is used to reduce the pathogens with the least harm to humans.

2. TESTING PATIENTS. Manufacturing a substance with the **INTENT** to prevent disease, defined by the FD&C Act and RCW as a drug, is

regulated by the FDA and Board of Pharmacy. Before FDA approval of drugs, they are tested for efficacy and safety first in animals, then in small groups of humans and finally in larger groups of humans. Randomized controlled trials to determine both efficacy and safety are required. A good margin of safety is to be provided. Pharmacokinetics is to be determined and documented. A legend of warning and dosage is drafted and approved by the FDA. Only after rigorous testing does the drug get approved by the FDA for use in humans.

Manufacturers are licensed and good manufacturing practices are required and monitored with oversight. Until a drug has been approved, not only is the drug illegal, but dispensing the drug is considered experimental and must follow laws and ethics of human subject research.

When the Board of Health considers this petition, the Board of Health must look at the concentration of fluoride added to water through the eyes and judgment of the FDA and not the CDC or EPA.

B. Concentration versus Dosage

The concentration of a substance such as fluoride, arsenic or lead is usually measured in parts per million (ppm) or milligrams of the substance per liter (mg/L).

In contrast, the dosage of a drug is usually measured as milligrams of a drug per kilogram of body weight (mg/Kg bw) of the patient. Putting a substance in public water and expecting a reasonably accurate dosage for the patient is problematic because at different ages the patient consumes different amounts of water based on their body size, such as infants on formula, and there is a significant variation in water consumption between patients of the same body weight. Diabetics, laborers, and athletes often drink more water. Concentration simply does not provide a reasonable dosage and can have a variation of more than ten fold.

C. Traditional Dosage of Fluoride (mg/Kg body weight).

To evaluate an appropriate concentration of fluoride in water, the Board of Health must first determine the desired dosage of fluoride for both efficacy and safety. In this case, without a doctor's supervision or the patient's consent, the protective determination must include dosage of fluoride for subpopulations (each age group, gender, race, etc.) and include compromised medical conditions such as kidney dysfunction, intestinal disorders, iodine deficiencies etc.

The efficacy of fluoridation is disputed. Perhaps due to the significant increases of fluoride from other sources, fluoridation no longer shows efficacy in decay reduction or reduction in dental expenses. This is a good time for the Board to once again review the evidence on efficacy provided in the June 9 petition requesting fluoride drugs used be required to have FDA approval.

> "Given the overlap among caries/fluorosis groups in mean fluoride intake and extreme variability in individual fluoride intakes, firmly recommending an "optimal" fluoride intake is problematic."[5]

> "The recommended optimal fluoride intake for children to maximize caries prevention and minimize the occurrence of dental fluorosis is often stated as being 0.05-0.07 mg/kg/day (Levy 1994; Heller et al. 1999, 2000). Burt (1992) attempted to track down the origin of the estimate of 0.05-0.07 mg/kg/day as an optimum intake of fluoride but was unable to find it." NRC 2006 p 68.

The so called "optimum" amount of fluoride is not based on scientific evidence or research but is simply a dental tradition, and ignorant of medical effects, an estimate which by default over time has been mistaken for fact.

The historically suggested optimal dosage of 0.05mg/Kg bw is excessive and without scientific support. The FDA cautions not to swallow even a pea size amount of toothpaste, which contains 0.25 mg of fluoride.

As we progress in this petition, consider a 5 Kg child's suggested "optimal" intake is 0.25 mg per day of fluoride, the same amount in a small pea size of toothpaste which the FDA warns not to swallow. And 0.25 mg/L is more than 60 times the mean level of fluoride in mother's milk.

The historical "optimal" amount is problematic. None the less, the sea of numbers below will make more sense if the Board of Health remembers both 0.05 mg/Kg bw dosage as the suggested "optimal" amount of fluoride and 0.25 mg as the "do not swallow" total intake warning required by the FDA for toothpaste.

1. Fluoride is Not Essential for Health

Ingesting fluoride is not essential. Fluoride has not been concluded essential for homeostasis or growth.[6] Many people, here and around the world, have excellent teeth without fluoride or fluoridated water. Perhaps the optimal level should be 0.0 ppm.

> "A re-examination of the pre-eruptive and post-eruptive mechanism of the anti-caries effects of fluoride: is there any anti-caries benefit from swallowing fluoride?"[7]

Freedom of choice must be given individuals to ingest or not ingest any substance which is not essential, not approved and highly toxic.

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[5] Warren J, Levy S, Froffitt B, Cavanaugh J, Kanellis M, Weber-Gasparoni K, Considerations on Optimal Fluoride Intake Using Dental Fluorosis and Dental Caries Outcomes- A Longitudinal Study, JPHD 2008

[6] Department of Health and Human Services, Review of Fluoride, Benefits and Risks, Report of the Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs, Public Health Service. P 7. "there is no conclusive evidence that fluorine or any of the fluoride compounds are essential for human homeostasis or growth (McIvor et al., 1985)."

[7] Limeback H, Community Dental Oral Epidemiology 1999 Feb;27(1):62-71

Careful brushing and flossing and a good diet can prevent dental caries and has the added benefit of reducing periodontal disease, heart disease, diabetes, obesity and more.

2. Fluoride Has Little Benefit, If Any.

Ingesting fluoride does not appear to reduce tooth decay. Researchers are "puzzled"[8] at "The mystery of declining tooth decay"[9] in developed countries. Comparing fluoridated with non-fluoridated countries, all developed countries have reduced tooth decay to similar levels. Ranking states within the USA by the percent of whole population on fluoridated water finds no benefit from fluoridation. Little or no cost savings in dental expenses have been achieved.

"An analysis of national survey data collected by the National Institute of Dental Research (NIDR) concludes that children who live in areas of the U.S. where the water supplies are fluoridated have tooth decay rates nearly identical with those who live in nonfluoridated areas"[10]

Some researchers suggest the "almost universal use of fluoridated toothpastes" has resulted in the decrease in tooth decay.[11]

Based on efficacy, the optimal concentration of fluoride in water is 0.0 ppm.

3. Target Population

The target population for fluoridation, fluoride ingestion, is arguably ages 1 to 8, or ages 4 to 6, or about 3% to 10% of the population. Remember, it is during growth spurts such as boys ages 4 to 6 on fluoridated water where we see an increase in osteosarcoma.

In brief, mother's milk contains almost no fluoride, so unless a person is suggesting mother's milk is "defective," infants should not have fluoridated water to drink or contained in formulas. Almost 40 years ago it was suggested fluoridated water provided 50 times more fluoride to infants. 20 years ago it was suggested fluoridated water gave 150 to 200 times more fluoride than mother's milk.[12] Current studies find mother's milk often has an undetected level of fluoride.

Toddlers should not drink more than one glass of fluoridated water (up to age 3) per day. After enamel has formed, age 6 to 8, fluoridated water has little or no theoretical or measured benefit. Regardless of the disagreement of benefit for ages 1 to 8 or ages 4 to 6, only a small 3 to 10% of the population is targeted with potential benefit from fluoridated water. Other methods of dispensing

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[8] Pizzo G, Piscopo MR, Pizzo I, Giuliana G, Community water fluoridation and caries prevention: a critical review, Clin Oral INvestig Sept 2007

[9] Mark Diesendorf, Nature 1986, page 125

[10] Chemical and Engineering News, May 8, 1989, Vol 57, Number 19.

[11] Featherstone John, Nutrition Today, 1987

[12] Ekstrand Jan, Fluoride Intake in Early Infancy, The Journal of Nutrition 119: 1856-1860, 1989.

fluoride to this small segment of the population are available. Protect the vulnerable and provide freedom of choice.

More details: Both the theoretical prevention of dental decay and the risk of dental fluorosis are during the development of tooth enamel. (See NRC Report 2006, p. 3, Chapter 3 and 4) In other words, all the population, 100%, are being treated with fluoride in the community water but only a small fraction of the total might benefit.

1 ppm of fluoride when ingested in water is not considered high enough to have significant effect of fluoride incorporating into the enamel and the duration of contact time on the teeth during drinking is too short to have significant effect.

Saliva is very low in fluoride, similar to blood levels (0.019 mg/L see p 17 NRC report; and mother's milk has been measured about 0.002-0.033 ppm[13]) and ingesting more fluoride does not appreciably alter the level of fluoride in the saliva. Thus fluoridated water has perhaps a potential for benefit systemically during tooth enamel development, until about age 6-8.

The 1998 recommendation by the American Academy of Pediatrics suggested no prescription fluoride (supplements, additional fluoride) before age 6 months and one cup of water (0.25mg of F) 6 mo. to 3 years of age.[14]

The "typical child" up to 3 years of age drinks significantly more water than one glass a day (typical is 350 – 450 ml of water a day). However, we should protect all children, not just the typical child and some children drink double the "typical child". In reality, the "typical child" should only consume about half the water they drink from fluoridated community water and the rest should be fluoride free (reverse osmosis, distilled or bottled water). Can you imagine explaining that to busy moms, or try telling dads and care givers they need to keep track of total water intake and limit intake to one glass. If Johnny is playing outside and thirsty, be sure to calculate how much water he has consumed and after about one glass of community water in soups, drinks, or foods, give him filtered water. Suppose Johnny has had his glass of water or mom runs out of bottled water and Johnny is still thirsty what should he drink, soda pop? Of course not.

The City and Public Health Educators have failed to educate and warn parents and care givers of infants that the community water should be avoided for infants? Parents have not been told that about half the water consumed by children up to the age of 3 should not be from community water. These bottled water costs to families, plus the environmental impact of plastics and bottled water use, need to be factored in to the total expenses of fluoridation.

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[13] NRC p. 30. "Hossny et al. (2003) reported fluoride concentrations in breast milk of 60 mothers in Cairo, Egypt, ranging from 0.002 to 0.01 mg/L [0.1-0.6 μM/L; median, 0.0032 mg/L (0.17 μM/L); mean, 0.0046 mg/L (0.24 μM/L)]. Cairo is considered nonfluoridated, with a reported water fluoride concentration of 0.3 mg/L (Hossny et al. 2003). Opinya et al. (1991) found higher fluoride concentrations in mothers' milk (mean, 0.033 mg/L; range, 0.011-0.073 mg/L), but her study population was made up of mothers in Kenya with an average daily fluoride intake of 22.1 mg. However, even at very high fluoride intakes by mothers, breast milk still contains very low concentrations of fluoride compared with other dietary fluoride sources. No significant correlation was established between the fluoride in milk and the intake of fluoride in the Kenyan study." (Opinya et al. 1991).

[14] Pediatrics May 1998 Vol. 95, Number 5 RE9511

Only a small fraction of fluoridated water is used for drinking. Of that, only a small fraction of people might benefit and measurements no longer detect significant measured benefit. The concentration of fluoride in water should be protective of all, especially babies and those who are chemically sensitive or are unable to tolerate fluoride.

IV. CURRENT TOTAL EXPOSURE OF FLUORIDE

The World Health Organization advises communities to first determine the current exposure to fluoride before adding fluoride to water. The Board of Health must determine individual current exposure and answer the question, "does the total fluoride exposure from all sources meet the desired dosage?"

> "The major sources of internal exposure of individuals to fluorides are the diet (food, water, beverages) and fluoride-containing dental products (toothpaste, fluoride supplements). Internal exposure to fluorides also can occur from inhalation (cigarette smoke, industrial emissions), dermal absorption (from chemicals or pharmaceuticals), ingestion or parenteral administration of fluoride-containing drugs, and ingestion of fluoride-containing soil." NRC 2006 p 19

A. For some, Fluoridated Water Alone Provides Excess Exposure

At 1 ppm fluoride, one liter of fluoridated water provides 1 mg of fluoride, four times the FDA warning and four times the suggested "optimal" amount for infants and 250 times the concentration of mother's milk.

> "Some subpopulations consume much greater quantities of water than the 2 L per day that EPA assumes for adults, including outdoor workers, athletes, and people with certain medical conditions, such as diabetes insipidus." NRC 2006 P 23

And

> "Average per capita ingestion of community or municipal water is estimated to be 927 mL/day (EPA 2000a; see Appendix B6). The estimated 90th percentile of the per capita ingestion of community water from that survey is 2.016 L/day. NRC 2006 P 23.

The Board of Health must be protective of everyone, 100%, not the 90th or 99th percentiles. When the city uses police powers to medicate everyone, then the city is responsible for the dosage based on total exposure and concentration of fluoride in the water and risks from the fluoride for each individual. If governments take someone's property, the government pays for the property. If governments take or damage an individual's health, then governments should

compensate those individuals. At least fluoride free water should be provided those not wanting fluoridated water.

In Appendix B, Table B-4, page 376, the NRC 2006 lists water consumption at the 99th percentile with several groups close to 5 liters of water a day and one is 5.356 L/day. At 1 ppm of fluoride, water alone for these people provides about 5 mg of fluoride per day, more than "optimal" from this source alone.

> "The U.S. Army's policy on fluid replacement for warm weather training calls for 0.5-1 quart/hour (0.47-0.95 L/hour), depending on the temperature, humidity, and type of work (Kolka et al. 2003; USASMA 2003). In addition, fluid intake is not to exceed 1.5 quarts/hour (1.4 liter/hour) or 12 quarts/day (11.4 L/day). The Army's planning factor for individual tap water consumption ranges from 1.5 gallons/day (5.7 L/day) for temperate conditions to 3.0 gallons/day (11.4 L/day) for hot conditions (U.S. Army 1983)."[15]

11.4 L/day or 11.4 mg of fluoride a day which is about 3 times the "optimal" dosage and over 40 times above the FDA warning, "Do Not Swallow."

> "Someone initially presenting with central or vasopressin-sensitive diabetes insipidus might ingest "enormous" quantities of fluid and may produce 3-30 L of very dilute urine per day (Beers and Berkow 1999) or up to 400 mL/kg/day (Baylis and Cheetham 1998). Most patients with central diabetes insipidus have urine volumes of 6-12 L/day (Robinson and Verbalis 2002)."[16]

Diabetics may ingest 12 liters/day or 12 mg per day of fluoride from water alone. When determining the concentration of fluoride added to water, the Board of Health has a duty to protect the health and safety of everyone, not just the mean.

> "Moderate and severe dental fluorosis have been reported in diabetes insipidus patients in other countries with drinking water containing fluoride at 0.5 mg/L (Klein 1975) or 1 mg/L (Seow and Thomsett 1994), and severe dental fluorosis with skeletal fluorosis has been reported with fluoride at 3.4 mg/L (Mehta et al. 1998). Greenberg et al. (1974) recommended that children with any disorder that gives rise to polydipsia and polyuria be supplied a portion of their water from a nonfluoridated source."[17]

Anyone suggesting the NRC report does not have critical information for those evaluating fluoridated water concentrations and safety has not read the report. The report does not deal with efficacy, but it has valuable information on

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[15] NRC 2006 p 26.
[16] NRC 2006 p 26
[17] NRC 2006 p 27

risk. Since the mid 1970's moderate and severe dental fluorosis, a sign of fluoride toxicity, has been reported at 0.5 mg/L and 1 mg/L fluoride in water.

It would be best for the Board of Health to lower the concentration of fluoride in water rather than have water districts supply a secondary source of fluoride-free water for babies, children, the military, prisoners, diabetics, those chemically sensitive and those refusing to give consent.

Many are ingesting too much fluoride from water alone.

B. Fluoride Exposure From Food

Many are ingesting too much fluoride from food alone.

The National Research Council report for the EPA on fluoride in drinking water provides a glimpse of fluoride in various foods. Here are a few examples which become a concern when the total fluoride exposure is considered. Remember 0.05 mg/Kg bw suggested "optimal" and 0.25 mg FDA warning.

The purpose of this section is for the Board of Health to understand some of the various sources of fluoride exposure and thus support for lowering the concentration of fluoride in water as requested in this petition.

> "Measured fluoride in samples of human breast milk is very low. Dabeka et al. (1986) found detectable concentrations in only 92 of 210 samples (44%) obtained in Canada, with fluoride ranging from <0.004 to 0.097 mg/L." NRC p 26

The purpose of that quotation is for the Board of Health to understand the fluoride concentration of mother's milk was not detected in more than half of the cohorts. If the Board of Health intends to protect the health of babies, based on mother's milk, the low end of the concentration of fluoride added to water should be 0.00 ppm.

> "Heilman et al. (1997) found 0.01 to 8.38 µg of fluoride per g of prepared infant foods. The highest concentrations were found in chicken (1.05-8.38 µg/g); other meats varied from 0.01µg/g (veal) to 0.66 µg/g (turkey). Other foods—fruits, desserts, vegetables, mixed foods, and cereals—ranged from 0.01 to 0.63 µg/g. The fluoride concentrations in most foods are attributable primarily to the water used in processing (Heilman et al. 1997); fluoride in chicken is due to processing methods (mechanical deboning) that leave skin and residual bone particles in the meat (Heilman et al. 1997; Fein and Cerklewski 2001). An infant consuming 2 oz (about 60 g) of chicken daily at 8 µg of fluoride per g would have an intake of about 0.48 mg (Heilman et al. 1997)." NRC p 30

The one serving of chicken would be the entire daily dose of fluoride for a 22 pound child even without any other fluoride from water, toothpaste, or other foods. And it would be double the FDA's warning, not to swallow.

" Fluoride concentrations in tea leaves range from 170 to 878 mg/kg in different types of tea, with brick tea generally having 2-4 times as much fluoride as leaf tea (Wong et al. 2003)." NRC 2006 p 31.
"Whyte et al. (2005) reported fluoride concentrations of 1.0-6.5 mg/L in commercial teas (caffeinated and decaffeinated) obtained in St. Louis (prepared with distilled water according to label directions)." NRC 2006 p 31.
"Kiritsy et al. (1996) reported fluoride concentrations in juices and juice-flavored drinks of 0.02-2.8 mg/L (mean, 0.56 mg/L) for 532 different drinks (including five teas) purchased in Iowa City (although many drinks represented national or international distribution); frozen-concentrated beverages were reconstituted with distilled water before analysis. White grape juices had the highest mean fluoride concentration (1.45 mg/L); upper limits on most kinds of juices exceeded 1.50 mg/L . . . . The high fluoride content of grape juices (and grapes, raisins, and wines), even when little or no manufacturing water is involved, is thought to be due to a pesticide (cryolite) used in grape growing (Stannard et al. 1991; Kiritsy et al. 1996; Burgstahler and Robinson 1997)." NRC 2006 p 31.
"R.D. Jackson et al. (2002) reported . . . mean daily fluoride ingestion for children 3-5 years old from food and beverages (including those prepared with community water) was estimated to be 0.454 mg in the low-fluoride town and 0.536 mg in the fluoridated town." NRC 2006 p 32.

C. SULFURYL FLUORIDE: POST-HARVEST FUMIGANT

After foods have been harvested, they must rapidly get to market and have a long shelf life. In the past bromine gas was used as a post-harvest fumigant to preserve the foods, but bromine apparently has been discontinued due to environmental concerns. Sulfuryl fluoride is replacing the bromine.

The advertisement for ProFume gas (DowAgro Science) with a good looking cookie below:

New Label, New Opportunities

A new label for ProFume® gas fumigant expands the list of labeled uses and simplifies the fumigation process. Now, more market segments, including food processing facilities, can use ProFume.

More...

ProFume® gas fumigant is a broad-spectrum postharvest fumigant developed by Dow AgroSciences LLC.

®ProFume is a federally Restricted Use Pesticide. Always read and follow label directions.

About ProFume Gas Fumigant
Phasing Out Methyl Bromide
Frequently Asked Questions
Latest News
Schedule a Fumigation/ Find a Representative
Contact Us

should be tempered with the warning label below:

The fluoride residue permitted on foods is significant and can increase the total fluoride exposure. DowAgroSciences, LLC, is confident not all of the foods will have the maximum fluoride permitted residues. Here are a few of the many foods which have permitted fluoride residue concentrations of fluoride:

Fig, plum, prune, grape, raisin, fruit 5 ppm
Almond, barly grain, rice grain 10 ppm
Pecan 23 ppm
Walnut 30 ppm
Wheat grain 25 ppm
Wheat germ 98 ppm
Refined oil 3 ppm
Egg 850 ppm
Dried egg 900 ppm

D. Fluoride Exposure In Dental Products and Supplements

The FDA is concerned that 0.25 mg of fluoride is too much to swallow. The FDA required toothpaste warning is not to swallow a pea size amount. A pea size of toothpaste contains 0.25 mg of fluoride, the same amount as one glass of fluoridated water. If the FDA warns not to swallow 0.25 mg of fluoride, the Board of Health should not force everyone to swallow that much in each glass of water.

> "More than 90% of children ages 2-16 years surveyed in 1983 or 1986 used fluoride toothpaste (Wagener et al. 1992). Of these children, as many as 15% to 20% in some age groups also used fluoride supplements or mouth rinses (Wagener et al. 1992). Using the same 1986 survey data, Nourjah et al. (1994) reported that most children younger than 2 years of age used fluoride dentifrices." NRC 2006 p 34.

> "Ophaug et al. (1980, 1985) estimated the intake of fluoride by small children (2-4 years) to be 0.125-0.3 mg per brushing; a 2-year-old child brushing twice daily would ingest nearly as much fluoride from the

toothpaste as from food and fluoridated drinking water combined (Ophaug et al. 1985).” NRC 2006 p 34.

The Board of Health should once again remember that when fluoridated water was initially recommended at 1 ppm, fluoridated dental products such as fluoridated toothpaste were not available and the concentration of fluoride in water was considered the only significant and common source of fluoride.

> “Levy (1993, 1994) and Levy et al. (1995a) reviewed a number of studies of the amount of toothpaste people of various ages ingest. Amounts of toothpaste used per brushing range from 0.2 to 5 g, with means around 0.4-2 g, depending on the age of the person. The estimated mean percentage of toothpaste ingested ranges from 3% in adults to 65% in 2-year-olds. Children who did not rinse after toothbrushing ingested 75% more toothpaste than those who rinsed. Perhaps 20% of children have fluoride intakes from toothpaste several times greater than the mean values, and some children probably get more than the recommended amount of fluoride from toothpaste alone, apart from food and beverages (Levy 1993, 1994). Mean intakes of toothpaste by adults were measured at 0.04 g per brushing (0.04 mg of fluoride per brushing for toothpaste with 0.1% fluoride), with the 90th percentile at 0.12 g of toothpaste (0.12 mg of fluoride) per brushing (Barnhart et al. 1974).
> Lewis and Limeback (1996) estimated the daily intake of fluoride from dentifrice (products for home use) to be 0.02-0.06, 0.008-0.02, 0.0025, and 0.001 mg/kg, for ages 7 months to 4 years, 5-11 years, 12-19 years, and 20+ years, respectively.” NRC 2006 p 34

> “Topical applications of fluoride in a professional setting can lead to ingestion of 1.3-31.2 mg (Levy and Zarei-M 1991) . . . Eklund et al. (2000), in a survey of insurance claims for more than 15,000 Michigan children treated by 1,556 different dentists, found no association between the frequency of use of topical fluoride (professionally applied) and restorative care. Although these were largely low-risk children, for whom routine use of professionally applied fluoride is not recommended, two-thirds received topical fluoride at nearly every office visit. The authors recommended that the effectiveness of professionally applied topical fluoride products in modern clinical practice be evaluated.” NRC 2006 p 35.

The lack of a reduction in dental expenses with the topical application of fluoride, is an example of never letting good research stand in the way of a profitable practice.

> “The dietary fluoride supplement schedule in the United States, as revised in 1994 by the American Dental Association, now calls for no supplements for children less than 6 months old and none for any child whose water contains at least 0.6 mg/L (Record et al. 2000; ADA 2005; Table 2-8). Further changes in recommendations for fluoride supplements have been suggested (Fomon and Ekstrand 1999; Newbrun 1999; Fomon et al.

2000), including dosages based on individual body weight rather than age (Adair 1999) and the use of lozenges to be sucked rather than tablets to be swallowed (Newbrun 1999), although others disagree (Moss 1999). The Canadian recommendations for fluoride supplementation include an algorithm for determining the appropriateness for a given child and then a schedule of doses; no supplementation is recommended for children whose water contains at least 0.3 mg/L or who are less than 6 months old (Limeback et al. 1998; Limeback 1999b)." NRC 2006 p 35

Reducing the concentration of fluoride to 0.6 ppm would be in keeping with 16 year old data from the American Dental Association. A reduction to 0.3 ppm would be in keeping with Canadian recommendations. However, most European Dental Associations no longer recommend fluoride supplements which would put the low level of a range of fluoridation at 0.00ppm.

D. Fluoride From Air

"For most individuals in the United States, exposure to airborne fluoride is expected to be low compared with ingested fluoride (EPA 1988); exceptions include people in heavily industrialized areas or having occupational exposure." NRC 2006 p 37

E. Fluoride from Soil

"Erdal and Buchanan (2005) estimated intakes of 0.0025 and 0.01 mg/kg/day for children (3-5 years), for mean and reasonable maximum exposures, respectively, based on a fluoride concentration in soil of 430 ppm. . . .

For children with pica (a condition characterized by consumption of nonfood items such as dirt or clay), an estimated value for soil ingestion is 10 g/day (EPA 1997). For a 20-kg child with pica, the fluoride intake from soil containing fluoride at 400 ppm would be 4 mg/day or 0.2 mg/kg/day. Although pica in general is not uncommon among children, the prevalence is not known (EPA 1997)." NRC 2006 p 38

F. Fluoride from Pesticides

"Cryolite and sulfuryl fluoride are the two pesticides that are regulated for their contribution to the residue of inorganic fluoride in foods. . . . Cryolite, sodium hexafluoroaluminate (Na_3AlF_6), is a broad spectrum insecticide that has been registered for use in the United States since 1957. Currently, it is used on many food (tree fruits, berries, and vegetables) and feed crops, and on nonfood ornamental plants (EPA 1996a).

The respective fluoride ion concentrations from a 200 ppm aqueous synthetic cryolite (97.3% pure) at pH 5, 7, and 9 are estimated at 16.8, 40.0, and 47.0 ppm (approximately 15.5%, 37%, and 43% of the total available fluorine) (EPA 1996a). . .

The dietary fluoride exposure thus estimated ranged from 0.0003 to 0.0031 mg/kg/day from cryolite, 0.0003 to 0.0013 mg/kg/day from sulfuryl

fluoride, and 0.005 to 0.0175 mg/kg/day from background concentration in foods (EPA 2004).” NRC 2006 p 40.

G. Fluoride From Fluorinated Organic Compounds.

“Many pharmaceuticals, consumer products, and pesticides contain organic fluorine (e.g., –CF3, –SCF3, –OCF3). . . .
Pradhan et al. (1995) reported an increased serum fluoride concentration from 4 µM (0.076 ppm) to 11 µM (0.21 ppm) in 19 children from India (8 months to 13 years old) within 12 hours after the initial oral dose of ciprofloxacin at 15-25 mg/kg. . . .
Other fluoride-containing organic chemicals go through more extensive metabolism that results in greater increased bioavailability of fluoride ion. . . .
Levy et al. (2001a) reported less than 3% systemic fluorouracil absorption in patients treated with 0.5% or 5% cream for actinic keratosis.
A group of widely used consumer products is the fluorinated telomers and polytetrafluoroethylene, or Teflon. EPA is in the process of evaluating the environmental exposure to low concentrations of perfluorooctanoic acid (PFOA) and its principal salts that are used in manufacturing fluoropolymers or as their breakdown products (EPA 2003b). PFOA is persistent in the environment.” NRC 2006 p. 41.

H. Fluoride From Aluminofluorides

“Human exposure to aluminofluorides can occur when a person ingests both a fluoride source (e.g., fluoride in drinking water) and an aluminum source; sources of human exposure to aluminum include drinking water, tea, food residues, infant formula, aluminum-containing antacids or medications, deodorants, cosmetics, and glassware (ATSDR 1999; Strunecka and Patocka 2002; Li 2003; Shu et al. 2003; Wong et al. 2003). Aluminum in drinking water comes both from the alum used as a flocculant or coagulant in water treatment and from leaching of aluminum into natural water by acid rain (ATSDR 1999; Li 2003). Exposure specifically to aluminofluoride complexes is not the issue so much as the fact that humans are routinely exposed to both elements.” NRC 2006 p 42.

I. Fluoride From Fluorosilicates

“Most fluoride in drinking water is added in the form of fluosilicic acid (fluorosilicic acid, H2SiF6) or the sodium salt (sodium fluosilicate, Na2SiF6), collectively referred to as fluorosilicates (CDC 1993). Of approximately 10,000 fluoridated water systems included in the CDC’s 1992 fluoridation census, 75% of them (accounting for 90% of the people served) used fluorosilicates. This widespread use of silicofluorides has raised concerns on at least two levels.
First, some authors have reported an association between the use of silicofluorides in community water and elevated blood concentrations of lead in children (Masters and Coplan 1999; Masters et al. 2000); this

> association is attributed to increased uptake of lead (from whatever source) due to incompletely dissociated silicofluorides remaining in the drinking water (Masters and Coplan 1999; Masters et al. 2000) or to increased leaching of lead into drinking water in systems that use chloramines (instead of chlorine as a disinfectant) and silicofluorides (Allegood 2005; Clabby 2005; Maas et al. 2005)." NRC 2006 p 43

V. DETERMINING FLUORIDE CONCENTRATION FOR WATER.

Although the precautionary principle may not be codified, certainly the Board of Health should be cautious. The Board should follow the Safe Drinking Water Act and the Food, Drug and Cosmetic Act when considering the safety and risks of fluoridation.

> "Due to misdirection by EPA management, who requested the report, the NRC committee identified only health effects known with total certainty. This is contrary to the intent of the Safe Drinking Water Act (SDWA), which requires the EPA to determine "whether any adverse effects can be reasonably anticipated, even though not proved to exist." Further misdirection by EPA consisted of instructing the committee not to identify a new MCLG—in other words, not to determine a safe level of fluoride in drinking water, and not to discuss silicofluorides, phosphate fertilizer manufacturing by-products used in most cities to fluoridate their water. Despite these restrictions, the committee broke new ground . . . On the basis of this information and the proper interpretation of the SDWA, the following are all adverse health effects: moderate dental fluorosis, stage I skeletal fluorosis (arthritis with joint pain and stiffness), decreased thyroid function, and detrimental effects on the brain, especially in conjunction with aluminum. The amount of fluoride necessary to cause these effects to susceptible members of the population is at or below the dose received from current levels of fluoride recommended for water fluoridation. The recommended Maximum Contaminant Level Goal (MCLG) for fluoride in drinking water should be zero[18]

Different methods for determining the appropriate concentration of fluoride can be used. When used with the intent to prevent tooth decay, fluoride is a drug and concentration should be evaluated with the same criteria used by the Food and Drug Administration. The FDA New Drug Application criteria, includes:

A. Labeling
B. Chemistry
C. Nonclinical pharmacology and toxicology
D. Human pharmacokinetics and bioavailability
E. Clinical microbiology
F. Clinical data

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[18] Carton, R Review of the 2006 United Stat4es National Research Council Report: Fluoride in Drinking Water, Fluoride 39(3)163-172 Jul-Sep 2006. http://www.fluorideresearch.org/393/files/FJ2006_v39_n3_p163-172.pdf

G. Safety update
H. Statistical section
I. Case Report Tabulations
J. Case Report Forms
K. Establishment description
L. Debarment certification
M. Field copy certification

The expense and time to develop protocol and pay experts to evaluate all those aspects of the fluoride drug seems to be a misuse of tax payer money. Certainly the Board should reconsider requiring water districts to use the services of the FDA (June 9, 2010 WASW Petition) rather than the Board taking on the responsibility of drug approval for one drug.

For example, the CDC and several state departments of health caution, "Recent studies have raised the possibility that mixing infant formula with fluoridated water, particularly for infants exclusively on a formula diet during the first year of life, may play a more important role in enamel fluorosis development than was previously understood."

A. Mother's Milk: The simplest and most powerful evidence to consider for the concentration of fluoride in water for babies is mother's milk. We must protect babies, our most vulnerable.

Mother's milk has a range of between "not detected and 0.10 ppm (100ppb) and should be the concentration range approved by the Board of Health. In non-fluoridated communities the mean level of fluoride in mother's milk was found to be 0.004 ppm. Based on mother's milk, a range of fluoride selected by the Board should be of 0.004 ppm (4 ppb) to 0. 10ppm (100 ppb).

Historical estimates suggested 0.05 mg/Kg/day of fluoride was "optimal." Infants often exceed the "optimal" amount of fluoride.

> "For water from all sources (direct, mixed with formula, etc.), the intake of fluoride by infants (Levy et al. 1995b) ranged from 0 (all ages examined) to as high as 1.73 mg/day (9 months old). . . . For ages 1.5-9 months, approximately 40% of the infants exceeded a mass-normalized intake level for fluoride of 0.07 mg/kg/day; for ages 12-36 months, about 10-17% exceeded that level (Levy et al. 2001b)." NRC 2006.

At least 40% of Infants to 9 months are ingesting too much fluoride and 10-17% up to age 36 months are ingesting too much fluoride.

B. Efficacy: Calculating an effective dose is more controversial. Without the FDA using their criteria for drug approval, some of the best evidence no longer shows efficacy from ingesting fluoride.

Measuring the costs to treat dental disease is a reasonable method for evaluating efficacy. Dental treatment costs include the possibility of a reduction in dental decay and possible adverse events such as increased tooth fractures

and what clinicians call “fluoride bombs” and treatments for dental fluorosis. Only one published study uses measured data of dental treatment costs and it found almost no difference between the fluoridated and non-fluoridated communities with an increase in dental costs for children in the largest fluoridated community. Historical studies did not find a reduction in dental expense. Only when authors make assumptions and estimates of those assumptions does fluoridation look good.

Dental decay rates are similar in communities with or without fluoridation. Perhaps total exposure has risen to the point that additional fluoride from water is no longer beneficial or perhaps ingestion of fluoride does not reduce dental decay. Because decay rates are similar regardless of fluoridated water, the Board should put most emphasis on safety and cost when determining fluoridation concentration.

C. Safety Concentration:

To determine the “safe” concentration of fluoride in water:

1) Identify the most sensitive end point (adverse health effect).

a. **0.5 ppm** Fluoride in water for diabetics (Klein 1975) and 1 ppm (Seow and Thomsett 1994),

b. **1.0 ppm** Fluoride in water for Osteosarcoma (Bassin 2006[19], Sandhu 2009[20])

c. **0.7 ppm** Fluoride in water for Hip Fractures (Diesendorf 1997)[21]

d. **0.0 ppm** Even without the addition of fluoride in water, dental fluorosis, a biomarker of excess fluoride ingestion occurs in about 1 out of 5 children. That means, one in five are ingesting too much fluoride even without fluoridation. Fluoridation increases dental fluorosis risk to 1 in 3 children.

e. **0.8 ppm** finds increased risk of neurotoxicity, severe dental fluorosis, stage II skeletal fluorosis, impaired glucose metabolism, impaired thyroid function and moderate dental fluorosis. (Thiessen)

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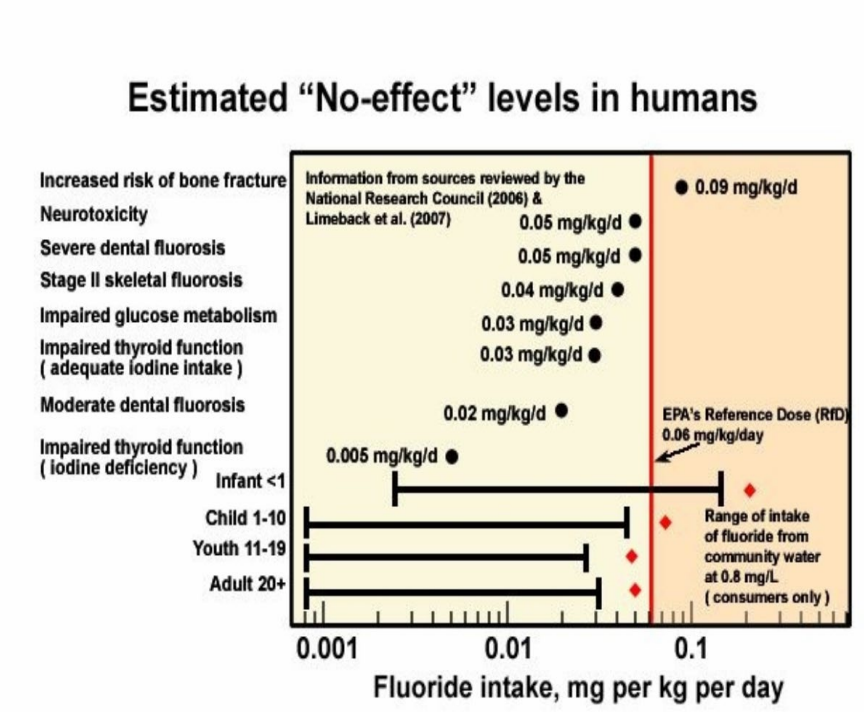
[19] Bassin E, Wypij D, Davis R, Mittleman M, Age-specific fluoride exposure in drinking water and osteosarcoma (United States), Cancer Causes Control (2006) 17:421-428.

[20] Sandhu R, Lal H, Kundu Z, Karb S, Serum Fluoride and Sialic Acid Levels in Osteosarcoma, Bio Trace Elem Res, DOI 10.1007/s12011-009-8382-1

[21] Diesendorf M, Colquhoun J, Spittle B, New Evidence on Fluoridation, Australian and New Zealand Journal of Public Health, 1997, 21 (2): 187-190



The Board must not glide over the above concentration and disease. Measured increases of disease indicate water has too much fluoride concentration and current levels are not protective for high risk individuals.

2) To protect high risk individuals, one must determine the lowest dose which causes that health effect in a human study, which is 0.5 ppm diabetes, 0.7 ppm hip fractures, 0.8 ppm neurotoxicity, severe dental fluorosis, stage II skeletal fluorosis, impaired glucose metabolism, impaired thyroid function and moderate dental fluorosis (LOAEL, lowest observed effect level often defined as an adverse alteration of morphology, function, capacity, growth, development).

3) Divide the known risk by a safety factor (usually 10) in order to cover the range of sensitivity expected in any human population. The maximum concentration of fluoride added to water should not exceed 0.05 ppm.

0.0 ppm to 0.08 ppm of fluoride is also the concentration of fluoride found in most mothers' milk.

In deference to the Board's opinion that they cannot abide by the FD&C Act, the lowest level of 0.001 ppm or 1ppb is recommended in this petition. And the upper level of 0.08 ppm or 80 ppb is recommended. Fluoridation concentration target of 0.05 ppm, in keeping with scientific evidence on total dosage, efficacy and safety.

VI. PETITION FOR WAC CHANGES: SUGGESTED WORDING

The proposed WAC changes do not affect the roughly 40 chemicals which may be added to treat water contaminants, odors, turbidity, or pathogens, in other words to make water safe and potable.

The suggested WAC changes are as follows in red and italics:

a. "WAC 246-290-460

(2) Where fluoridation is practiced, purveyors shall maintain fluoride concentrations in the range *0.001 through 0.08 mg/L* ~~0.8 through 1.3 mg/L~~ throughout the distribution system.

(3) Where fluoridation is practiced, purveyors shall take the following actions to ensure that concentrations remain at optimal levels and that fluoridation facilities and monitoring equipment are operating properly: . . . "

(iv) If a split sample is found by the certified lab to be:
(A) Not within the range *0.001 through 0.08 mg/L* ~~of 0.8 to 1.3 mg/l~~, the purveyor's fluoridation process shall be considered out of compliance.

Should the Board want additional citations, we would be pleased to provide them.

Sincerely Yours,

Bill Osmunson DDS, MPH
Washington Action for Safe Water
1418 – 112th Ave NE 200
Bellevue, WA 98004
425.455.2424

STATE OF WASHINGTON
WASHINGTON STATE BOARD OF HEALTH
PO Box 47990 • Olympia, Washington 98504-7990

November 16, 2010

Mr. William Osmunson, DDS, MPH, President
Washington Action for Safe Water
1418 – 112th Ave NE, Suite 200
Bellevue, WA 98004

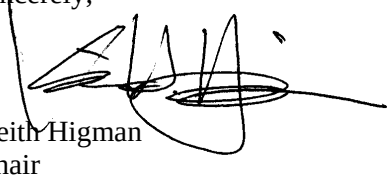
Dear Dr. Osmunson:

This letter provides formal notice that the Washington State Board of Health has denied your petition for rule making received on October 29, 2010 requesting the Board to add language to WAC 246-290-460 regarding water fluoridation. You asked the Board to require group A water systems with average fluoride concentrations above 10 part per billion (ppb) or without the ability to measure low concentrations of fluoride to include a notice in customers' bills. The notice would state: "The Washington State Board of Health finds the fluoride level in this water may contribute to lower IQ and an increase in mental retardation." This was the seventh petition for rule making you submitted to the Board this year regarding this rule.

The Board looks to the U.S. Environmental Protection Agency (EPA) for standards and recommendations regarding the safety of drinking water. EPA standards allow fluoride concentrations in water more than a hundred times greater than 10 ppb and consider the water to be safe for consumers without such an advisory statement as recommended by the petitioner. (10 ppb equals 0.01 part per million or 0.01 milligram per liter.) The rule proposal is also not supported by recommendations of the 2006 report of the Committee on Fluoride in Drinking Water, National Research Council. Although this Board is not a research agency, it believes the rule change you have requested is not consistent with the majority of scientific opinion at this time.

The Board handled your request as a petition for rule making under RCW 34.05.330 and Board Policy 2005-001, Responding to Petitions for Rule Making. The statute requires the Board to respond within 60 days of receipt. RCW 34.05.330(3) allows a person to appeal a petition's denial to the Governor within 30 days. The Board's policy allows the Board Chair to respond to a petition for rule making without the petition being placed on a meeting agenda for full Board consideration. If you have questions about this decision, please contact Craig McLaughlin, Executive Director of the Board, at 360-236-4106 or craig.mclaughlin@doh.wa.gov.

Sincerely,



Keith Higman
Chair

cc: Michelle Davis, Department of Health
Gregg Grunenfelder, Department of Health
State Board of Health Members

GERALD STEEL, PE
ATTORNEY-AT-LAW
7303 YOUNG ROAD NW
OLYMPIA, WA 98502
Tel/fax (360) 867-1166

December 28, 2012

EPA Adm. Lisa Jackson
U.S. EPA Headquarters
Ariel Rios Bldg. Mail Code 1101A
1200 Pennsylvania Ave. NW
Washington D.C. 20460

Re: Request for EPA's Official Interpretation of Status of MOU 225-79-2001 ("1979 MOU")

Dear EPA Administrator Lisa Jackson:

I am writing this letter on behalf of Washington Action for Safe Water ("WASW"), Our Water-Our Choice! (OWOC!), and Protect the Peninsula's Future ("PPF") to get the EPA's viewpoint on the 1979 MOU between EPA and FDA (MOU 225-79-2001, Federal Register of July 20, 1979 (44 FR 42775) Attachments A-1 to A-8 hereto) and the EPA's viewpoint on the EPA 1988 Notice (Federal Register of July 7, 1988 (53 FR 25586) Attachments A-9 to A-12 hereto) regarding the control of public drinking water additives. We ask two questions:

Question 1: From the viewpoint of EPA, did the 1979 MOU intend to take away from FDA, and give to EPA, responsibility for regulating public drinking water additives intended for preventative health care purposes and unrelated to contamination of public drinking water?

Question 2: If from the viewpoint of EPA, the 1979 MOU intended to take away from FDA, and give to EPA, responsibility for regulating public drinking water additives intended for preventative health care purposes and unrelated to contamination of public drinking water, did the EPA 1988 Notice terminate the 1979 MOU regarding such EPA responsibility?

Attachments A-13 to A-17 provide my analysis relevant to Question 1 and Attachments A-18 to A-19 provide my analysis relevant to Question 2.

We are sorry to hear reports that you will be leaving the EPA in January, 2013.[1] We ask that our questions be answered before you leave, if possible.

Respectfully,

Gerald Steel, WSBA #31084
Attorney for WASW, OWOC!, & PPF

Attachments: A-1 to A-19

[1] http://www.latimes.com/news/nationworld/nation/la-na-epa-jackson-20121228,0,4172552.story

Federal facilities. Prior to making a final recommendation to the Administrator, U.S. EPA, the Regional Administrator, Region V, is providing opportunity for public comment on the State of Wisconsin request. Any interested person may comment upon the State request by writing to the U.S. EPA, Region V Office, 230 South Dearborn Street, Chicago, Illinois 60604. Attention: Permit Branch. Such comments will be made available to the public for inspection and copying. All comments or objections received by August 22, 1979, will be considered by U.S. EPA before taking final action on the Wisconsin request for authority to issue permits to Federal facilities.

The State's request, related documents, and all comments received are on file and may be inspected and copied (@ 20 cents/page) at the U.S. EPA, Region V Office, in Chicago.

Copies of this notice are available upon request from the Enforcement Division of U.S. EPA, Region V, by contacting Dorothy A. Price, Public Notice Clerk (312–353–2105), at the above address.

Dated: July 13, 1979.

John McGuire,

Regional Administrator.

[FR Doc. 79–22872 Filed 7–19–79; 8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

ENVIRONMENTAL PROTECTION AGENCY

[FRL 1275–4]

Drinking Water Technical Assistance; Implementation Plan for Control of Direct and Indirect Additives to Drinking Water and Memorandum of Understanding Between the Environmental Protection Agency and the Food and Drug Administration

AGENCY: Environmental Protection Agency and Food Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) have executed a memorandum of understanding (MOU) with regard to the control of direct and indirect additives to and substances in drinking water. The purpose of the MOU is to avoid the possibility of overlapping jurisdiction between EPA and FDA with respect to control of drinking water additives. The agreement became effective on June 22, 1979.

ADDRESS: Submit comments to: Victor J. Kimm, Deputy Assistant Administrator for Drinking Water, Environmental Protection Agency (WH–550), Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: David W. Schnare, Ph.D., Office of Drinking Water (WH–550), Environmental Protection Agency, Washington, D.C. 20460, (202) 755–5643; or Gary Dykstra, Enforcement Policy Staff (HFC–22), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, (301) 443–3470.

SUPPLEMENTARY INFORMATION: In the spirit of interagency cooperation and to avoid the possibility of overlapping jurisdiction over additives and other substances in drinking water, FDA and EPA have entered into a memorandum of understanding to avoid duplicatve and inconsistent regulation. In brief, the memorandum provides that EPA will have primary responsibility over direct and indirect additives and other substances in drinking water under the Safe Drinking Water Act, the Toxic Substances Control Act, and the Federal Insecticide, Fungicide and Rodenticide Act. FDA will have responsibility for water, and substances in water, used in food and for food processing and for bottled water under the Federal Food, Drug and Cosmetic Act.

Pursuant to the notice published in the Federal Register of October 3, 1974, (39 FR 35697) stating that future memoranda of understanding, and agreements between FDA and others would be published in the Federal Register, the following memorandum of understanding is issued:

Memorandum of Understanding Between the Environmental Protection Agency and the Food and Drug Administration

I. Purpose

This Memorandum of Understanding establishes an agreement between the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) with regard to the control of direct and indirect additives to and substances in drinking water.

EPA and FDA agree:

(1) That contamination of drinking water from the use and application of direct and indirect additives and other substances poses a potential public health problem;

(2) That the scope of the additives problem in terms of the health significance of these contaminants in drinking water is not fully known;

(3) That the possibility of overlapping jurisdiction between EPA and FDA with respect to control of drinking water additives has been the subject of Congressional as well as public concern;

(4) That the authority to control the use and application of direct and indirect additives to and substances in drinking water should be vested in a single regulatory agency to avoid duplicative and inconsistent regulation;

(5) That EPA has been mandated by Congress under the Safe Drinking Water Act (SDWA), as amended, to assure that the public is provided with safe drinking water;

(6) That EPA has been mandated by Congress under the Toxic Substances Control Act (TSCA) to protect against unreasonable risks to health and the environment from toxic substances by requiring, *inter alia*, testing and necessary restrictions on the use, manufacture, processing, distribution, and disposal of chemical substances and mixtures;

(7) That EPA has been mandated by Congress under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, to assure, *inter alia*, that when used properly, pesticides will perform their intended function without causing unreasonable adverse effects on the environment; and,

(8) That FDA has been mandated by Congress under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended, to protect the public from, *inter alia*, the adulteration of food by food additives and poisonous and deleterious substances.

It is the intent of the parties that;

(1) EPA will have responsibility for direct and indirect additives to and other substances in drinking water under the SDWA, TSCA, and FIFRA; and,

(2) FDA will have responsibility for water, and substances in water, used in food and for food processing and responsibility for bottled drinking water under the FFDCA.

II. Background

(A) *FDA Legal Authority.* "Food" means articles used for food or drink for man or other animals and components of such articles. [FFDCA § 201(f)]. Under Section 402, *inter alia*, a food may not contain any added poisonous or deleterious substance that may render it injurious to health, or be prepared, packed or handled under unsanitary conditions. Tolerances may be set, under Section 403, limiting the quantity of any substance which is required for the production of food or cannot be avoided in food. FDA has the authority under Section 409 to issue food additive regulations approving, with or without conditions, or denying the use of a "food additive." That term is defined in Section 201(s) to include any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, if such substance is not generally recognized as safe.

In the past, FDA has considered drinking water to be a food under Section 201(f). However, both parties have determined that the passage of the SDWA in 1974 implicitly repealed FDA's authority under the FFDCA over water used for drinking water purposes. Under the express provisions of Section 410

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of the FFDCA, FDA retains authority over bottled drinking water. Furthermore, all water used in food remains a food and subject to the provisions of the FFDCA. Water used for food processing is subject to applicable provisions of FFDCA. Moreover, all substances in water used in food are added substances subject to the provisions of the FFDCA, but no substances added to a public drinking water system before the water enters a food processing establishment will be considered a food additive.

(B). *EPA Legal Authority.* The SDWA grants EPA the authority to control contaminants in drinking water which may have any adverse effect on the public health, through the establishment of maximum contaminant levels (MCLs) or treatment techniques, under Section 1412, which are applicable to owners and operators of public water systems. The expressed intent of the Act was to give EPA exclusive control over the safety of public water supplies. Public water systems may also be required by regulation to conduct monitoring for unregulated contaminants under Section 1445 and to issue public notification of such levels under Section 1414(c).

EPA's direct authority to control additives to drinking water apart from the existence of maximum contaminant levels or treatment techniques is limited to its emergency powers under Section 1431. However, Section 1442(b) of the act authorizes EPA to "collect and make available information pertaining to research, investigations, and demonstrations with respect to providing a dependably safe supply of drinking water together with appropriate recommendations therewith."

TSCA gives EPA authority to regulate chemical substances, mixtures and under some circumstances, articles containing such substances or mixtures. Section 4 permits EPA to require testing of a chemical substance or mixture based on possible unreasonable risk of injury to health or the environment, or on significant or substantial human or environmental exposure while Section 8 enables EPA to require submission of data showing substantial risk of injury to health or the environment, existing health and safety studies, and other data. For new chemical substances, and significant new uses of existing chemical substances, Section 5 requires manufacturers to provide EPA with premanufacturing notice. Under Section 6 the manufacture, processing, distribution, use, and disposal of a chemical substance or mixture determined to be harmful may be restricted or banned. Although Section 3(2)(B) of TSCA excludes from the definition of "chemical substance" food and food additives as defined under FFDCA, the implicit repeal by the SDWA of FDA's authority over drinking water enables EPA to regulate direct and indirect additives to drinking water as chemical substances and mixtures under TSCA.

The FIFRA requires EPA to set restrictions on the use of pesticides to assure that when used properly, they will not cause unreasonable adverse effects on the environment. EPA may require, *inter alia*, labeling which specifies how, when, and where a pesticide may be legally used. In addition, EPA has, under Section 409 of the FFDCA, required FIFRA registrants at times to obtain a food additive tolerance before using a pesticide in or around a drinking water source. Such tolerances establish further restrictions on the use of a pesticide which are enforceable against the water supplier as well as the registrant of the pesticide.

III. Terms of Agreement

(A) EPA's responsibilities are as follows:

(1) To establish appropriate regulations, and to take appropriate measures, under the SDWA and/or TSCA, and FIFRA, to control direct additives to drinking water (which encompass any substances purposely added to the water), and indirect additives (which encompass any substances which might leach from paints, coatings or other materials as an incidental result of drinking water contact), and other substances.

(2) To establish appropriate regulations under the SDWA to limit the concentrations of pesticides in drinking water; the limitations on concentrations and types of pesticides in water are presently set by EPA through tolerances under Section 409 of the FFDCA.

(3) To continue to provide technical assistance in the form of informal advisory opinions on drinking water additives under Section 1442(b) of the SDWA.

(4) To conduct and require research and monitoring and the submission of data relative to the problem of direct and indirect additives in drinking water in order to accumulate data concerning the health risks posed by the presence of these contaminants in drinking water.

(B). FDA's responsibilities are as follows:

(1) To take appropriate regulatory action under the authority of the FFDCA to control bottled drinking water and water, and substances in water, used in food and for food processing.

(2) To provide assistance to EPA to facilitate the transition of responsibilities, including:

(a) To review existing FDA approvals in order to identify their applicability to additives in drinking water.

(b) To provide a mutually agreed upon level of assistance in conducting literature searches related to toxicological decision making.

(c) To provide a senior toxicologist to help EPA devise new procedures and protocols to be used in formulating advice on direct and indirect additives to drinking water.

IV. Duration of Agreement

This Memorandum of Understanding shall continue in effect unless modified by mutual consent of both parties or terminated by either party upon thirty (30) days advance written notice to the other.

This Memorandum of Understanding will become effective on the date of the last signature.

Dated: June 13, 1979.

Douglas M. Costle,

Administrator, Environmental Protection Agency.

Dated: June 22, 1979.

Donald Kennedy,

Administrator, Food and Drug Administration.

Implementation Plan

EPA is concerned that direct and indirect additives may be adding harmful trace chemical contaminants into our Nation's drinking water during treatment, storage and distribution. Direct additives include such chemicals as chlorine, lime, alum, and coagulant aides, which are added at the water treatment plant. Although these chemicals themselves may be harmless, they may contain small amounts of harmful chemicals if their quality is not controlled. Indirect additives include those contaminants which enter drinking water through leaching, from pipes, tanks and other equipment, and their associated paints and coatings. This notice is being published in the Federal Register to solicit public comment on EPA's implementation plan to assess and control direct and indirect additives in drinking water.

Legal Authorities

EPA and the Food and Drug Administration (FDA) signed a Memorandum of Understanding which recognizes that regulatory control over direct and indirect additives in drinking water is placed in EPA. The two agencies agreed that the Safe Drinking Water Act's passage in 1974 implicitly repealed FDA's jurisdiction over drinking water as a 'food' under the Federal Food, Drug and Cosmetic Act (FFDCA). Under the agreement, EPA now retains exclusive jurisdiction over drinking water served by public water supplies, including any additives in such water. FDA retains jurisdiction over bottled drinking water under Section 410 of the FFDCA and over water (and substances in water) used in food or food processing once it enters the food processing establishment.

In implementing its new responsibilities, EPA may utilize a variety of statutory authorities, as appropriate. The authorities are identified in Appendix A.

Under the Safe Drinking Water Act, EPA has authority to set and enforce maximum contaminant levels and treatment techniques in drinking water for ubiquitous contaminants, to conduct research, to offer technical assistance to States and to protect against imminent

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hazards should such situations arise. Under the Toxic Substances Control Act, EPA has authority to review all new chemicals proposed for use related to drinking water, to mandate toxicological testing of existing and new chemicals where there is evidence that such materials may pose an unreasonable risk to health and the environment as well as authority to limit some or all uses of harmful chemicals. Pesticide use is regulated by EPA under the Federal Insecticide, Fungicide and Rodenticide Act. Thus, EPA believes it has adequate authority to deal with additives to drinking water where they may pose a problem.

Past Actions

For more than ten years, the Public Health Service and other organizations which have become part of EPA have provided advisory opinions on the toxicological safety of a variety of additives to drinking water. These historical informal opinions reflect a variety of information provided by manufacturers and reflect changing toxicological concerns over the years. As such, they will require detailed review over the next few years.

General Approach

EPA intends to begin its responsibility over additives to drinking water with a series of analytical studies to determine the composition and significance of the health risks posed by contaminants related to direct and indirect additives to drinking water. A first step in this process will be monitoring studies of the contaminants actually getting into drinking water from generic categories of additives like bulk chemicals, paints and coatings, pipes and equipment.

In the initial six to twelve months, EPA will develop interim administrative procedures, testing protocols, and decision criteria for future toxicological advisories to the States. These will be distributed for public comment once they are developed. All existing opinions will remain in effect until a general review of past opinions can be undertaken using the new procedures. During this development phase, no new opinions will be rendered unless a proposed product can be shown to be virtually identical to a product for which an opinion has already been rendered, on the basis of chemical formulation and production process. New products or new uses of existing products which are proposed for use in drinking water will be subject to the pre-manufacture notice procedures of TSCA.

A more detailed outline of the steps to be taken by EPA follows.

1. *Problem Definition.*—EPA will contract for *in situ* monitoring to determine use patterns and the contribution of trace contaminants to drinking water from:

a. bulk chemicals.

b. generic classes of paints and coatings.

c. pipes and equipment.

d. coagulant aids.

EPA has already contracted with the National Academy of Sciences to develop a CODEX system of quality control standards for chemicals (direct additives) used in the treatment of drinking water. This effort will take about three years to complete. When finished, the CODEX system, modeled on the existing FDA-inspired CODEX system for chemicals used in processing food, will be largely self-enforcing.

For the indirect additives listed in items b and c above, considerable effort will be expended to identify the trace contaminants involved before the related health risks can be fully evaluated and appropriate recommendations for future use can be assessed.

2. *Review of Past Advisories.*—The same data base derived from *in situ* monitoring will serve as a basis for a structured reassessment of past toxicological advisories which will be conducted by generic classes of use e.g., paints, coagulant aides, etc. Past opinions will be reviewed to insure conformance with and satisfaction of new test protocols and decision criteria that will be developed.

3. *Future Toxicological Advisories.*—Once initial procedures, test protocols and decision criteria are developed, EPA will resume offering toxicological opinions to the States.

General Policy

In assessing additives to drinking water, EPA will be guided by a policy of reducing public health risks to the degree it is feasible to do so. In such determinations, EPA will evaluate the risks and benefits associated with the materials of concern and their substitutes. Economic impacts of agency actions will also be analyzed.

Notwithstanding these procedures, EPA would use its authorities to protect against any direct or indirect additive to drinking water when data and information indicate that the use of any additive may pose an undue risk to public health.

Implementation

To fulfill this program, resources from the Office of Drinking Water, the Office of Research and Development, and the Office of Toxic Substances will be used. In addition, EPA looks forward to the cooperation of FDA and other Federal regulatory bodies. EPA intends to involve interested industry groups, independent testing groups, State regulatory bodies, interested members of the public, and industry standards groups, in a continued effort to ensure the safety of the Nation's drinking water.

Finally, EPA may recommend specialized legislative authority to regulate additives to drinking water should a situation arise for which legal authorities prove inadequate.

Lead responsibility for this new Federal initiative will be in EPA's Office of Drinking Water. Public comments on any or all aspects of the proposed program are requested, and should be directed to the address given in the opening sections of this notice.

Dated: July 13, 1979.

Thomas C. Jorling,

Assistant Administrator for Water and Waste Management.

Appendix A

Safe Drinking Water Act

Section 1412—establishment of national primary drinking water regulations applicable to public water systems to control contaminants in drinking water which may have any adverse effect on human health. This may include maximum contaminant levels, treatment techniques, monitoring requirements, and quality control and testing procedures.

Section 1431—use of emergency powers where a contaminant which is present in water, or is likely to enter a public water system, may present an imminent and substantial endangerment to the health of persons.

Section 1445—establishment of monitoring and reporting requirements applicable to public water systems.

Section 1450—authority to prescribe such regulations as are necessary or appropriate to carry out the Administrator's functions under the Act.

Toxic Substances Control Act

Section 4—testing of chemical substances and mixtures.

Section 5—pre-manufacture notice required for new chemicals or significant new uses.

Section 6—regulation of hazardous chemical substances and mixtures which pose an unreasonable risk of injury to health or the environment, including restrictions on manufacture, processing, distribution, and use.

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Section 7—imminent hazards authority including seizure and other relief through civil court action.

Section 8—reporting and retention of information as required by the Administrator, including health and safety studies and notice to the Administrator of substantial risks.

Section 10—research and development. Development of systems for storing, retrieving and disseminating data.

Section 11—inspections and subpenas and other enforcement and general administration provisions therein.

Federal Insecticide, Fungicide and Rodenticide Act

Section 3—registration of pesticides, including imposition of restrictions and labeling requirements.

Section 6—suspension and cancellation procedures.

[FR Doc. 79-22222 Filed 7-18-79; 8:45 am]

BILLING CODE 6560-01-M

BILLING CODE 4110-03-M

FEDERAL COMMUNICATIONS COMMISSION

[Report No. A-1a]

FM Broadcasting Applications Accepted for Filing and Notification of Cut-off Date; Erratum

Released: July 12, 1979.

The FM Application listed below was inadvertently included on the acceptance/cut-off notice, Report No. A-1, BC Mimeo No. 18676, released on June 25, 1979.

BPH-790108AE (New): Creston, Pennsylvania, Sherlock-Hart Broadcasting, Inc.
Req.: 94.3 MHz, Channel 232A.
ERP: 0.600 kW, HAAT: 600 feet.

Accordingly, the application is removed from the acceptance/cutoff list and the August 8, 1979, cutoff date is deleted.

Federal Communications Commission.

William J. Tricarico,

Secretary.

[FR Doc. 79-22423 Filed 7-19-79; 8:45 am]

BILLING CODE 6712-01-M

FEDERAL LABOR RELATIONS AUTHORITY

Official Time of Employees Involved in Negotiating Collective Bargaining Agreements

AGENCY: Federal Labor Relations Authority.

ACTION: Notice Relating to Official Time.

SUMMARY: This notice principally relates to the interpretation of section 7131 of the Federal Service Labor-Management Relations Statute (92 Stat. 1214) on the questions of whether employees who are on official time under this section while representing an exclusive representative in the negotiation of a collective bargaining agreement are entitled to payments from agencies for their travel and per diem expenses, and whether the official time provisions of section 7131(a) of the Statute encompass all negotiations between an exclusive representative and an agency, regardless of whether such negotiations pertain to the negotiation or renegotiation of a basic collective bargaining agreement. The notice further invites interested persons to address the impact, if any, of section 7135(a)(1) of the Statute (92 Stat. 1215) on such interpretation, and to submit written comments concerning these matters.

DATE: Written comments must be submitted by the close of business on August 24, 1979, to be considered.

ADDRESS: Send written comments to the Federal Labor Relations Authority, 1900 E Street, NW., Washington, D.C. 20424.

FOR FURTHER INFORMATION CONTACT: Harold D. Kessler, Deputy Executive Director, 1900 E Street, NW., Washington, D.C. 20424, (202) 632-3924.

SUPPLEMENTARY INFORMATION: The Federal Labor Relations Authority was established by Reorganization Plan No. 2 of 1978, effective January 1, 1979 (43 FR 36037). Since January 11, 1979, the Authority has conducted its operations under the Federal Service Labor-Management Relations Statute (92 Stat. 1191).

Upon receipt of requests and consideration thereof, the Authority has determined, in accordance with 5 CFR 2410.3(a) (1978) and sections 7105 and 7135(b) of the Statute (92 Stat. 1196, 1215), that an interpretation is warranted concerning section 7131 of the Statute (92 Stat. 1214). Interested persons are invited to express their views in writing on this matter, as more fully explained in the Authority's notice set forth below:

To Heads of Agencies, Presidents of Labor Organizations and Other Interested Persons

The Authority has received a request from the American Federation of Government Employees (AFGE) for a statement of policy and guidance concerning whether employees representing an exclusive representative in the negotiation of a collective bargaining agreement are entitled to payments from agencies for their travel and per diem expenses under the official time provisions of section 7131 of the Federal Service Labor-Management Relations Statute (92 Stat. 1214). Additionally, the National Federation of Federal Employees (NFFE) has requested a major policy statement as to the application of the official time provisions of section 7131(a) of the Statute (92 Stat. 1214) to all negotiations between an exclusive representative and an agency, regardless of whether such negotiations pertain to the negotiation or renegotiation of a basic collective bargaining agreement. AFGE has raised a similar issue in its request.

The Authority hereby determines, in conformity with 5 CFR 2410.3(a) (1978) and section 7135(b) of the Statute (92 Stat. 1215), as well as section 7105 of the Statute (92 Stat. 1196), that an interpretation of the Statute is warranted on the following:

(1) Whether employees who are on official time under section 7131 of the Statute while representing an exclusive representative in the negotiation of a collective bargaining agreement are entitled to payments from agencies for their travel and per diem expenses.

(2) Whether the official time provisions of section 7131(a) of the Statute encompass all negotiations between an exclusive representative and an agency, regardless of whether such negotiations pertain to the negotiation or renegotiation of a basic collective bargaining agreement.

Before issuing an interpretation on the above, the Authority, pursuant to 5 CFR 2410.6 (1978) and section 7135(b) of the Statute (92 Stat. 1215), solicits your views in writing. You are further invited to address the impact, if any, of section 7135(a)(1) of the Statute (92 Stat. 1215) on the above matters and to submit your views as to whether oral argument should be granted. To receive consideration, such views must be submitted to the Authority by the close of business on August 24, 1979.

Issued, Washington, D.C., July 13, 1979.

Federal Labor Relations Authority.

Ronald W. Haughton,

Chairman.

Henry B. Frazier III,

Member.

[FR Doc. 79-22447 Filed 7-19-79; 8:45 am]

BILLING CODE 6325-01-M

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MOU number: 225-79-2001

Memorandum of Understanding

Between
The Environmental Protection Agency

and

The Food and Drug Administration

I. Purpose:

This Memorandum of Understanding establishes an agreement between the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) with regard to the control of direct and indirect additives to and substances in drinking water.

EPA and FDA agree:

A. That contamination of drinking water from the use and application of direct and indirect additives and other substances poses a potential public health problem;

B. That the scope of the additives problem in terms of the health significance of these contaminants in drinking water is not fully known;

C. That the possibility of overlapping jurisdiction between EPA and FDA with respect to control of drinking water additives has been the subject of Congressional as well as public concern;

D. That the authority to control the use and application of direct and indirect additives to and substances in drinking water should be vested in a single regulatory agency to avoid duplicative and inconsistent regulation;

E. That EPA has been mandated by Congress under the Safe Drinking Water Act (SDWA), as amended, to assure that the public is provided with safe drinking water;

F. That EPA has been mandated by Congress under the Toxic Substances Control Act (TSCA) to protect against unreasonable risks to health and the environment from toxic substances by requiring, inter alia, testing and necessary restrictions on the use, manufacture, processing, distribution, and disposal of chemical substances and mixtures;

G. That EPA has been mandated by Congress under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, to assure, inter alia, that when used properly, pesticides will perform their intended function without causing unreasonable adverse effects on the environment; and,

H. That FDA has been mandated by Congress under the Federal Food, Drug, and

Cosmetic Act (FFDCA), as amended, to protect the public from, inter alia, the adulteration of food by food additives and poisonous and deleterious substances.

It is the intent of the parties that:

A. EPA will have responsibility for direct and indirect additives to and other substances in drinking water under the SDWA, TSCA, and FIFRA; and,

B. FDA will have responsibility for water, and substances in water, used in food and for food processing and responsibility for bottled drinking water under the FFDCA.

II. Background:

A. FDA Legal Authority

"Food" means articles used for food or drink for man or other animals and components of such articles. (FFDCA Section 201(f)). Under Section 402, inter alia, a food may not contain any added poisonous or deleterious substance that may render it injurious to health, or be prepared, packed or handled under unsanitary conditions. Tolerances may be set, under Section 406, limiting the quantity of any substance which is required for the production of food or cannot be avoided in food. FDA has the authority under Section 409 to issue food additive regulations approving, with or without conditions, or denying the use of a "food additive." That term is defined in Section 201(s) to include any substance the intended use of which results or may reasonable be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, if such substance is not generally recognized as safe.

In the past, FDA has considered drinking water to be a food under Section 201(f). However, both parties have determined that the passage of the SDWA in 1974 implicitly repealed FDA's authority under the FFDCA over water used for drinking water purposes. Under the express provisions of Section 410 of the FFDCA, FDA retains authority over bottled drinking water. Furthermore, all water used in food remains a food and subject to the provisions of the FFDCA. Water used for food processing is subject to applicable provisions of FFDCA. Moreover, all substances in water used in food are added substances subject to the provisions of the FFDCA, but no substances added to a public drinking water system before the water enters a food processing establishment will be considered a food additive.

B. EPA Legal Authority

The SDWA grants EPA the authority to control contaminants in drinking water which may have any adverse effect on the public health, through the establishment of maximum contaminant levels (MCLs) or treatment techniques, under Section 1412, which are applicable to owners and operators of public water systems. The expressed intent of the Act was to give EPA exclusive control over the safety of public water supplies. Public water systems may also be required by regulation to conduct monitoring for unregulated contaminants under Section 1445 and to issue public notification of such levels under Section 1414(c).

EPA's direct authority to control additives to drinking water apart from the existence of maximum contaminant levels or treatment techniques is limited to its emergency powers under Section 1431. However, Section 1442(b) of the Act authorizes EPA to "collect and make available information pertaining to research, investigations, and demonstrations with respect to providing a dependably safe supply of drinking water together with appropriate recommendations therewith."

TSCA gives EPA authority to regulate chemical substances, mixtures and under some circumstances, articles containing such substances or mixtures. Section 4 permits EPA

to require testing of a chemical substance or mixture based on possible unreasonable risk of injury to health or the environment, or on significant or substantial human or environmental exposure while Section 8 enables EPA to require submission of data showing substantial risk of injury to health or the environment, existing health and safety studies, and other data. For new chemical substances, and significant new uses of existing chemical substances, Section 5 requires manufacturers to provide EPA with pre-manufacturing notice. Under Section 6 the manufacture, processing, distribution, use, and disposal of a chemical substance or mixture determined to be harmful may be restricted or banned. Although Section 3(2)(B) of TSCA excludes from the definition of "chemical substance" food and food additives as defined under FFDCA, the implicit repeal by the SDWA of FDA's authority over drinking water enables EPA to regulate direct and indirect additives to drinking water as chemical substances and mixtures under TSCA.

The FIFRA requires EPA to set restrictions on the use of pesticides to assure that when used properly, they will not cause unreasonable adverse effects on the environment. EPA may require, inter alia labeling which specifies how, when, and where a pesticide may be legally used. In addition, EPA has, under Section 409 of the FFDCA, required FIFRA registrants at times to obtain a food additive tolerance before using a pesticide in or around a drinking water source. Such tolerances establish further restrictions on the use of a pesticide which are enforceable against the water supplier as well as the registrant of the pesticide.

III. Terms of Agreement:

A. EPA's responsibilities are as follows:

1. To establish appropriate regulations, and to take appropriate measures, under the SDWA and/or TSCA, and FIFRA, to control direct additives to drinking water (which encompass any substances purposely added to the water), and indirect additives (which encompass any substance which might leach from paints, coatings or other materials as an incidental result of drinking water contact), and other substances.

2. To establish appropriate regulations under the SDWA to limit the concentrations of pesticides in drinking water; the limitations on concentrations and types of pesticides in water are presently set by EPA through tolerances under Section 409 of the FFDCA.

3. To continue to provide technical assistance in the form of informal advisory opinions on drinking water additives under Section 1442(b) of the SDWA.

4. To conduct and require research and monitoring and the submission of data relative to the problem of direct and indirect additives in drinking water in order to accumulate data concerning the health risks posed by the presence of these contaminants in drinking water.

B. FDA's responsibilities are as follows:

1. To take appropriate regulatory action under the authority of the FFDCA to control bottled drinking water and water, and substances in water, used in food and for food processing.

2. To provide assistance to EPA to facilitate the transition of responsibilities, including:

a) To review existing FDA approvals in order to identify their applicability to additives in drinking water.

b) To provide a mutually agreed upon level of assistance in conducting literature searches related to toxicological decision making.

c) To provide a senior toxicologist to help EPA devise new procedures and protocols to be used in formulating advice on direct and indirect additives to drinking water.

IV. Duration of Agreement:

This Memorandum of Understanding shall continue in effect unless modified by mutual consent of both parties or terminated by either party upon thirty (30) days advance written notice to the other.

This Memorandum of Understanding will become effective on the date of the last signature.

Approved and Accepted for the Environmental Protection Agency

Signed by: Douglas P. Costle
Administrator
Environmental Protection Agency

Date: June 12, 1979

Approved and Accepted for the Food and Drug Administration

Signed by: Donald Kennedy
Administrator
Food and Drug Administration

Date: June 22, 1979

Domestic MOUs

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ENVIRONMENTAL PROTECTION AGENCY

[OW-FRL-3410-1]

Drinking Water Technical Assistance; Termination of the Federal Drinking Water Additives Program

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA), Office of Drinking Water (ODW), has operated an advisory program that gives technical assistance to concerned parties on the use of drinking water additives. On May 17, 1984, EPA proposed to terminate major elements of this Federal program and to assist in the establishment of a private-sector program which would offer assistance in evaluating drinking water additives. 49 FR 21004. EPA solicited proposals from qualified nongovernmental, nonprofit organizations for assistance under a cooperative agreement to establish a credible and efficient program in the private sector.

On September 17, 1985, EPA selected a consortium consisting of the National Sanitation Foundation (NSF), the American Water Works Association Research Foundation (AWWARF), the Conference of State Health and Environmental Managers (COSHEM), and the Association of State Drinking Water Administrators (ASDWA) to receive funds under a cooperative agreement to develop the private-sector program. EPA believes that the NSF-led program has proceeded satisfactorily. NSF Standard 60, covering many direct additives, was adopted on December 7, 1987; and NSF Standard 61, covering indirect additives, was adopted on June 3, 1988. Other standards are forthcoming. The NSF-led program has begun offering testing, certification, and listing services, as described in 49 FR 21004, for certain classes of products covered by these standards. Accordingly, as the NSF-led program becomes operational, EPA will phase out its activities in this area, as described in this notice.

DATE: Any written comments on implementing this notice should be submitted to the address below by September 6, 1988.

ADDRESSES: Submit comments to: Mr. Arthur H. Perler, Chief, Science and Technology Branch, Office of Drinking Water (WH-550D), U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460. A copy of all comments will be available for review during normal business hours at the U.S. Environmental Protection Agency, Criteria and Standards Division, Science and Technology Branch, Room 931ET, 401 M Street, SW., Washington, DC 20460. For further information on the NSF-led private-sector program, including standards development and testing, certification, and listing services, contact: Director, Drinking Water Additives Program, National Sanitation Foundation, P.O. Box 1468, Ann Arbor, MI 48106; or call (313) 769-8010. For information on alternative testing, certification, and listing programs, contact individual State regulatory authorities or the American Water Works Association, Technical and Professional Department, 6666 Quincy Avenue, Denver CO, 80235, or call (303) 794-7711. For information on the directory of products certified as meeting the criteria in a NSF standard, contact the American Water Works Association Research Foundation, 6666 Quincy Avenue, Denver CO, 80235, or call (303) 794-7711.

FOR FURTHER INFORMATION CONTACT: Mr. Arthur H. Perler, Chief, Science and Technology Branch, Office of Drinking Water (WH-550D), U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460, or call (202) 382-2022.

I. Introduction

The Safe Drinking Water Act (SDWA) (42 U.S.C. 300f *et seq.*) provides for enhancement of the safety of public drinking water supplies through the establishment and enforcement of national drinking water regulations. The Environmental Protection Agency (EPA) has the primary responsibility for establishing the regulations, and the States have the primary responsibility for enforcing such regulations. The regulations control contaminants in drinking water which may have any adverse effect on public health. Section 1412, 42 U.S.C. 300g-1. The regulations include maximum contaminant levels (MCLs) or treatment techniques and monitoring requirements for these contaminants. Sections 1401 and 1412; 42 U.S.C. 300f and 300g-1. EPA also promulgates monitoring requirements for unregulated contaminants. Section 1445; 42 U.S.C. 300j-4. In addition, EPA has broad authorities to provide technical assistance and financial assistance (e.g., grants, cooperative agreements) to States and to conduct research. Sections 1442, 1443, 1444; 42 U.S.C. 300j-1, 300j-2, 300j-3.

The Agency has established MCLs for a number of harmful contaminants that occur naturally or pollute public drinking water supplies. In addition to such contaminants, there is a possibility that drinking water supplies may be contaminated by compounds "added" to drinking water, either directly or indirectly, in the course of treatment and transport of drinking water. Public water systems use a broad range of chemical products to treat water supplies and to maintain storage and distribution systems. For instance, systems may directly add chemicals such as chlorine, alum, lime, and coagulant aids in the process of treating water to make it suitable for public consumption. These are known as "direct additives." In addition, as a necessary function of maintaining a public water system, storage and distribution systems (including pipes, tanks, and other equipment) may be fabricated from or painted, coated, or treated with products which may leach into or otherwise enter the water. These products are known as "indirect additives." Except to the extent that direct or indirect additives consist of ingredients or contain contaminants for which EPA has promulgated MCLs, EPA does not currently regulate the levels of additives in drinking water.

In 1979, EPA executed a Memorandum of Understanding (MOU) with the U.S. Food and Drug Administration (FDA) to establish and clarify areas of authorities with respect to control of additives in drinking water. 44 FR 42775, July 20, 1979. FDA is authorized to regulate "food additives" pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA). (21 U.S.C. 301 *et seq.*). Both agencies acknowledged in the MOU that "passage of the SDWA in 1974 repealed FDA's authority under the FFDCA over water used for drinking water purposes." The MOU stated that FDA would continue to have authority for taking regulatory action under the FFDCA to control additives in bottled drinking water and in water used in food and for food processing. The MOU went on to say that EPA had authority to control additives in public drinking water supplies.

While the SDWA does not require EPA to control the use of specific additives in drinking water, EPA has provided technical assistance to States and public water systems on the use of additives through the issuance of advisory opinions on the acceptability of many additive products. EPA has provided this technical assistance pursuant to its discretionary authority in section 1442(b)(1) to "collect and make available information pertaining to research, investigations and demonstrations with respect to

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providing a dependable safe supply of drinking water together with appropriate recommendations in connection therewith." EPA has additional authorities under the Toxic Substances Control Act (TSCA) (15 U.S.C. 2601 *et seq.*) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136 *et seq.*) that could be used to control additives in drinking water. TSCA authorizes EPA to regulate a new chemical substance before it is manufactured or any existing chemical substance before it is manufactured or processed for a use that EPA has determined to be a "significant new use." Although an additive product might come within the jurisdiction of TSCA, EPA has never invoked this authority. EPA has used its authority under FIFRA to control the use of pesticides, disinfectants, and certain other additives. For a more complete discussion of these authorities, see the MOU. 44 FR 42776.

In 1980, EPA declared a moratorium on the issuance of new advisory opinions on additives pending a review of past advisory opinions and the establishment of uniform test protocols and decision criteria. However, between 1980 and 1984, EPA continued to issue advisory opinions in cases where the new additive products were virtually identical to products previously reviewed. Resource constraints and the need to implement mandatory provisions of the SDWA precluded the Agency from implementing the comprehensive program originally envisioned for the issuance of additives advisory opinions. Thus, the Agency was not able to review the technical data supporting previous submissions (approximately 2,300 products from 525 manufacturers) nor was it able to develop test protocols or decision criteria for the consistent evaluation of new products. The result has been long delays in processing manufacturer petitions, inability to review and accept completely new products, and acceptance of products simply because they were virtually identical to older products. Hence, few products have been thoroughly evaluated for the safety of their formulations based on the latest scientific information.

Recognizing the need for continuing technical assistance in evaluating additive products and for providing advice to States and public water systems on the toxicological aspects of additive products, the Agency proposed to terminate its attempts to institute a formal advisory program, and to solicit proposals from nongovernmental, nonprofit organizations to establish such a program in the private sector. The Agency believed that the proposal to assist in the establishment of a private-sector program was consistent with, and would best serve the goals of, the SDWA.

On May 17, 1984, EPA formally announced its intention to transfer the program to the private sector, which would function as to many other voluntary product-standard programs. 49 FR 21004. This was accomplished by requesting proposals from qualified organizations or consortia of organizations for the competitive award of a cooperative agreement designed to provide incentive for the establishment of a private-sector program. The 1984 notice stated that:

- EPA expected the activity to be self-supporting.
- EPA would maintain an active interest in the development of the program, without assuming responsibility for or directing its approach.
- EPA would continue to establish regulations under the SDWA, FIFRA, and/or TSCA, as needed, for chemicals in treated, distributed drinking water that may originate as additives.
- Establishment of such a program would be consistent with the Administration's initiatives in the area of regulatory reform and offered an opportunity for an innovative alternative to regulation.

The May 1984 notice requested public comments on the proposal and solicited applications from qualified nongovernmental, nonprofit organizations for partial funding of the developmental phase of the program under a cooperative agreement. The response to the solicitation for comments indicated strong public support for the proposed approach. EPA received 108 public comments on the proposal. All but six supported this "third-party" approach. However, despite the Agency's open competition, EPA received only one application for financial assistance. The applicant was a consortium, led by the National Sanitation Foundation, which included the American Water Works Association Research Foundation, the Conference of State Health and Environmental Managers, and the Association of State Drinking Water Administrators. This single proposal met all of the basic criteria articulated in the May 1984 notice. Furthermore, EPA believed that the single applicant was very likely to succeed, because it represented an organization experienced in private-sector consensus standard-setting, State regulators, and water utilities.

EPA awarded the cooperative agreement to the NSF consortium on September 17, 1985, and committed funding of $185,000 to NSF over a three-year period. The non-Federal (consortium and participating industry) contribution during the first three years of the program was projected to be approximately $1.4 million.

The NSF program has the following major objectives:

- To develop systematic, consistent, and comprehensive voluntary consensus standards for public health safety evaluation of all products (previously EPA-accepted as well as new) intended for use in drinking water systems.
- To obtain broad-based participation in the standard-setting program from industry, States, and utilities.
- To provide for regular periodic review, update, and revision of the standards.
- To undertake needed research, testing, evaluation, and inspections and to provide the followup necessary to maintain the program.
- To establish a separate program for testing, evaluation, certification, and listing of additive products.
- To widely disseminate information about the program, and to make information about conforming products available to users.
- To maintain the confidentiality of all proprietary information.
- To fully establish the third-party program on a self-supporting basis.

NSF's established standard-setting process utilizes a tiered structure. Each standard is drafted by a task group and then presented to a Joint Committee, which includes 12 industry, 12 user, and 12 regulatory members. Following successful Joint Committee balloting, standards are reviewed by the Council of Public Health Consultants, which is a high level advisory group consisting of technical and policy experts from regulatory agencies and academia.

NSF has established task groups to develop standards for the product categories listed below. Each task group includes a member representing the regulatory agencies and a member representing the utilities. All manufacturers expressing interest in a particular product task group may participate as members of that group. Therefore, task group membership is predominately manufacturers. In addition, a group of health effects consultants is addressing the toxicological and risk considerations for various product categories. NSF's role in the standard-setting process is administrative, that is, to bring together experts from government, industry,

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utilities, users, and other relevant groups so that a standard which reflects a consensus of these interests can be developed. In addition, NSF staff provide technical leadership and laboratory support. Product categories and correspoding task groups are:

- Protective Materials.
- Chemicals for Corrosion and Scale Control, Softening, Precipitation, Sequestering, and pH Adjustment.
- Coagulation and Flocculation Chemicals.
- Miscellaneous Treatment Chemicals.
- Joining and Sealing materials.
- Process Media.
- Pipes and Related Products.
- Disinfection and Oxidation Chemicals.
- Mechanical Devices.

All of the task groups have made satisfactory progress during the term of the cooperative agreement. In addition, the health effects consultants have endorsed the bases of the standards. Standards have been drafted for all product categories, and final standards were published and implemented as follows:

Standard 60, December 1987

- Chemicals for Corrosion and Scale Control, Softening, Precipitation, Sequestering, and pH Adjustment.
- Disinfection and Oxidation Chemicals.
- Miscellaneous Treatment Chemicals (selected).

Standard 61, June 1988

- Process Media.

Development of the remaining standards is on schedule, and publication and implementation are expected on the following schedule:

Standards 60 and 61, expected October 1988

- Protective Materials.
- Coagulation and Flocculation Chemicals.
- Miscellaneous Treatment Chemicals (additional).
- Joining and Sealing Materials.
- Pipes and Related Products.
- Mechanical Devices.

EPA believes that the NSF program is successfully pursuing all of its objectives. Furthermore, the program is strongly supported by user and regulatory sectors. AWWARF, COSHEM, ASDWA, the Great Lakes Upper Mississippi River Board, the American Water Works Association (AWWA) (including the Utilities and Standards Councils and the Regulatory Agencies Division), and the Association of Metropolitan Water Agencies, among others, have voiced strong support for the third-party program. The AWWA recently joined the NSF-led consortium and urged EPA to support national uniform accreditation of certifying entities for additives products. To date, more than 60 manufacturers are full participants in the standard-setting program.

The cooperative agreement between EPA and the consortium requires NSF to establish both a standard-setting program and a service for testing, certification, and listing. These are completely separate activities. EPA's intent is to support the development of a widely accepted uniform standard for each category of products while encouraging the development of competing sources for testing, certification, and listing. The cooperative agreement assures that at least one sound and reliable product-evaluation service will be available to manufacturers, i.e., the consortium. However, the consortium's standards will allow for entities other than NSF to be evaluators of products.

EPA recognizes the authority and responsibility of the individual States to determine the acceptability of drinking water additives. Hence, it is up to the States and utilities to determine the suitability of any "third-party" certification. AWWARF will maintain a directory of products approved by all organizations claiming to conduct evaluations under Standards 60 and 61. However, AWWARF will not judge the competence or reliability of these organizations.

II. Announcement of Phase-Down of EPA's Additives Program

During the developmental phase of the NSF consortium's program, EPA has continued to review products and process requests for advisory opinions on a limited basis. The May 1984 notice stated that, "EPA does not intend to develop further interim administrative procedures, testing protocols or decision criteria for future evaluation of additive products. The use of existing informal criteria will continue until a third-party or alternative program is operational * * *. EPA may not be able to process all requests for opinions on additive products before the establishment of a cooperative agreement with a third party. The large volume of currently pending requests makes it unlikely that additional requests will be completely processed by that date." Likewise, EPA, in its acknowledgment letters to manufacturers requesting opinions on new products, explains that the Agency is, "* * * making a concerted effort to process petitions as quickly as possible. However, EPA may not be able to process your request for an opinion on an additive product before the establishment of an alternative program as described in the **Federal Register**, Vol. 49, No. 97, 21003–8, May 17, 1984." Product reviews and issuance of advisory opinions have been limited to:

- Products composed entirely of other products which EPA had previously determined to be acceptable;
- Products composed entirely of ingredients which have been determined to be acceptable by EPA or the FDA, or other Federal agencies, for addition to potable water or aqueous foods;
- Products composed entirely of ingredients listed in the "Water Chemicals Codex," National Academy of Sciences, November 1982, and in the "Water Chemicals Codex: Supplementary Recommendations for Direct Additives," National Academy of Sciences, 1984;
- Certain other products of particular interest to EPA or to other Federal agencies; and
- Products which, if effectively excluded from the marketplace by lack of approval, might jeopardize public health or safety.

Continued processing of petitions during the development of the private-sector program minimized disruption of the marketplace from the viewpoint of manufacturers whose business depended in part on EPA acceptance of products, users who required water treatment products for the production of safe drinking water, and State officials who rely on the advice of EPA.

EPA believes that NSF is moving expeditiously and on schedule toward the full establishment of a third-party program covering products intended for use in drinking water systems. Priorities for standards development and implementation of a testing, certification, and listing program for various product categories have been based upon need, interest, complexity, and availability of information for developing standards. Direct drinking water additives were assigned high priority for the following reasons: (1) Use of direct additives is widespread in drinking water systems, so there are large population exposures to these chemicals; (2) as direct additives to drinking water, they present greater potential for water contamination than indirect mechanisms (e.g., migration from protective paints in pipes and storage tanks); and (3) the National Academy of Sciences' *Water Chemicals Codex* provided a good starting point for development of standards.

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As originally planned, EPA is beginning to phase out the Agency's additives evaluation program. Thus, EPA will not accept new petitions or requests for advisory options after the date of this notice. While EPA will continue to process requests which are pending and those received on or before July 7, 1988, petition evaluations not completed by October 4, 1988, will be returned to the submitter. After that date, EPA will no longer evaluate additive products.

Petitions which are completely evaluated by October 5, 1988, will be added to the quarterly list of acceptable products published shortly after that date. That quarterly list will be the last such list issued by EPA. On April 7, 1990, EPA will withdraw its list of acceptable products, and the list and the advisories on these additives will expire. This means that: (1) The various lists published by EPA under the titles *Report on Acceptable Drinking Water Additives, Report on Coagulant Aids for Water Treatment, Report on Concrete Coatings/Admixture for Water Treatment, Report on Detergents, Sanitizers and Joint Lubricants for Water Treatment, Report on Evaporative Suppressants for Water Treatment, Report on Liners/Grouts/Hoses and Tubings for Water Treatment, Report on Miscellaneous Chemicals for Water Treatment, Report on Protectivce Paints/Coatings for Water Treatment,* and any and all other lists of drinking water products issued by EPA or its predecessor agencies regarding drinking water additives will be invalid after April 7, 1990; and (2) advisory opinions on drinking water additives issued by EPA and predecessor agencies will be invalid after that date.

EPA believes that, while in the past every effort has been made to provide the best possible evaluations, all products should be evaluated against carefully developed and considered nationally uniform standards. Many of the currently listed products were evaluated and accepted up to 20 years ago and have not been reevaluated since that time. Numerous products have been accepted because they were virtually identical to or were repackagings of older products. The result is that few products have been completely evaluated for the safety of their original or current formulations vis-a-vis the latest toxicological, chemical, and engineering information. A uniform evaluation of all products, old and new, will result in consistent quality of products, and will assure fair and equitable treatment to all manufacturers and distributors.

Henceforth, parties desiring to have existing or new products evaluated against the NSF standards should contact NSF or other organizations offering such evaluations. To contact NSF about the drinking water additives program write to: David Gregorka, National Sanitation Foundation, P.O. Box 1468, Ann Arbor, MI 48106, or call (313) 769–8010. Information on alternatives to NSF evaluation may be obtained by contacting State regulatory agencies or the AWWA, Technical and Professional Department, 6666 Quincy Avenue, Denver Co, 80235, or call (303) 794–7711, which is addressing certifier accreditation.

EPA believes that the 21 months between today and the expiration date of EPA's last list is sufficient time for manufacturers to submit their products to NSF or other certification entities for evaluation. The first NSF list will be published prior to April 7, 1990, thereby preventing any disruption in the marketplace. Furthermore, NSF had indicated that it will consider current EPA and other regulatory evaluations when evaluating products in order to ensure a smooth transition. States may choose to rely on the last EPA quarterly list of products until their individual programs for accepting private-sector certification are fully implemented.

Parties desiring to market drinking water additive products are reminded that the individual States have the authority to regulate the sale and/or use of specific products as they see fit. Thus, reliance upon a particular standard or organization to certify that a product complies with a particular standard must be acceptable to the State in which the supplier wishes to do business.

Discontinuation of the additives program at EPA does not relieve the Agency of its statutory responsibilities. If contamination resulting from third-party sanctioned products occurs or seems likely, EPA will address that issue with appropriate drinking water regulations or other actions authorized under the SDWA. EPA is a permanent member of the NSF program Steering Committee, and senior EPA staff and management will continue to participate in this and other programs designed to assure that high-quality products are employed in the treatment of public drinking water. Also, the Agency will continue to sponsor research on contaminants introduced in public water supplies during water treatment, storage, and distribution.

III. Comments

Although this notice does not include a proposed or final regulation, EPA welcomes comments and suggestions that would assist the Agency in implementing the additives program phasedown. Please address all comments and suggestions to: Mr. Arthur H. Perler, Chief, Science and Technology Branch, Office of Drinking Water (WH–550D), U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460.

Date: June 16, 1988.

William Whittington,

Acting Assistant Administrator for Water.

[FR Doc. 88–15232 Filed 7–6–88; 8:45 am]

BILLING CODE 6560–50–M

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Analysis Relevant to Question 1

Preface

The Federal Register of July 20, 1979 (44 FR 42775-78) gave notice ("1979 Notice") of adoption of a Memorandum of Understanding ("1979 MOU") between FDA and EPA and provided the text of the 1979 MOU. (Attachments A-1 to A-4 hereto.) Attachments A-5 to A-8 hereto is another copy of the same 1979 MOU in a easier-to-read format. The purpose of the 1979 Notice according to the Title of the Notice was to address "Drinking Water Technical Assistance" and to provide an "Implementation Plan for Control of Direct and Indirect Additives to Drinking Water" and to announce the 1979 MOU between EPA and FDA regarding these subjects. (Attachment A-1 hereto.)

The Summary in the 1979 Notice states that the FDA and EPA have executed a MOU "with regard to the control of direct and indirect additives to and substances in drinking water." Our Question 1 focuses on the control of direct additives to public drinking water. Further, our Question 1 focuses on control of those direct additives intended for preventative health care purposes and unrelated to contamination of public drinking water. Our Question 2 focuses on whether the EPA 1988 Notice of Termination of the Federal Drinking Water Additives Program from the viewpoint of EPA gave Notice to the public and FDA that EPA was terminating the 1979 MOU as it was authorized to do by section IV of the 1979 MOU.

Analysis

As you know the FDA and HHS are the federal agencies who have primary control over substances intended for use in the prevention of disease (referred to herein as "preventative health care purposes"). (*See* 21 USC 321(g)(1)(B).) When the EPA Administrator was asked if EPA had regulatory authority over drugs that are additives to public drinking water, EPA's Safe Drinking Water Hotline responded that pursuant to SDWA Section 1412(b)(11), EPA is prohibited from regulating "the addition of any substance for preventative health care purposes unrelated to contamination of drinking water. (Attachment A-16 hereto.)

Upon close examination of the 1979 Notice and 1979 MOU, it is clear that FDA negotiated the 1979 MOU only with respect to its legal authority over "food" and "food additives." (Attachment A-1 to A-2 and A-6 hereto.) There is no mention in the 1979 Notice or 1979 MOU that EPA would get, and FDA would no longer have, responsibility over public drinking water additives intended for preventative health care purposes and unrelated to contamination of public drinking water. (Attachments A-1 to A-8.) Therefore we submit that EPA should respond, "No," to our Question 1: From the viewpoint of EPA, the 1979 MOU did not take away from FDA, and give to EPA, responsibility for regulating public drinking water additives intended for preventative health care purposes (i.e. substances intended for use in the prevention of disease) and unrelated to contamination of public

drinking water.

This view is supported by the Dietary Supplement Health and Education Act of 1994 (Pub. L. 103-417; "DSHEA"). Under this Act, a mineral additive is a dietary supplement. (21 USC 321(ff)(1)(B).) Also under this Act, a mineral additive is regulated as a food except when it meets the definition of a drug. (21 USC 321(ff)(postscript) ("except for purposes of [21 USC 321(g)(1) defining a drug] a dietary supplement shall be deemed to be a food").)

> A dietary supplement is deemed to be "food," [21 USC] 321(ff), which is defined in part as "articles used for food or drink for man or other animals," [21 USC] § 321(f)(1), except when it meets the definition of a "drug," which is defined in part as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals."

(*Alliance for Natural Health U.S. v. Sebelius*, 714 F.Supp.2d 48, 50 (D.D.C. 2012).) Therefore, the 1979 MOU appears to have been intended to give EPA, and not FDA, responsibility for regulating public drinking water additives related to contamination of public drinking water. But the 1979 MOU was not intended to give EPA responsibility over public drinking water additives intended for preventative health care purposes and unrelated to contamination of public drinking water. (Attachment A-16 hereto.)

So while the 1979 MOU seeks to give responsibility to EPA over substances in public drinking water that would otherwise be considered food additives by the FDA, there is no language in the 1979 MOU that should be interpreted as seeking to give responsibility to EPA over substances added to public drinking water for preventative health care purposes that are not validly considered food additives but which rather are considered drugs.

The Federal Supreme Court urges a broad application of the definition of drugs in 21 USC 321(g)(1)(B) concerning substances intended for use in the prevention of disease:

> Congress intended to define "drug" [in 21 U.S.C. 321(g)(1)(B)] far more broadly than does the medical profession. . . . The word "drug" is a term of art for the purposes of the Act, encompassing far more than the strict medical definition of that word.
>
> . . . .
>
> Congress fully intended that the Act's coverage be **as broad as its literal language indicates** - and, equally clear, broader than any strict medical definition might otherwise allow. . . . the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health.
>
> . . . .
>
> we must take care not to narrow the coverage of a statute short of the point where Congress indicated it should extend.

(United States v. An Article of Drug . . . Bacto-Unidisk, 394 U.S. 784, 793-801, 89 S.Ct.

1410, 22 L.Ed.2d 726 (1969) (emphasis supplied).)

The 1979 MOU states:

> In the past, FDA has considered drinking water to be a food under Section 201(f). However, both parties have determined that the passage of the SDWA in 1974 implicitly repealed FDA's authority under the FFDCA over water used for drinking water purposes.

(Attachment A-1 and A-6.) The 1979 Notice also states:

> EPA and the Food and Drug Administration (FDA) signed a Memorandum of Understanding which recognizes that regulatory control over direct and indirect additives in drinking water is placed in EPA. The two agencies agreed that the Safe Drinking Water Act's passage in 1974 implicitly repealed FDA's jurisdiction over drinking water as a **"food"** under the Federal Food, Drug, and Cosmetic Act (FFDCA). Under the agreement, EPA now retains exclusive jurisdiction over drinking water served by public water supplies, including any additives in such water.

(Attachment A-2 hereto.)

Read together, the intent of the 1979 MOU was to agree that FDA would no longer exercise responsibility over public drinking water additives and public drinking water as foods. The 1979 Notice and 1979 MOU did not state and did not intend that FDA would no longer exercise responsibility over public drinking water additives and public drinking water as drugs.

Therefore, we urge EPA to answer Question 1 by stating: From the viewpoint of EPA, the 1979 MOU did not take away from FDA, and give to EPA, responsibility for regulating public drinking water additives intended for preventative health care purposes (i.e. substances intended for use in the prevention of disease) and unrelated to contamination of public drinking water.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 11 2012

OFFICE OF
WATER

Patrick Jayson Reeners
317 Malone Dr.
Gallatin, TN 37066

Dear Mr. Reeners:

Thank you for your letter dated August 2, 2012 to Lisa Jackson, Administrator of the Environmental Protection Agency (EPA), in which you shared your concerns regarding drugs as water additives or drug claims associated with public drinking water. Your letter was forwarded to EPA's Safe Drinking Water Hotline for response.

Under provisions of the Safe Drinking Water Act (SDWA), public water systems are required to meet strict standards for quality before drinking water is distributed for human consumption. EPA establishes drinking water regulations and works with state agencies to ensure that public water systems are in compliance with these regulations. Under SDWA, EPA is mandated to establish national primary drinking water regulations (NPDWRs) for contaminants in order to protect public health. Some of these standards include both enforceable Maximum Contaminant Levels (MCL) and non-enforceable Maximum Contaminant Level Goals (MCLGs). Other standards require that specific treatment techniques be used for contaminant removal.

The following are specific responses to the questions in your letter:

1. Does EPA have regulatory authority over drugs that are water additives to public drinking water?

EPA has authority to establish drinking water standards to address health risks associated with exposure to contaminants in public drinking water systems. EPA also has authority to require the addition of disinfectants to public water systems to protect against microorganisms (see SDWA Section 1412(b)(8)). However, as provided in SDWA Section 1412(b)(11), EPA is prohibited from setting a national primary drinking water standard that requires the addition of any substance for preventive health care purposes unrelated to contamination of drinking water.

2. Does EPA have regulatory authority over drug claims made for substances added to public drinking water?

Not under the Safe Drinking Water Act. The federal Food and Drug Administration (FDA) is the lead federal agency with respect to drug regulation and drug claims.

A-16

3. If EPA doesn't have authority over drugs and drug claims associated with public drinking water, what agency does have the authority?

See answer to question 2.

4. If EPA does have regulatory authority over drugs and drug claims associated with public drinking water what is the contact information for the section or person in charge of exercising the authority within EPA?

As noted earlier, the FDA is the lead federal agency with respect to drug regulation and drug claims.

Thank you for your letter.

EPA Safe Drinking Water Hotline
1-800-426-4791
Outreach Process Partners, LLC
Contractor to EPA
www.epa.gov/safewater.com

A-17

Analysis Relevant to Question 2

Preface

The Federal Register of July 20, 1979 (44 FR 42775-78) gave notice ("1979 Notice") of adoption of a Memorandum of Understanding ("1979 MOU") between FDA and EPA and provided the text of the 1979 MOU. (Attachments A-1 to A-4 hereto.) Attachments A-5 to A-8 hereto is another copy of the same 1979 MOU in a easier-to-read format. The purpose of the 1979 Notice according to the Title of the Notice was to address "Drinking Water Technical Assistance" and to provide an "Implementation Plan for Control of Direct and Indirect Additives to Drinking Water" and to announce the 1979 MOU between EPA and FDA regarding these subjects. (Attachment A-1 hereto.)

The Summary in the 1979 Notice states that the FDA and EPA have executed a MOU "with regard to the control of direct and indirect additives to and substances in drinking water." Our Question 1 focuses on the control of direct additives to public drinking water. Further, our Question 1 focuses on control of those direct additives intended for preventative health care purposes and unrelated to contamination of public drinking water. Our Question 2 focuses on whether the EPA 1988 Notice of Termination of the Federal Drinking Water Additives Program from the viewpoint of EPA gave Notice to the public and FDA that EPA was terminating the 1979 MOU as it was authorized to do by section IV of the 1979 MOU.

Analysis

The 1979 MOU, in Section III, provides the Terms of Agreement of the MOU. (Attachments A-2, A-7 and A-8 hereto.) The 1979 MOU, in Section IV, provides that the 1979 MOU would continue in effect unless modified by mutual consent of the both parties or terminated by either party upon thirty days notice. (Attachments A-2 and A-8.)

Term of Agreement III(A)(1) of the 1979 MOU is that EPA would establish regulations "to control direct additives to drinking water (which encompass any substances purposely added to the water)." Term of Agreement III(A)(3) of the 1979 MOU is that EPA would "continue to provide technical assistance in the form of informal advisory opinions on drinking water additives." EPA made these Agreements in good faith but by 1988 decided that it would terminate these Agreements.

Section IV of the 1979 MOU provides the mechanism for terminating the 1979 MOU and its Agreements. Our reading of this section is that if one party gives Notice published in the Federal Register that it will not abide by a Term of Agreement, and the other party does not agree to modify the MOU accordingly, then the Notice terminates the MOU after 30 days. Any modified MOU must be published in the Federal Register:

> Pursuant to the notice published in the Federal Register of October 3, 1974 (39 FR 35697) stating that future memoranda of understanding and agreements between FDA and others would be published in the Federal Register . . .

(Attachment A-1 hereto.)

EPA published in the Federal Register of July 7, 1988 (53 FR 25586) a notice ("1988 Notice"). (Attachments A-9 to A-12 hereto.) The purpose of the 1988 Notice according to its Title was to address EPA "Drinking Water Technical Assistance" and to provide for "Termination of the Federal Drinking Water Additives Program."

The Summary in the 1988 Notice states that EPA "has operated an advisory program that gives technical assistance to concerned parties on the use of drinking water additives." (Attachment A-9 hereto.) The Summary announces that "EPA will phase out its activities in this area." (*Id.*) In a later section of the 1988 Notice, EPA states that on April 7, 1990 it will end its advisory program on drinking water additives. (Attachment A-12 hereto.)

This is a unilateral modification of Term of Agreement III(A)(3) of the 1979 MOU. There has been no revised MOU issued and published in the Federal Register and so the 1988 Notice serves to terminate the 1979 MOU.

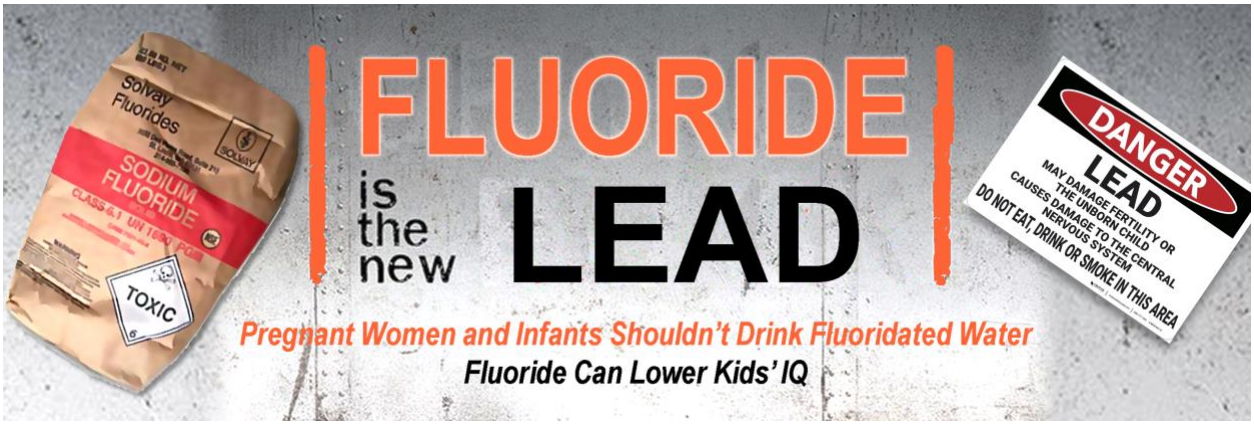
The 1988 Notice also provides that EPA does not intend to develop regulations that would control any substances purposely added to the water pursuant to Term of Agreement III(A)(1). It admits that "EPA does not currently regulate the levels of additives in drinking water." (Attachment A-9 hereto.) The 1988 Notice describes how EPA was encouraging the development of a third-party voluntary product-standard program. (Attachments A-9 to A-12 hereto.) The 1988 Notice states that EPA expected the "States and utilities to determine the suitability of any "third-party" certification. (Attachment A-11 hereto.) The 1988 Notice defers to the authority of the individual States "to regulate the sale and/or use of specific products as they see fit." (Attachment A-12 hereto.) The 1988 Notice states that:

> If contamination resulting from third-party sanctioned products occurs or seems likely, EPA will address that issue with appropriate drinking water regulations or other actions authorized under the SDWA.

(Attachment A-12 hereto.) So EPA announced it did not intend to regulate all substances purposely added to the water but only have regulations related to contamination of public drinking water as defined in the SDWA.

This is a unilateral modification of Term of Agreement III(A)(1) of the 1979 MOU. There has been no revised MOU issued and published in the Federal Register and so the 1988 Notice must serve to terminate the 1979 MOU. If EPA answers "No" to Question 1, it should answer "N/A" to Question 2. If EPA answers "Yes" to Question 1, it should answer "Yes" to Question 2: The 1988 Notice did terminate the 1979 MOU regarding EPA responsibilities.

FAN Bulletin #3 on NTP. Ver5. Word count = 1,800.



Fluoride is the New Lead

Same Loss of IQ,
Same Industry Denials,
Same Tactics of Lead Industry Now Used by Dental Interests

The National Toxicology Program (NTP) report {link to a FAN copy} on fluoride's neurotoxicity confirms what experts have been suggesting: that ***fluoride is the new lead*** in its ability to lower IQ in children. Over the past five years experts in toxicology and epidemiology have equated the harm to developing brains from fluoride to that from lead.

Experts: "on par with lead"

Editors from the *Journal of the American Medical Association (JAMA)* described the IQ drop of -4.5 IQ points in one study [Christakis & Rivera 2019]:

> "An effect size which is sizeable – on par with lead."

David Bellinger, author of over 400 epidemiology papers on neurotoxic chemicals including over 100 on lead, said [NPR 2019]:

> "It's actually very similar to the effect size that's seen with childhood exposure to lead."

Christine Till, leader of a research team that has published rigorous studies of fluoride neurotoxicity funded by the National Institutes of Health (NIH) [Canada CTV 2019]:

> "4.5 points is a dramatic loss of IQ, comparable to what you'd see with lead exposure."

And [Farmus 2021]:

> "A 2- to 4-point decrement in PIQ [Performance IQ] may seem like a small difference at the individual level. However, a small shift in the mean of IQ scores at the population level translates to *millions of lost IQ points* given the ubiquity of fluoride exposure." (*emphasis* added)

Philippe Grandjean, editor-in-chief of the journal *Environmental Health*, and author of over 600 peer-reviewed papers on toxicity of fluoride, lead, mercury, perfluorinated compounds (like PFAS), and other chemicals [Grandjean 2013 book & website]:

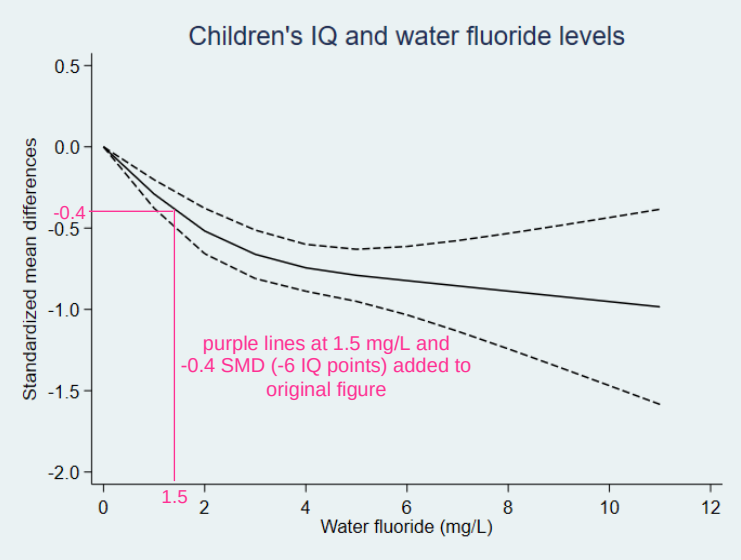
> "Fluoride seems to fit in with lead, mercury and other poisons that cause chemical brain drain."

NTP final report confirms similar loss of IQ from fluoride as from lead

The NTP's final report on fluoride neurotoxicity supports these experts' conclusions. NTP found an average loss of 7 IQ points in 55 studies that compared child IQ of a higher fluoride group to that of a lower fluoride group. NTP also conducted a so-called dose-response meta-analysis to look at the relationship between fluoride dose and IQ loss by combining results from many studies at different exposure levels. They found that as water fluoride concentrations rose from 0.0 to 1.5 mg/L (milligrams per liter, equivalent to parts per million or ppm), the average IQ dropped about 6 IQ points. Artificial fluoridation is generally at a concentration of 0.7 mg/L water fluoride so is squarely in this range.

NTP finds loss of IQ at doses from fluoridated water

The dose-response curve calculated by NTP is shown in their eFigure 17, reproduced here:



The units of Standardized Mean Differences (SMD) can be converted to IQ points by multiplying by 15, so for example, an SMD of -2.0 is equivalent to -30 IQ points.

The graph shows no safe threshold and the slope of the solid line representing the relationship between exposure and loss of IQ is actually steepest in the low exposure range directly applicable to artificially fluoridated water. In the NTP's own words: "there was no obvious threshold as illustrated by [eFigure 17]". [NTP2023 BSC charge documents p 326 of PDF].{add link}

Dental groups use same tactics as lead industry used to defend lead

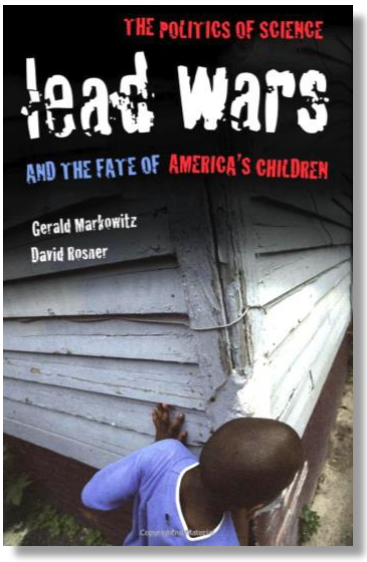
Fluoridation advocates, mostly dentists, have been falsely claiming the NTP review did not find evidence of neurotoxicity below 1.5 mg/L water fluoride, or that the evidence below 1.5 mg/L is unclear. Some have even claimed the NTP found a safe threshold at 1.5 mg/L water fluoride. Some fluoridation advocates go so far as to claim there is no evidence fluoride is neurotoxic at any level, or that the only studies finding adverse effects are at levels "far higher" than pregnant mothers and children would get from fluoridated water.

Similar dismissals were made by the lead industry about what was called "low-level" lead exposures more than 30 years ago. The amount and quality of evidence available today showing fluoride causes IQ loss can be compared with what was available for "low-level" lead in 1990. At that time, a review and meta-analysis by Herbert Needleman, groundbreaking medical researcher in childhood lead poisoning, was published in the *Journal of the American Medical Association (JAMA)* [Needleman

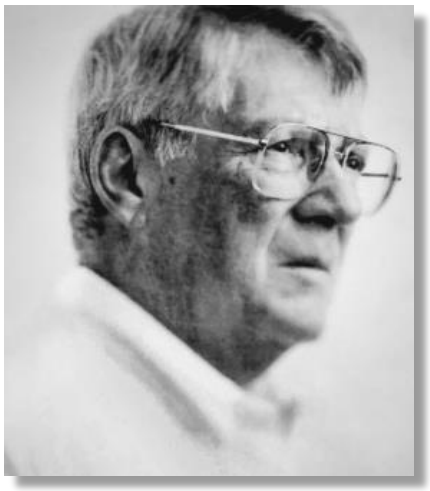
1990]. There were only 12 human studies considered high-quality. It is worth noting that none were of designs considered as high quality as are available now with longitudinal cohort studies of fluoride. Furthermore, the lead studies were in populations with lead levels from 2x to 4x higher than the average childhood lead level at the time and up to 30x higher than average child blood lead levels today. The study children mostly had 30-60 μg/dL (microgram per deciliter) blood lead, whereas the average at the time was 15 μg/dL. Today the average child blood lead is down to 1 μg/dL because of the banning of lead paint and gasoline. Those bans were largely a result of Needleman's research and his meta-analysis. A typical loss of IQ in the higher-lead-exposure groups compared with the lower-exposure groups was about 4 IQ points [Needleman 1979a]. Compare that to the 7 IQ point loss from fluoride found in the NTP's meta-analysis. The fluoride studies evaluated by NTP today show greater loss of IQ from a stronger body of evidence than was available for lead at the time of Needleman's 1990 meta-analysis.

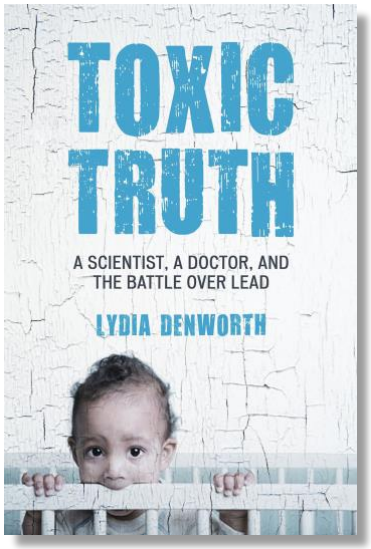
Shoot the messenger

There was heated controversy at the time over Needleman's findings on low-level lead and IQ, with the lead industry making many of the same arguments as now are being made by dental interests with fluoride [Needleman 1979b letters, Needleman 1982]. There were even scurilous personal attacks against Needleman claiming scientific misconduct, but he was always vindicated [Bill Moyers 2002 video, Denworth 2008, Markowitz 2013]. That same lead industry tactic has now been used by dental interests against scientists who have conducted the most rigorous fluoride-IQ studies. But the personal attacks today are worse. With lead, the claims of scientific misconduct were against a single researcher, Needleman. With fluoride, the dental advocates lodged formal complaints of scientific misconduct against all nine members of a research team at five different universities. All five universities completely exonerated the scientists, but their work was severely disrupted by the need to defend themselves against the false accusations, on top of the personal stress that accompanies charges that can wreck a scientific career. The fluoridation advocates that filed the complaints had been advised by their own legal counsel that the accusations were false, yet they filed them anyways.



Herbert Needleman, MD





Blame the victim

The lead industry also tried a tactic of "blaming the victim", arguing that blood lead was higher in low-IQ children not because the lead had caused the reduction in IQ, but because low-IQ children tended to eat more lead paint chips [Cole 1979]. This was easily proven wrong by Needleman [Needleman 1979b, Needleman 1982]. Today, some of the most extreme dentist defenders of fluoride are offering a similar "blame the victim" argument to try to explain away all the studies finding reduced IQ with higher fluoride. Jaynath Kumar, the California state dental director who by his own words is "paid to promote fluoridation" {make the quote a link to a video or audio clip of him saying that}, is arguing that in studies in China where fluoride exposures cause high rates of severe dental fluorosis the smarter people move to areas with lower fluoride, thereby reducing the average IQ for the population of unfortunate people who are not smart enough to leave. Not only is Kumar's "reverse causality" explanation pure speculation, it is easily disproven by the high quality studies in Canada and Mexico City [Green 2019, Bashash 2017]. These were not in areas considered "endemic fluorosis" so there were no high rates of severe dental fluorosis.

The tactics now being used by dental interests to protect the policy of fluoridation are disturbingly similar to those used by the lead industry. They are also the same tactics used by the tobacco industry, the asbestos industry, and other industries making toxic products. Their intent is to delay action for years, by manufacturing doubt about the science. A cigarette industry executive famously described this strategy, saying "Doubt is our product" [Brown & Williamson 1969].

If we squander years in debate on fluoride, we risk the same harm to brains of millions of children that resulted from delayed recognition of low-level lead harm. The evidence on fluoride is more than sufficient to begin taking protective action now.

Fluoridation today causing more lost IQ points amongst US children than lead

Estimates of the total child IQ points currently being lost due to fluoridated water in the US are greater than those being lost from childhood lead poisoning [Neurath 2020, Neurath 2021].

Fluoride truly is the new lead. Fluoride is causing substantially greater population-wide loss of IQ today than lead. Two-thirds of Americans receive drinking water that has had fluoride added and dental interests are calling for expanding fluoridation. In contrast, lead was banned from paint and gasoline starting in the 1970s and as a result child blood lead levels have steadily declined to a tiny fraction of what they were before the bans. Only a few percent of the population exceed the latest CDC guideline of 5 μg/dL. In Needleman's day almost all children greatly exceeded today's lead guideline [Pirkle 1994].

To be clear, lead poisoning has not been eliminated. There are still tens of thousands of children who are lead poisoned, especially from old leaded paint or situations such as in Flint, Michigan. There, a switch to corrosive water leached lead from pipes and caused more than a doubling of the percentage of children with blood lead exceeding the CDC guideline of 5 μg/dL, from 5% to 12% [Zahran 2017]. As terrible as the Flint case was, it is estimated that only about 500 children had their blood lead raised above the 5 μg/dL guideline. Compare that to 210 million people with fluoridated water in the US. They are exposed to fluoride which the new scientific evidence suggests is putting each new generation at risk for lowered IQ.

Fluoridation in the US is equivalent to 17,917 "Flints" every year, in terms of harm to kids' developing brains. That is the number of water systems where fluoride is added.

As the distinguished toxicologist and long-time director of NTP Linda Birnbaum stated along with two co-authors who have conducted the highest quality studies of fluoride and IQ [Lanphear 2020]:

> "When do we know enough to revise long-held beliefs? We are reminded of the discovery of neurotoxic effects of lead that led to the successful banning of lead in gasoline and paint. Despite early warnings of lead toxicity, regulatory actions to reduce childhood lead exposures were not taken until decades of research had elapsed and millions more children were poisoned."

Fluoride is the new lead, but worse.

Also see these FAN Bulletins on the NTP fluoride neurotoxicity report {or press releases}: [FAN 2023-03-15, FAN 2023-03-16].

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NOTES:

Needleman 1997 discusses a very rigged NAS committee that include Kehoe as a consultant [NAS/NRC 1972] and a much more balanced NAS committee that later corrected the errors of the first [NAS/NRC 1980].
Needleman1997 Patterson vs Kehoe on Pb.pdf

Needleman congressional testimony on CSPAN, 1991:
https://www.c-span.org/video/?20139-1/lead-contamination-control-act-1991

he succinctly describes problem and solution in his 5 minute initial oral presentation

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Possible table to allow comparison between evidence in 1990 for Pb versus evidence today for F.
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Table comparing Needleman 1990 meta-analysis of Pb to NTP 2022 meta-analysis of F

	1990 meta-analysis of **Lead (Pb)**	2022 meta-analysis of **Fluoride (F)**
Reference	Needleman 1990	NTP 2022
Number of studies	12	55
Average exposure of all studies	30 to 60 ug/dL blood Pb	About 2 mg/L water F and 2 mg/L urine F
Average US population exposure at time of studies	15 ug/dL	0.9 mg/L urine F in fluoridated areas
Ratio of study exposure to population exposure	2x to 4x	2x
IQ point loss found in studies	-4 IQ points	-7 IQ points

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Kirkman Laboratories, Inc. 1/13/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Seattle District
Pacific Region
22215 26th Avenue SE, Suite 210
Bothell, WA 98021

Telephone: 425-302-0340
FAX: 425-302-0402

January 13, 2016

OVERNIGHT DELIVERY
SIGNATURE REQUIRED

In reply refer to Warning Letter SEA 16-07

David K. Humphrey
Chief Executive Officer and President
Kirkman Laboratories, Inc.
10639 Professional Circle
Reno, Nevada 89521

WARNING LETTER

Dear Mr. Humphrey:

The United States Food and Drug Administration (FDA) conducted an inspection of your drug manufacturing facility, Kirkman Laboratories, Inc., located at 6400 Rosewood St., Lake Oswego, Oregon on June 3, 2015, through June 24, 2015. This inspection revealed that your firm is marketing the following unapproved new drugs: Kirkman Laboratories, Inc. Flura-Drops ® Sodium Fluoride drops, 2.21 mg; Perry Medical Fluorabon Drops USP; Kirkman Laboratories, Inc. 1.1 mg Cherry Dye-Free Sodium Fluoride Tablets; and Kirkman Laboratories, Inc. 2.21 mg Cherry Dye-Free Sodium Fluoride Tablets, in violation of section 505(a) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 355(a)]. Additionally, FDA has determined that these products are misbranded drugs in violation of section 502 and 503 of the Act [21 U.S.C. §§ 352 and 353], as detailed below.

A. Unapproved New Drug Violations

Based on the information collected during the recent inspection, you manufacture and/or distribute unapproved new drugs in violation of sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)].

The unapproved new drugs include, but are not limited to:

- Kirkman Laboratories, Inc. Flura-Drops® Sodium Fluoride Drops, 2.21 mg (NDC 58223-517), which is labeled "for once daily, self-administered, systemic use as a dental caries preventive in pediatric patients";
- Perry Medical Fluorabon Drops USP, 0.25mg (NDC 11763-524), which is labeled "as an aid in the prevention of dental caries";
- Kirkman Laboratories, Inc. 1.1 mg Cherry Dye-Free Sodium Fluoride Tablets (NDC 58223-678), which is labeled "as an aid in the prevention of dental caries"; and
- Kirkman Laboratories, Inc. 2.21 mg Cherry Dye-Free Sodium Fluoride Tablets (NDC 58223-679), which is labeled "as an aid in the prevention of dental caries."

The above products are drugs within the meaning of section 201(g)(1) of the Act [21 U.S.C. § 321(g)(1)], because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans. Further, as labeled, these drugs are "new drugs" within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective under the conditions prescribed, recommended, or suggested in their labeling. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the drug. There are no FDA-approved applications on file for the drugs listed above. The marketing of these drugs, or other new drugs, without an approved application constitutes a violation of the Act.**[1]**

B. Misbranding Violations

The above products also are "prescription drugs" as defined in section 503(b)(1)(A) of the Act [21 U.S.C. § 353(b)(1)(A)], because, in light of their toxicity or potential for harmful effects, or the method of their use, or the collateral measures necessary for their use, they are not safe for use except under the supervision of a practitioner licensed by law to administer them.[1]

Because these prescription drug products are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for them so that a layman can use them safely for their intended uses. Consequently, the labeling of your firm's unapproved prescription drug products fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(l) of the Act [21 U.S.C. § 352(f)(1)]. Because your drugs lack required approved applications, they are not exempt under 21 CFR 201.115 from the requirements of section 502(f)(1) of the Act. The above products also are misbranded under section 503(b)(4)(A) of the Act [21 U.S.C. § 353(b)(4)(A)], because the labels fail to bear the symbol "Rx Only." The introduction or delivery for introduction into interstate commerce of these drugs therefore violates sections 301(a) of the Act [21 U.S.C. § 331(a)].

C. Conclusions

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist in connection with your products. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal actions without further notice, including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. You should discontinue marketing all of the unapproved prescription drugs manufactured at your facility immediately. Additionally, FDA may withhold approval of requests for export certificates or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A re-inspection may be necessary to verify corrective

actions have been completed.

FDA requests that you contact CDER's Drug Shortages Staff immediately at drugshortages@fda.hhs.gov so that we can work with you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture, as required under 21 U.S.C. § 356c(a), and to allow FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Please notify this office in writing within fifteen (15) working days of receiving this letter of the steps you have taken to bring your firm into compliance with the law. Your response should include each step that has been taken or will be taken to correct the violations and prevent their recurrence. If the corrective action cannot be completed within fifteen (15) working days of receiving this letter, state the reason for the delay and the timeframe within which the corrections will be completed. Please include copies of any documentation demonstrating that corrections have been made. If you no longer manufacture or market your fluoride products, your response should indicate, including the reasons that, and the date on which, you ceased production.

Your reply should be sent to the following address: U.S. Food and Drug Administration, 22215 26th Avenue SE, Suite 210, Bothell, Washington 98021 to the attention of Maria P. Kelly-Doggett, Compliance Officer. If you have any questions regarding any issues in this letter, please contact Compliance Officer Maria Kelly-Doggett by telephone at 425-302-0427.

Sincerely,
/S/
Miriam R. Burbach
District Director

cc: Lawrence A. Newman
Chief Operating Officer Technical & Regulatory Affairs
Kirkman Laboratories, Inc.
6400 Rosewood St.
Lake Oswego, Oregon 97035

---

1 Over-the-Counter (OTC) fluoride dentifrice drug products are subject to the final rule for Anticaries Drug Products for OTC Human use found in 21 CFR 355. As described in 21 CFR 355.60, the professional labeling allows for anticaries fluoride treatment rinses that are specifically formulated so they may be swallowed (fluoride supplements) and are provided to health professionals (but not to the general public) to contain additional dosage information. This additional information cannot be directed to consumers and the product must be in accordance with 21 CFR 355.60. The Flura-Drops® Sodium Fluoride Drops, 2.21 mg (NDC 58223-517), Fluorabon Drops USP, 0.25mg (NDC 11763-524), 1.1 mg Cherry Dye-Free Sodium Fluoride Tablets (NDC 58223-678), and 2.21 mg Cherry Dye-Free Sodium Fluoride Tablets (NDC 58223-679) labels and labeling do feature additional dosage information (i.e., professional labeling information) and as such, the information is inappropriately directed to consumers. Additionally, 21 CFR 355.60 only allows additional dosage information for children 3 to under 14 years of age. These products all indicate for use down to age 6 months. Furthermore, a fluoride tablet is not a dosage form permissible under the final rule.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 21 2000

The Honorable Ken Calvert
Chairman
Subcommittee on Energy and Environment
Committee on Science
House of Representatives
Washington, D.C. 20515-6301

Dear Mr. Chairman:

Thank you for the letter of May 8, 2000, to Dr. Jane E. Henney, Commissioner of Food and Drugs, regarding the use of fluoride in drinking water and drug products. We apologize for the delay in responding to you.

We have restated each of your questions, followed by our response.

1. **If health claims are made for fluoride-containing products (e.g. that they reduce dental caries incidence or reduce pathology from osteoporosis), do such claims mandate that the fluoride-containing product be considered a drug, and thus subject the product to applicable regulatory controls?**

Fluoride, when used in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animal, is a drug that is subject to Food and Drug Administration (FDA) regulation. FDA published a final rule on October 6, 1995, for anticaries drug products for over-the-counter (OTC) human use (copy enclosed). This rule establishes the conditions under which OTC anticaries drug products are generally recognized as safe and effective and not misbranded. The rule has provisions for active ingredients, packaging conditions, labeling, and testing procedures that are required by manufacturers in order to market anticaries products. A new drug application (NDA) may be filed for a product containing fluoride that does not meet the provisions stated in the final rule. As you know, the Environmental Protection Agency regulates fluoride in the water supply.

2. Are there any New Drug Applications (NDA) on file, that have been approved, or that have been rejected, that involve a fluoride-containing product (including fluoride-containing vitamin products) intended for ingestion with the stated aim of reducing dental caries? If any such NDA's have been rejected, on what grounds were they rejected? If any such NDA have been approved, please provide the data on safety and efficacy that FDA found persuasive.

No NDAs have been approved or rejected for fluoride drugs meant for ingestion. Several NDAs have been approved for fluoride topical products such as dentifrices and gels. Fluoride products in the form of liquid and tablets meant for ingestion were in use prior to enactment of the Kefauver-Harris Amendments (Drug Amendments of 1962) to the Food, Drug, and Cosmetic Act in which efficacy became a requirement, in addition to safety, for drugs marketed in the United States (U.S.). Drugs in use prior to 1962 are being reviewed under a process known as the drug efficacy study implementation (DESI). The DESI review of fluoride-containing products has not been completed.

3. Does FDA consider dental fluorosis a sign of over exposure to fluoride?

Dental fluorosis is indicative of greater than optimal ingestion of fluoride. In 1988, the U.S. Surgeon General reported that dental fluorosis, while not a desirable condition, should be considered a cosmetic effect rather than an adverse health effect. Surgeon General M. Joycelyn Elders reaffirmed this position in 1994.

4. Does FDA have any action-level or other regulatory restriction or policy statement on fluoride exposure aimed at minimizing chronic toxicity in adults or children?

The monograph for OTC anticaries drug products sets acceptable concentrations for fluoride dentifrices, gels and rinses (all for topical use only). This monograph also describes the acceptable dosing regimens and labeling including warnings and directions for use. FDA's principal safety concern regarding fluoride in OTC drugs is the incidence of fluorosis in

children. Children under two years of age do not have control of their swallowing reflex and do not have the skills to expectorate toothpaste properly. Young children are most susceptible to mild fluorosis as a result of improper use and swallowing of a fluoride toothpaste. These concerns are addressed in the monograph by mandating maximum concentrations, labeling that specifies directions for use and age restrictions, and package size limits.

Thanks again for contacting us concerning this matter. If you have further questions, please let us know.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

Enclosure
"Final Rule/Federal Register - October 6, 1995
Over-the-Counter Anticaries Drug Products"

Web site administrator's note:
To perform query to access this document
Enter: http://www.access.gpo.gov/su_docs/aces/aces140.html
Enter: checkmark for 1995 Volume 60
Enter: On: 10/06/95
Enter: Search terms: anticaries

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
GENERAL COUNSEL

February 14, 2013

Gerald Steel, PE
7303 Young Road NW
Olympia, WA 98502

Dear Mr. Steel:

This is in response to your letter of December 28, 2012 to EPA Administrator Lisa Jackson in which you asked several questions about the status of an MOU between EPA and the Federal Drug Administration (FDA) published in 1979. I am replying on behalf of her.

Your first question is whether, from the viewpoint of EPA, the purpose of a 1979 Memorandum of Understanding (MOU) between EPA and the Federal Drug Administration (FDA) was "to take away from FDA, and give to EPA, responsibility for regulating public drinking water additives intended for preventative health care purposes and unrelated to contamination of public drinking water?" Your second question is whether, if that was the purpose of the 1979 MOU, the MOU was terminated through a subsequent Federal Register notice.

The answer to your first question is no, so there is no need to address your second question. The purpose of the MOU was not to shift any responsibilities between the Agencies. Rather, it was to help facilitate effective coordination of our respective legal authorities. Under the Safe Drinking Water Act (SDWA), EPA is the lead federal agency with responsibility to regulate the safety of public water supplies. EPA does not have responsibility for substances added to water solely for preventative health care purposes, such as fluoride, other than to limit the addition of such substances to protect public health or to prevent such substances from interfering with the effectiveness of any required treatment techniques. SDWA Section 1412(b)(11); see also A Legislative History of the Safe Drinking Water Act, Committee Print, 97th Cong, 2d Session (February 1982) at 547. The Department of Health and Human Services (HHS), acting through the FDA, remains responsible for regulating the addition of drugs to water supplies for health care purposes.

The 1979 MOU was intended to address contamination of drinking water supplies as a result of direct or indirect additives to drinking water, not to address the addition of substances solely for preventative health purposes. 44 Fed. Reg. 42775 (July 20, 1979) ("EPA and FDA agree: (1) that *contamination* of drinking water from the use and application of direct and indirect additives and other substances poses a potential public health problem...")(emphasis added). It was intended to avoid potentially duplicative regulation of "food", which FDA had, in the past, considered to include drinking water. 44 Fed. Reg. 42775 (July 20, 1979). The MOU did not address drugs or other substances added to water for health care purposes.

I hope that this has adequately answered your inquiry. Please do not hesitate to contact Carrie Wehling of my staff (202-564-5492) if you have further questions about this.

Sincerely,

Steven M. Neugeboren
Associate General Counsel
Water Law Office

FLUORIDATION PRODUCTS (FLUORIDATED WATERS (TAP OR BOTTLED) AND FLUORIDATION CHEMICAL ADDITIVES) ARE DRUGS

by

Gerald Steel PE
Attorney-at-Law
geraldsteel@yahoo.com

ABSTRACT: This paper presents a legal analysis that demonstrates that fluoridation products (fluoridated waters (tap or bottled) and fluoridation chemical additives) are drugs under the jurisdiction and responsibility of the federal Food and Drug Administrative (FDA) when the intended use is prevention of tooth decay disease.

(A public paper released October 29, 2016)

TABLE OF CONTENTS

ATTACHMENTS

ABBREVIATIONS

ANDA	Abbreviated New Drug Application
ANSI	American National Standards Institute
CFR	Code of Federal Regulations
DSHEA	Dietary Supplement Health and Education Act
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FDCA	[federal] Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
HHS	Health and Human Services
MCL	Maximum Contaminant Level
MOU	Memorandum of Understanding
NDA	New Drug Application
NRC	National Research Council
NSF	National Sanitation Foundation (now International)
OTC	Over-The-Counter
SDWA	Safe Drinking Water Act
TSCA	Toxic Substances Control Act
USC	United States Code

1. Review of federal drug laws and regulations

a. The 1906 and 1938 Acts of Congress

Drug regulation in the United States began with the Colonies and States adopting isolated laws as early as 1736. (Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 703-04 (D.C. Cir. 2007).) As early as 1848, the United States began limited drug regulation. (*Id*. at 704.) Congress adopted more comprehensive drug statutes in the Food and Drugs Act of 1906, which prohibited the manufacture of any drug that was "adulterated or misbranded." (*Id*. at 705.) This Act defined "drug" as:

> all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals;

and defined "food" as including "articles used for food [and] drink." (Food and Drugs Act of 1906 (emphasis supplied), 34 Stat. 768 (1906).)

Initially, this Act did not regulate false claims of the curative power of a drug but this was changed by Congress in 1912. (Samuels v. United States, 232 F. 536, 545 (8th Cir. 1916).) The 1906 Act, as amended, did not require government approval before a drug was introduced into the market. (United States v. Hiland, 909 F.2d 1114, 1125 (8th Cir. 1990).) This changed with the adoption by Congress of the federal Food, Drug, and Cosmetic Act ("FDCA") of 1938 which required a FDA approved new drug application ("NDA") to demonstrate a drug was safe before entering the market. (Samuels at 545.) No new approvals were required for drugs marketed under the 1906 Act only if their conditions of use remained unchanged. (*Id*.)

b. In 1952, after Congress defined prescription drugs, the FDA announced it would not enforce the FDCA for fluoridated public water

The Durham-Humphrey Amendment of 1951 (65 Stat. 648) for the first time explicitly defined two classes of medications (prescription and over-the-counter ("OTC")). (Christopher v. SmithKline Beecham Corp., 635 F.3d 383, 385 (9th Cir. 2011).) In 1952, in response to this amendment, the FDA adopted a regulation stating:

> (a) The program for fluoridation of public water supplies recommended by the Federal Security Agency, through the Public Health Service, contemplates the controlled addition of fluorine at a level optimum for the prevention of dental caries.
> (b) Public water supplies do not ordinarily come under the provisions of the Federal Food, Drug, and Cosmetic Act. . . .
> (c) The Federal Security Agency will regard water supplies containing fluorine, within the limitations recommended by the Public Health Service, as not actionable under the Federal Food, Drug, and Cosmetic Act.

(Former 21 CFR 3.27 (1952); 17 FR 6732; *infra* at B 23.) This regulation was recodified to former 21 CFR 250.203 in 1975. (40 FR 13996; *infra* at B 24.) It was published, as amended, in 1995. (*Infra* at B 25-26.)

c. In 1996 the FDA reversed its position to not enforce the FDCA regarding fluoridated water after the EPA/FDA MOU was terminated and after Congress adopted the DSHEA that defined minerals as drugs if used to prevent specific diseases

In 1996, the FDA determined that its 1952 regulation was obsolete or no longer necessary and the regulation was revoked. (61 FR 29476; *infra* at B 27.) The revocation of former 21 CFR 250.203 occurred after the federal Environmental Protection Agency ("EPA") announced the "Termination of the Federal Drinking Water Additive Program" effective April 7, 1990. (53 FR 25586-89; CP 142-45; *infra* at B 28-31.) The first and major Term of Agreement

of a 1979 Memorandum of Understanding ("MOU") between FDA and EPA was having EPA develop and operate the federal regulatory drinking water additives program:

> III. Terms of Agreement
>
> A. EPA's responsibilities are as follows:
>
> 1. To establish appropriate regulations, and to take appropriate measures, under the SDWA and/or TSCA, and FIFRA, to control direct additives to drinking water (which encompass any substances purposely added to the water)

(44 FR 42775-78; *infra* at B 33 and at B 38.) Arguably, EPA's Federal Register announcement of termination of its regulatory Federal Drinking Water Additives Program was effective notice to FDA that EPA was terminating the 1979 MOU and EPA was no longer obligated by this MOU to establish and operate a federal regulatory program to control direct additives to drinking water. (44 FR 42776, *infra* at B 33 and B 39 ("This [MOU] shall continue in effect unless . . . terminated by either party upon thirty (30) days advance written notice to the other.”))

The revocation of former 21 CFR 250.203 also occurred after the adoption by Congress of the Dietary Supplement Health and Education Act of 1994 (Pub. L. 103-417; "DSHEA"). This 1994 Act of Congress clarified Congressional intent that mineral additives [including fluoride] are drugs if the intended use is to prevent disease:

> A dietary supplement is deemed to be "food," [21 USC] 321(ff), which is defined in part as "articles used for food or drink for man or other animals," *Id*. § 321(f)(1), **except** when it meets the definition of a "drug," which is defined in part as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals."

(Alliance for Natural Health U.S. v. Sebelius, 714 F.Supp.2d 48, 50 (D.D.C. 2010) (emphasis supplied.)) Under the DSHEA, dietary supplements include minerals. (21 USC 321(ff)(1)(B);

infra at B 42.) **In adopting the DSHEA in 1994, Congress clarified its intent that fluoride minerals when used to prevent disease are drugs under federal law.** (21 USC 321(ff)(postscript), *infra* at B 43.) In 2000, the FDA Commissioner concurs.[1] (*Infra* at B 44.)

d. The 1962 Amendments to the 1938 Act

The Congress amended the FDCA in 1962 to change the standard for approval of a NDA or abbreviated NDA ("ANDA") from "safe" to "safe and effective" for the intended use. (Samuels at 545.) For drugs with approved NDAs under the 1938 Act to retain these NDAs, they were required to demonstrate they were effective. (*Id*.; Weinberger v. Hynson, Wescott & Dunning, Inc, 412 U.S. 609, 612-15, 93 S.Ct. 2469, 37 L.Ed.2d 207 (1973).)

e. In 1972, the FDA established a new approval process for non-prescription drugs

In 1972, the FDA established a new approval process for non-prescription drugs. (21 CFR Part 330.) This process resulted in the establishment of over-the-counter ("OTC") monographs for various drug classifications including a monograph for anticaries drug products that do not require a prescription. (21 CFR Part 355.) The final rule for the anticaries drug monograph is in 60 FR 52473-510. Amendments to this final rule are in 60 FR 57927, 61 FR 52285-87, 64 FR 13296, and 68 FR 24879-80. This final rule, as amended, provides that all OTC anticaries drug products introduced to the market after April 7, 1997 must comply with general conditions in 21 CFR 330.1 and with anticaries monograph conditions in 21 CFR Part

[1] Congress specifically asked FDA to address the relationship of "fluoride in drinking water and drug(s)." (*Infra* at B 44.) The FDA responded, in part, stating "the Environmental Protection Agency regulates fluoride in the water supply." (*Id*.) But EPA had terminated its water additive program more than ten years earlier. (*Supra* at B 2-3.) So FDA was referring to EPA regulating the Maximum Contaminant Level ("MCL") for fluoride that triggers clean-up under the SDWA and was not referring to regulation of fluoride additives for health care purposes.

355; otherwise a NDA or ANDA is required.

> On or after [April 7, 1997] no OTC drug product that is subject to the monograph and that contains a nonmonograph condition . . . may be initially introduced . . . into interstate commerce unless it is the subject of an approved application or abbreviated application.

(60 FR 52474; 61 FR 52285.) Also, it should be noted that FDA regulations provide that any anticaries drug that includes hydrogen fluoride requires a NDA. (21 CFR 310.545(a)(2) and (b).) Typical specification sheets for water treatment certified Fluorosilicic Acid show a significant portion of the fluoride comes from hydrogen fluoride. (*Infra* at B 47.) Some of the fluoride in water treatment certified Sodium Fluoride also comes from hydrogen fluoride. (*Infra* at B 50.)

2. <u>All drinking waters are drugs when fluoridation chemicals are added with intent to prevent, mitigate and/or prophylactically treat tooth decay disease</u>

a. The FDCA explicitly makes articles drugs when intended for use in the treatment, mitigation and/or prevention of disease

> The term "drug" means
> (A) articles recognized in the official United States Pharmacopoeia . . .; and
> (B) **articles intended for use in the** diagnosis, cure, **mitigation, treatment, or prevention of disease in man** or other animals; and
> (C) articles (other than food) intended to affect the structure of any function of the body of man or other animals; and
> (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). . . .

(21 USC 321(g)(1); *infra* at B 41; emphasis supplied.) The language quoted has not been amended since it was originally adopted in the 1938 Act. (52 Stat. 1041.)

b. Fluoridated drinking waters (bottled or tap (from public water systems)), and fluoridation chemical additives (whether or not certified under NSF/ANSI Standard 60) are drugs under 21 USC 321(g)(1) when the intended use is to aid in the prevention, mitigation and/or prophylactic treatment of dental caries disease (tooth decay, cavities)

Based on 21 USC 321(g)(1)(B) when fluoridated drinking water is intended to aid in the prevention, mitigation and/or prophylactic treatment of dental caries disease (tooth decay, cavities) it is a drug under the FDCA. **There is nothing in the FDCA that would suggest otherwise and HHS and FDA have not made the claim that there is.** Similarly, based on 21 USC 321(g)(1)(B) fluoridation chemical additives that are intended to aid in the prevention, mitigation and/or prophylactic treatment of dental caries disease are drugs under the FDCA. When fluoridation chemical additives are intended for use as a component of fluoridated drinking water, then these fluoridation chemical additives are also drugs under 21 USC 321(g)(1)(D). There is no provision in the FDCA that would cause either fluoridated tap water or fluoridated bottled water to not be considered a drug when the intended use is to aid in the prevention, mitigation and/or prophylactic treatment of dental caries disease (tooth decay, cavities).

c. It should be presumed that the intended use of fluoridation chemical additives and fluoridated waters (bottled or tap) using such additives is to aid in the prevention, mitigation and/or prophylactic treatment of dental caries disease (tooth decay, cavities)

Today, in almost every state, water fluoridation chemical additives are required to be certified to ANSI/NSF Standard 60. For example, in Washington State:

> Any treatment chemicals, with the exception of commercially retailed hypochlorite compounds such as unscented Clorox, Purex, etc., added to water intended for potable use must comply with ANSI/NSF Standard 60. The maximum application dosage recommendation for the product certified by the ANSI/NSF Standard 60 shall not be exceeded in practice.

WAC 246-290-220(3). NSF, an author of ANSI/NSF Standard 60, states in its 2008 NSF Fact Sheet on Fluoridation Chemicals:

> Water fluoridation . . . . Fluoride is added to water for the public health benefit of preventing and reducing tooth decay

(*Infra* at B 73.) In 2011, HHS confirmed its belief that:

> Community water fluoridation is the most cost-effective method of delivering fluoride for the prevention of tooth decay.

(76 FR 2386; *infra* at B 51.)

The FDA has concluded that the intended use is implied for fluoride additives to prevent tooth decay. The FDA finds that intended use "may be shown by the circumstances surrounding the distribution of the article." (21 CFR 801.4.) The FDA states:

> in some instances, the mere presence of certain therapeutically active ingredients could make a product a drug even in the absence of drug claims. In these cases, the intended use would be implied because of the known or recognized drug effects of the ingredient (e.g. fluoride in a dentifrice).

(59 FR 6088.) The intended use of added fluoride in drinking water is also implied and should be presumed. The FDA's interpretation of "intent" is entitled to "considerable deference." (Young v. Community Nutrition Institute, 476 U.S. 974, 981, 106 S.Ct. 2360, 90 L.Ed.2d 959 (1986).) The Washington State Board of Health states,

> The Board considers it self-evident that the purpose of water fluoridation is to help prevent tooth decay.

(*Infra* at B 52.)

The CDC states, "Tooth decay (dental caries) is an infectious, multifactorial disease." (Infra at B 54.) The FDA defines "dental caries" as "A disease of calcified tissues of teeth characterized by demineralization of the inorganic portion and destruction of the organic matrix" and defines "anticaries drug" as "A drug that aids in the prevention and prophylactic treatment of

dental cavities (decay, caries). (21 CFR 355.3(c) and (d).)

d. The language in 21 USC 321(g)(1)(B) defining drugs must be interpreted "as broad as its literal language indicates"

As early as 1916, the federal Supreme Court concurred that products that were otherwise defined as "foods" would be "drugs" under the federal statute[2] when labeling for the substance includes statements of therapeutic (including preventative) effect. (Seven Cases v. United States, 239 U.S. 510, 513-14, 36 S.Ct. 190, 60 L.Ed. 411 (1916).)

After the 1938 Act was adopted, the federal Supreme Court again concurred that "food products" will be "drugs" based on intended use and "labeling." (Kordel v. United States, 335 U.S. 345, 346, 69 S.Ct. 106, 93 L.Ed. 52 (1948).) In 1969, the federal Supreme Court, in finding a product was a drug, explained:

> Congress intended to define "drug" [in 21 USC 321(g)(1)(B)] far more broadly than does the medical profession. . . . The word "drug" is a term of art for the purposes of the Act, encompassing far more than the strict medical definition of that word.

(United States v. An Article of Drug . . . Bacto-Unidisk, 394 U.S. 784, 793, 89 S.Ct. 1410, 22 L.Ed.2d 726 (1969).) The Bacto-Unidisk Court continued:

> Congress fully intended that the Act's coverage be **as broad as its literal language indicates** - and, equally clear, broader than any strict medical definition might otherwise allow. . . . **the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health.**

(*Id*. at 798; emphasis supplied.) The Bacto-Unidisk Court finally directed,

> we must take care not to narrow the coverage of a statute short of the point where Congress indicated it should extend.

---

[2] The relevant portion of the federal statute are quoted *supra* at B 1.

(*Id*. at 801.)

In the construction of federal statutes, "the decisions of the Supreme Court of the United States are binding" upon all. (Beezer v. City of Seattle, 62 Wn.2d 569, 573, 383 P.2d 895 (1963).) Therefore, HHS and FDA and every court is required to construe the definition of drug as "articles intended for use in the . . . prevention of disease" as "broad as its literal language indicates." (*Supra*.)

e. Foods must be regulated as drugs if the "intended use" is to prevent disease

Interpretation of federal statutes by other federal courts are entitled to great weight. (Beezer at 573.) A long line of federal court cases has found that articles normally regulated as "foods" will be regulated as "drugs" if the intended use is to treat or prevent a disease:

> The word "drug" is defined in 21 U.S.C. s 321(g)(1)(B) to include:
>
> articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals . . .
>
> Thus, it is the intended use of an article which determines whether or not it is a "drug," and even the most commonly ingested foods and liquids are "drugs" within the meaning of the [FDCA] if their intended use falls within the definition of s 321(g)(1)(B).

Gadler v. United States, 425 F.Supp. 244, 246-47 (D.Minn. 1977); *see* Nutrilab, Inc. v. Schweiker, 713 F.2d 335, 336 (7th Cir. 1983); *see also* Bradley v. United States, 264 F.79 (5th Cir., 1920) where the court specifically found "mineral water" to be a "drug" when it is intended to treat disease.

In the determination of whether fluoridation products (fluoridated waters (tap or bottled) and fluoridation chemical additives) are drugs,

> the only question under the [FDCA] is whether the intended use of the product is to prevent disease, not whether the product actually prevents disease.

(United States v. Bowen, 172 F.3d 682, 686 (9th Cir. 1999).) Intent "may be derived or inferred from [any] relevant source." (National Nutritional Foods Ass'n v. Mathews, 557 F.2d 325, 334 (2nd Cir. 1977).) As discussed previously, it should be presumed that the "intended use" of fluoridation products is to prevent dental caries (tooth decay) disease. (*Supra* at B 6-8.)

f. The DSHEA further clarifies the intent of Congress that fluorides, which are minerals, that are added to drinking water to prevent the disease of dental caries, are drugs

Perhaps partly in response to the FDA's refusal to enforce the FDCA for fluoridated water supplies (*supra* at B 2), Congress adopted the DSHEA in 1994, with explicit statutory language that made fluoride a drug when used with intent to prevent disease. Fluoride, being a mineral, is a dietary supplement under DSHEA. (21 USC 321(ff)(1)(B); *infra* at B 42.) Minerals are normally regulated as foods except when they are drugs. (21 USC 321(ff)(postscript) ("**except** for purposes of [21 USC 321(g)(1) defining drugs] a dietary supplement shall be deemed to be a food;") *infra* at B 43 (emphasis supplied).)

g. Congress did not intend to exempt public water or water additives from the reach of federal drug laws

In 1974, Congress passed the Safe Drinking Water Act ("SDWA"). (88 Stat. 1661; codified at 42 USC 300f et seq.) The SDWA empowered the EPA to set standards for the control of contaminants in drinking water. (42 USC 300g-1(b); *see* In re Groundwater Cases, 154 Cal.App.4th 659, 677 (2007).) The SDWA authorizes EPA to adopt national primary drinking water regulations applicable to "public water systems." (42 USC 300f(1); *see* 42 USC

300f(4)(A).) Under the SDWA, national primary drinking water regulations identify contaminants that have adverse effects on human health and specify a maximum contaminant level ("MCL") for such contaminants. (42 USC 300f(1).) Pursuant to its authority under the SDWA, the EPA has since established MCLs for a wide variety of contaminants. (*See* 40 CFR Pt. 141 for substantive regulations, Pt. 142 for implementation regulations, and Pt. 143 for national secondary drinking water regulations that are not enforceable.) The fluoride MCL is 4.0 mg/l (four milligrams per liter which is 4 parts per million (ppm)). (40 CFR 141.62(b)(1).)

But there is no SDWA statutory provision or implementing regulation that addresses or sets standards for fluoridation chemical additives.[3] (SDWA; 40 CFR Part 141 et seq.) Therefore, there is no possible statutory conflict where Congress intended the SDWA to interfere with the FDCA or FDA authority to regulate drugs. If Congress wanted to exempt public drinking water from the definition of drugs in 21 USC 321(g)(1)(B) it certainly had the knowledge of how to do it (it had previously exempted "food" from subsection (1)(C)) and it certainly had the opportunity to do it in any one of the more than 20 significant amendments made to the FDCA since 1980. (*Infra* at B 56-57.) The SDWA did not explicitly or implicitly repeal any drug provision of the FDCA or any drug authority of the FDA.

h. Arguably, the 1979 EPA/FDA MOU has been terminated but never did restrict FDA authority over drugs

i. <u>The 1979 MOU</u>

In 1979, EPA and FDA entered into an MOU where FDA agreed not to enforce its food

[3] There is a SDWA statutory provision that directs the EPA to keep away from regulating drugs. (42 USC 300g-1(b)(11) ("No national primary drinking water regulation may require the addition of any substance for preventive health care purposes unrelated to contamination of drinking water."))

authority over public drinking water in exchange for EPA creating a federal regulatory drinking water additives program. (*Infra* at B 32-39.) In the FDCA, Congress gave FDA authority to regulate foods to ensure they are "safe" (21 USC 393(b)(2)(A)) and drugs to ensure they are "safe and effective" (21 USC 393(b)(2)(B)). Normally for drinking water, only food regulations would be applicable and prior to 1979, the FDA generally regulated drinking water as a food. (*Infra* at B 32 and B 37.) But after passage of the SDWA, EPA and FDA were concerned that FDA's "food" authority and EPA's "public drinking water" authority might result in "duplicative and inconsistent regulations" so they entered an MOU. (*Supra* at B 2-3, *Infra* at B 32.) In the MOU, FDA agreed not to use its "food" authority to regulate public drinking water, based on a commitment that EPA would adopt federal regulations to control additives in public drinking water. (*Supra* at B 2-3, *Infra* at B 32-33.)

There is no mention in the MOU that FDA would, or could, give up its "drug" authority over public drinking water and public drinking water additives. (Infra at B 32-39.) Congress required "drugs" to be "effective" (21 USC 393(b)(2)(B)) and Congress never gave EPA authority to regulate drug effectiveness. The MOU inartfully states:

> [EPA and FDA] have determined that the passage of the SDWA in 1974 implicitly repealed FDA's authority under the [FDCA] over water used for drinking water purposes.

(*Infra* at B 32.) Read in context with the other provisions of the MOU this can only possibly be true with respect to FDA's "food" authority and cannot be true with respect to FDA's "drug" authority. (*Infra* at B 32-34; *See* Board of Governors of the Federal Reserve System, 474 U.S. 361, 368, 106 S.Ct. 681, 88 L.Ed.2d 691 (1986) ("agency interpretation" cannot "alter the clearly expressed intent of Congress."))

In a subsequent section, the MOU states:

> [EPA and FDA] agreed that the Safe Drinking Water Act's passage in 1974 implicitly repealed FDA's jurisdiction over **drinking water as a "food"** under the [FDCA].

(*Infra* at B 33; emphasis supplied.) Thus the MOU itself clarifies that the MOU only was intended to address FDA's regulations regarding "food." The MOU also inartfully states:

> Under the agreement, EPA now retains exclusive jurisdiction over drinking water served by public water supplies, including any additives in such water.

(*Infra* at B 33.) In context of the whole agreement, EPA does not have exclusive jurisdiction when public drinking waters, and public drinking water additives, are "drugs" because Congress has given exclusive jurisdiction over drugs to the FDA. (21 USC 393(b)(2)(B); FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 126, 120 S.Ct. 1291, 146 L.Ed.2d 121 (2000).) Congress has clearly defined "drugs" in 21 USC 321(g)(1). Further EPA claims no authority that would give it jurisdiction over the determination of "effectiveness" of drugs. (*Infra* at B 32-35.)

ii. Arguably, the 1979 MOU is terminated

In 1988, EPA published in the Federal Register a "Notice"that it was terminating EPA's commitment to FDA to create a federal regulatory drinking water additives program. (53 FR 25586-89; *infra* at B 28-31.) In this 1988 Notice, EPA admits that it "does not currently regulate the levels of additives in drinking water." (*Infra* at B 28.) EPA explained that the "SDWA does not require EPA to control the use of specific additives in drinking water." (*Infra* at B 28.) It states,

> Resource constraints and the need to implement mandatory provisions of the SDWA precluded the Agency from implementing the comprehensive program originally

envisioned . . .

(*Infra* at B 29.) The Notice describes how EPA was cooperating with a private third-party organization to have that organization take over the development and monitoring of standards for public drinking water additives and explained that it would be "up to the States and utilities to determine the suitability of any 'third-party' certification." (*Infra* at B 28-30.) Then it announced that effective April 7, 1990, it would withdraw all EPA and predecessor agency lists of acceptable water additive products and all EPA and predecessor agency advisory opinions on drinking water additives. (*Infra* at B 31.) EPA stated that "Discontinuance of the additives program at EPA does not relieve the Agency of its statutory responsibilities." (*Infra* at B 31.)

Arguably, EPA's Federal Register published Notice that it was terminating its commitment to FDA to create a regulatory federal drinking water additives program was effective notice to FDA that EPA was exercising its option to terminate the MOU. *(Supra* at B 2-3.) Thus, arguably, the 1979 MOU was terminated by 1990 and EPA removed the cloud over FDA's "food" jurisdiction regarding public fluoridated water. FDA never lost "drug" jurisdiction over fluoridated water, but its policy, that it would not enforce this jurisdiction, remained in effect from 1952 to 1996. (*Supra* at B 2-3.)

i. The intent of Congress clearly establishes that water fluoridation products are drugs under the FDCA

In 1916, the federal Supreme Court concurred that Congress in adopting the 1906 Act directed that food be regulated as a drug when therapeutic (including preventative) effects are intended. (*Supra* at B 8.) In the 1938 Act, Congress significantly broadened, instead of limited, the definition of drugs. (*Compare supra* at B 1 and B 5.) In 1948, the federal Supreme Court

again concurred "food products" will be "drugs" depending on intent and "labeling." (*Supra* at B 8.)

In 1952, the FDA stated it would not enforce the FDCA for fluoride added to public water supplies. (*Supra* at B 2.) In 1969, the federal Supreme Court ruled that the FDCA definition of drugs is "as broad as its literal language indicates." (*Supra* at B 8-9.) In 1994, the Congress again specifically clarified that minerals will be drugs if they fall within the broad definition of drugs. (*Supra* at B 3-4 and 10.) In 1996, the FDA revoked its policy that it would not enforce the FDCA for fluoride added to public water supplies. (*Supra* at B 2.)

Every department and agency and court is bound by the intent of Congress as explained by the federal Supreme Court. (*Supra* at B 9.) Therefore, the FDA should find that water fluoridation products (fluoridated waters (tap or bottled) and fluoridation chemical additives) are drugs under federal law and regulation when the intended use is to aid in the prevention, mitigation, and/or prophylactic treatment of dental caries disease (tooth decay, cavities). And based on the history of fluoridation, it should be presumed that this is the intended use of water fluoridation products. (*Supra* at B 9-10.)

3. HHS, acting through the FDA, is responsible for regulating the addition of fluoride to public drinking water

_____ Despite the Federal Supreme Court ruling in Bacto-Unidisk (*supra* at B 8-9), HHS and FDA appear to now argue that certain fluoridation products (fluoridated public waters and fluoridation chemical additives) are not drugs. It is uncontested by HHS and FDA that these fluoridation products are articles intended to prevent dental caries disease in man. (*Supra* at B 6-8.) Under Bacto-Unidisk and other federal court rulings (*supra* at B 7 to B 9), these fluoridation

products are therefore within the definition of a "drug" in 21 USC 321(g)(1)(B).

However, HHS and FDA interpret the Safe Drinking Water Act of 1974 (SDWA) as removing HHS and FDA jurisdiction over these fluoridation products:

> *Congress did not intend for FDA to regulate the addition of fluoride to public drinking water for dental caries prevention as a drug under the FD&C Act. Instead, Congress intended that the U.S. Environmental Protection Agency (EPA) regulate fluoride in public drinking water as a potential contaminant under the Safe Drinking Water Act of 1974 (SDWA).*

(*Infra* at B 59 and B 66: B 58 to B 62 is a November 21, 2014 letter from HHS Principal Deputy Assistant Secretary for Health Dr. Wanda Jones to Ms. McEtheney; B 63 to B 68 is a December 23, 2013 Request for Review to Jill Warner, FDA Associate Commissioner for Special Medical Programs from Gerald Steel (FDA has not yet responded to this Request for Review).)

HHS and FDA argue that the SDWA provides:

> that within the limits thus set by EPA, state and local governments be permitted, but not required, to fluoridate public drinking water to help prevent dental caries.

(*Infra* at B 59 and B 66.) Thus, HHS and FDA argue that under their interpretation of the SDWA, FDA has no responsibility to regulate such fluoridation products that are articles that meet the definition of a drug in 21 USC 321(g)(1)(B).

The fundamental problem with this HHS and FDA interpretation of the SDWA is that it is in conflict with the EPA interpretation of the SDWA. The SDWA gives administrative authority to the EPA. (42 USC 300f(7 and 8).) Along with administrative authority comes the sole agency power to interpret the Act. Chevron USA v. NRDC, 467 U.S. 837, 842-45, 104 S.Ct. 2778, 81 L.Ed.2d 694 (1984).

Steven M. Neugeboren is the Associate General Counsel in charge of the Water Law Office of the EPA. The Water Law Office is responsible for interpreting the SDWA.[4] Mr. Neugeboren states:

> Under the Safe Drinking Water Act (SDWA), EPA is the lead federal agency with responsibility to regulate the safety of public water supplies. EPA does not have responsibility for substances added to water solely for preventative health care purposes, such as fluoride, other than [to meet maximum contaminant limits.] The Department of Health and Human Services (HHS), acting through the FDA, remains responsible for regulating the addition of drugs to water supplies for health care purposes.

(*Infra* at 69-70 - February 14, 2013 letter written on behalf of EPA Administrator Lisa Jackson to Gerald Steel.) Therefore the EPA's interpretation of the SDWA is that this Act does not affect the responsibility of the FDA "for regulating the addition of drugs to water supplies for health care purposes." Therefore HHS and FDA misinterpret Congressional intent when they state:

> Congress did not intend for FDA to regulate the addition of fluoride to public drinking water for dental caries prevention as a drug under the FD&C Act.

(Infra at B 59 and B 66.)

HHS and FDA are correct that the SDWA does give EPA lead responsibility for regulating the safety of public water supplies to protect against adverse health effects. Except for authorizing regulation of the maximum contaminant level for fluorides, the SDWA does not address state and local governments fluoridating public drinking water to help prevent dental caries. But the state and local governments which fluoridate must comply with all applicable laws and regulations including federal drug laws in the FDCA, state drug and fluoridation laws,

[4] http://www2.epa.gov/aboutepa/about-office-general-counsel-ogc#water

federal drug regulations, and state drug and fluoridation regulations. The EPA has determined that state fluoridation regulations are not related to the SDWA. (*Infra* at B 71-72 - November 17, 2011 letter written on behalf of EPA Region 10 Administrator to Gerald Steel.)

Under this analysis and the interpretations of the SDWA by the EPA: HHS and FDA should find that fluoridation products are drugs when they meet the definition of a drug in 21 USC 321(g)(1)(B). HHS, acting through the FDA, has responsibility to regulate these drugs to ensure that they are safe and effective.

4. FDA should request registration of all water fluoridation products as drugs pursuant to 21 CFR Part 207

It is requested that FDA request registration of all water fluoridation products as drugs pursuant to 21 CFR Part 207. In most states, lists of public water purveyors making fluoridated waters are available from State Health Departments. In most states, fluoridation chemical additives must be certified to meet ANSI/NSF Standard 60. (*Supra* at B 6.) There are only three organizations that certify products to ANSI/NSF Standard 60 and their web addresses are www.nsf.org/, www.ul.com/eph/, and www.wqa.org/. These organizations can be contacted to get current lists of ANSI/NSF Standard 60 certified fluoridation chemical additive products and manufacturers.

To facilitate determination of the legal drug status of these fluoridation products, it is requested that FDA request for each fluoridation product, for each year the product was marketed or proposed for future use, a copy of all certificates of analysis and product labeling (both on any packaging and from any other documents (electronic, print, or otherwise) describing the product or describing the purpose of using fluoride additives, or describing the conditions of use that are

recommended or suggested.) For water purveyors, the documents describing the purpose of fluoride additives, likely would include documents associated with the decision to begin fluoridation and documents, including materials sent to customers, that later describe on-going reasons for fluoridation. Because certification to ANSI/NSF Standard 60 began around 1990, it is expected that fluoridation chemical additive labeling was changed around that time to declare certification. It is likely that all fluoridation product manufactures will be required to get approved new drug applications or approved abbreviated new drug applications.

5. FDA should find that fluoridation products are not "safe and effective"

Once it accepts jurisdiction, FDA should find that fluoridation products are not safe and effective as drugs. While this is a subject that will only be addressed after HHS and FDA accept drug jurisdiction over fluoridation products, it is useful to point out the harms that HHS and FDA are allowing to occur because they have not accepted drug jurisdiction over fluoridation products.

An important overview was provided in the York Review in 2000 (M. McDonagh, P. Whiting, M. Bradley, et al., "A Systematic Review of Water Fluoridation," NHS Centre for Reviews and Dissemination, The University of York, Report 18 (2000) which is available at: (http://www.york.ac.uk/inst/crd/CRD_Reports/crdreport18.pdf). The potential harms explored by the York Review include dental fluorosis, hip fracture, other bone fractures, cancer, Down's syndrome, mortality, senile dementia, goitre, lowered IQ, hypersensitivity, and skeletal fluorosis. (York Review at 52, 54, 59-60.) The York Review concludes that except for dental fluorosis, no "confident statements" can be made regarding these "potential harms." (York Review at page xiv.) In other words, these other "potential harms" could not be ruled out by the available scientific literature.

a. Dental fluorosis is an out-of-control harm of water fluoridation

There is scientific consensus that fluoridated water causes dental fluorosis. HHS reported that 41% of people who were 12 to 15 years old in 1999 to 2004 had dental fluorosis with this dental fluorosis being moderate or severe for 3.6% of these people (one in twenty eight people). (76 FR 2385.) Even if water fluoridation is reduced to 0.7 mg/l fluoride as HHS now recommends, the number of people with dental fluorosis is likely to increase because in 1992 when these people were 0 to 8 years old, only 56% of the people in the United States received fluoridated water. Today a much higher percentage of people receive fluoridated water.

b. The FDA has already concluded that fluoride OTC products should not be swallowed except under professional supervision

The FDA has already concluded that fluoride OTC anti-cavity products should not be swallowed except under professional supervision. (21 CFR Part 355.) Fluoridation chemical additives are intended to be mixed with water and swallowed by everyone. At a minimum, fluoridated water is harmful to infants and children under 6. Warnings are required for OTC products to avoid swallowing by infants and even children under six. (21 CFR 355.50.) Bottled water regulations do not even allow a health claim for fluoridated water marketed to infants. (www.fda.gov/food/ingredientspackaginglabeling/labelingnutrition/ucm073602.htm)

c. York Review studies repeatedly show that artificial water fluoridation increases risk of hip fracture in people 65+ years old

The York Review was limited to review of human epidemiological studies of water fluoridation (around 1 mg/l fluoride). Over 3,200 primary studies were identified but only 9 studies met relevance criteria and measured risk of hip fracture for people 65+ years old in fluoridated areas compared to the risk in unfluoridated areas. (York Review at 10 and 48.) For

these 9 studies, there were only 4 analyses that produced statistically significant data (i.e. the relative risk of 1.0 was not in the 95% Confidence Interval). Each of these statistically significant analyses show an increased risk of hip fracture for people 65+ years old living in fluoridated areas. The studies are identified in the York Review at page 48 as:

Author (Year)	Sex	Relative Risk	95% Confidence Interval
Jacqmin-Gadda (1998)	Both	2.43	(1.1, 5.3)
Danielson (1992)	Women	1.27	(1.1, 1.5)
Jacobsen (1992)	Women	1.08	(1.06, 1.10)
Jacobsen (1992)	Men	1.17	(1.13, 1.22)

Relative Risk is defined as the risk of an adverse effect with exposure to a treatment (here fluoridated water) relative to risks for those who do not receive the treatment. (York Review at 99.) A ratio of 1.0 indicates no increased risk over receiving no treatment. (*Id*.) A ratio greater than 1.0 indicates the risk is higher in the group that did receive the treatment. (*Id*.) A ratio less than 1.0 indicates the risk of the adverse effect is higher in the group that did not receive treatment. (*Id*.) A Relative Risk of 1.27 means that there is a 27% higher risk of hip fractures when living in a fluoridated area (for 65+ year old women in the Danielson (1992) analysis).

Hip fracture for people 65+ years old is a significant health impact in the United States. "About 300,000 Americans are hospitalized for a hip fracture every year." (Connett (2010) at page 173.) The Irish Forum (2002) (Forum on Fluoridation (Dublin, Ireland: Stationery Office, 2002) online at http://fluoridealert.org/re/fluoridation.forum.2002.pdf found that "Fracture of the hip is a major cause of morbidity and mortality [disease and death] in persons 65 years of age and older."

> Aside from the fact that one in five patients die within 6 months of the fracture occurring, hip fractures lead to serious disability. Many basic functions such as dressing, climbing stairs, walking and transferring are markedly interfered with following a fracture. This can result in loss of both confidence and independence and an increased risk of development of medical complications.

(Irish Forum (2002) at 121.)

d. Fifty human studies agree that higher fluoride exposure is associated with a mental health impact that lowers IQ levels in children

Lowered IQ in persons who drink fluoridated water as infants and children is a significant mental health concern. The National Research Council (2006) states, "It is apparent that fluorides have the ability to interfere with the functions of the brain." (NRC, Fluoride in Drinking Water - A Scientific Review of EPA's Standards (Washington D.C.; The National Academies Press, 2006.) As of September, 2016, 50 of 57 human studies found elevated fluoride exposure is associated with reduced IQ and 45 animal studies have found fluoride exposure impairs the learning and/or memory capacity of animals. (http://fluoridealert.org/studies/brain01/)

> The lowest level at which IQ has been lowered (with borderline iodine deficiency) was at 0.88 ppm [fluoride in drinking water] (Lin et al., 1991) or at 1.26 ppm (without iodine as a complicating factor). It is very clear that there is no margin of safety to protect all children drinking water in the range 0.7 to 1.2 ppm.

Dec. 12, 2014 email from Paul Connett, PhD., then Director, Fluoride Action Network.

e. Drinking fluoridated water increases risk of hypothyroidism disorder

A large observational study was published in the online Journal Of Epidemiology and Community Health, a British Medical Journal (BMJ) publication, on February 24, 2015 that found rates of diagnosed hypothyroidism (underactive thyroid) were at least 30% higher in areas with artificial fluoridation. (Peckham (2015) -J Epidemiol Community Health doi:10.1136/jech-2014-204971.) The study states that thyroid dysfunction is a common endocrine disorder. The National

Research Council ((2006) at 223 called fluoride an endocrine disrupter and at 218 expresses concern about "the inverse correlation between asymptomatic hypothyroidism in pregnant mothers and the IQ of the offspring."

f. Boys drinking fluoridated water when they are 6 to 8 years old have a five to seven-fold greater risk of contracting bone cancer by the age of twenty

Regarding cancer, an unrefuted published primary study, Bassin (2006) (Bassin E. B. et al., "Age-specific Fluoride Exposure in Drinking Water and Osteosarcoma (United States)," Cancer Causes and Control 17, no. 4 (May 2006) 421-28) reports that boys who drink fluoridated water when they are 6 to 8 years old will have a five- to sevenfold greater risk of contracting osteosarcoma (bone cancer) by the age of twenty. This is a deadly disease. This result was first suggested by Perry Cohn in 1992. (*See* Connett (2010) at pages 187-94.) The twofold increase in cortical bone defects in the fluoridated city in the Kingston-Newburgh study (*supra* at B 20.) was described in 1955 and again in 1977 as being "strikingly similar to that of osteogenic sarcoma [now called osteosarcoma]." (*See* Connett (2010) at page 181-94.)

6. <u>FDA has correctly determined that fluoridated bottled water is a drug when there is a claim that "this drinking water is intended for use in the prevention of tooth decay disease"</u>

In a September 23, 2015 letter (B 74-75 hereto), the FDA found that fluoridated bottled water with 0.7 mg/l fluoride would be a drug if the claim is made that "this drinking water is intended for use in the prevention of tooth decay disease." In fact, fluoridated bottled water with this claim would be an "anticaries drug" as that term is defined by the FDA in 21 CFR 355.3(c) and (d). (*Supra* at B 7-8.) Such fluoridated bottled waters when introduced after April 7, 1997 would be required to have an approved New Drug Application (NDA) or Abbreviated NDA

(ANDA) because they would not be able to meet requirements of 21 CFR Part 355 which do not allow anticaries drugs to be swallowed without professional supervision. (*See supra* at B 4-5.) Under current law, it would be illegal to distribute such fluoridated bottled water in interstate commerce without an approved NDA or ANDA. Because such fluoridated bottled waters would be drugs, the fluoridation chemical additives, which are a component of such fluoridated bottled waters, would also be drugs. (21 USC 321(g)(1)(D).)

7. FDA must now find that fluoridated tap water is a drug when there is a claim that "this drinking water is intended for use in the prevention of tooth decay disease"

FDA must now find that fluoridated tap water is a drug when there is a claim that this drinking water is intended for use in the prevention of tooth decay disease. The FDA must also find that the fluoridation chemical additives, which are a component of such fluoridated tap waters, are also drugs. (USC 321(g)(1)(D).) The FDCA allows no distinction between fluoridated waters with the same contents whether they are served as drinking water either from a bottle or from a tap. Both are anticaries drugs under the FDCA if the drinking water is intended for use in the prevention of tooth decay disease. More generally, fluoridated drinking waters are anticaries drugs if the intended use is to aid "in the prevention and prophylactic treatment of dental cavities (decay, caries)." (21 CFR 355(3)(c).)

Today, as fluoridated water purveyors modify their fluoridated waters to meet the latest HHS recommendation to add fluoride to get 0.7 mg/l fluoride in the finished water, these water purveyors are making a new drug and are subject to new drug requirements for an approved NDA or ANDA and subject to the FDA requirements to show that their unique products are safe and effective.

The FDA can no longer rely on its prior reasoning (*Infra* at B 59 and B 66) that the intent of the SDWA was to eliminate FDA authority and responsibility under the FDCA to regulate substances that qualify as anticaries drugs under the USC and CFR. EPA is the agency with final agency authority to interpret the SDWA, and EPA interprets the SDWA to not remove the authority of HHS, acting through the FDA, regarding "regulating the addition of drugs to water supplies for health care purposes." (*Infra* at B 69.)

So while it is true that state and local governments may be permitted to fluoridate drinking waters to help prevent dental caries, they must do so in compliance with local, state, and federal laws and regulations which include federal requirements to consider such fluoridated waters to be drugs if the drinking waters are "intended for use in the prevention of tooth decay disease" or if the drinking waters otherwise meet the definition of drugs in section 201(g)(1) of the FDCA (21 USC 321(g)(1)). FDA, acting on behalf of HHS, has the authority and responsibility to regulate drugs by implementing the applicable federal laws and regulations and by adopting regulations when necessary to fulfill its responsibilities.

It is time for the FDA to be responsible and to require fluoridation products (fluoridated waters (tap or bottled) and fluoridation chemical additives) to be federally regulated as drugs when the intended use is prevention of tooth decay disease.

customs Form 4449 showing the name of the airport, date and time of arrival, date and time of departure and purpose of the visit. The permit shall be surrendered to the collector of customs at the port of final clearance for a foreign destination, who shall satisfy himself prior to the issuance of clearance that the aircraft received proper customs treatment while in this country. The permit shall then be returned to the collector of customs at the port of issue.

(2) A copy of the permit shall be retained by the collector at the port where issued. If within 60 days after the issuance of such permit the said collector does not receive a report of the outward clearance of the aircraft covered thereby, the matter shall be reported to the supervising customs agent for investigation.

(3) Civil aircraft registered in the United States arriving from a foreign country with passengers carried for hire or merchandise, after proper customs treatment of their cargo (passengers carried for hire or merchandise), may be allowed to proceed upon their identity being established.

This order shall become effective on the date of its publication in the FEDERAL REGISTER.

(R. S. 161, sec. 23, 5 Stat. 892, as amended, sec. 24, 43 Stat. 166, R. S. 251, secs. 624, 644, 46 Stat. 759, 761, secs. 201, 367, 58 Stat. 683, 706, sec. 7, 44 Stat. 57, as amended; 5 U. S. C. 22, 8 U. S. C. 102, 222, 19 U. S. C. 66, 1624, 1644, 42 U. S. C. 202, 270, 49 U. S. C. 177)

[SEAL] D. A. STRUBINGER,
Acting Commissioner of Customs.
JOHN S. GRAHAM,
Acting Secretary of the Treasury.
W. P. DEARING,
Acting Surgeon General,
U. S. Public Health Service.
JOHN L. THURSTON,
Acting Federal Security Administrator.
PHILIP B. PERLMAN,
Acting Attorney General.

JULY 17, 1952.

[F. R. Doc. 52-8054; Filed, July 22, 1952; 8:55 a. m.]

[T. D. 53046]

PART 10—ARTICLES CONDITIONALLY FREE, SUBJECT TO A REDUCED RATE, ETC.

SUPPLIES FOR VESSELS OF WAR

The Department of State has furnished the Treasury Department an up-to-date list of countries which permit the withdrawal of supplies free of duty and tax by vessels of war of the United States while in ports of those countries. Therefore, § 10.59 (d), Customs Regulations of 1943 (19 CFR 10.59 (d)), containing a list of countries whose vessels of war shall be accorded the privilege of withdrawing supplies free of customs duties and internal-revenue tax while in ports of the United States, as provided for in section 309 (a), Tariff Act of 1930, as amended, is further amended to read as follows:

§ 10.59 *Exemption from customs duties and internal revenue tax.* * * *

(d) The privilege shall be accorded to vessels of war of the following countries:

Argentina.
Australia.
Belgium.
Brazil.
Canada.
Chile.
Colombia.
Cuba.
Denmark.
The Dominican Republic.
Ethiopia.
Finland.
France.
Great Britain.
Greece.
Haiti.
India.
Ireland.
Mexico.
The Netherlands.
New Zealand.
Nicaragua.
Norway.
Panama.
The Philippines.
El Salvador.
Spain.
Sweden.
Thailand.
Turkey.
Union of South Africa.
Uruguay.
Venezuela.

(Sec. 5, 52 Stat. 1080; 19 U. S. C. 1309)

[SEAL] FRANK DOW,
Commissioner of Customs.

Approved: July 16, 1952.

JOHN S. GRAHAM,
Acting Secretary of the Treasury.

[F. R. Doc. 52-8025; Filed, July 22, 1952; 8:48 a. m.]

TITLE 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Federal Security Agency

PART 3—STATEMENTS OF GENERAL POLICY OR INTERPRETATION

FLUORIDATED WATER AND PROCESSED FOODS CONTAINING FLUORIDATED WATER

Pursuant to section 3 of the Administrative Procedure Act (60 Stat. 237, 238; 5 U. S. C. 1002), the following statement of policy is issued:

§ 3.27 *Status of fluoridated water and foods prepared with fluoridated water under the Federal Food, Drug, and Cosmetic Act.* (a) The program for fluoridation of public water supplies recommended by the Federal Security Agency, through the Public Health Service, contemplates the controlled addition of fluorine at a level optimum for the prevention of dental caries.

(b) Public water supplies do not ordinarily come under the provisions of the Federal Food, Drug, and Cosmetic Act. Nevertheless, a substantial number of inquiries have been received concerning the status of such water under the provisions of the act and the status, in interstate commerce, of commercially prepared foods in which fluoridated water has been used.

(c) The Federal Security Agency will regard water supplies containing fluorine, within the limitations recommended by the Public Health Service, as not actionable under the Federal Food, Drug, and Cosmetic Act. Similarly, commercially prepared foods within the jurisdiction of the act, in which a fluoridated water supply has been used in the processing operation, will not be regarded as actionable under the Federal law because of the fluorine content of the water so used, unless the process involves a significant concentration of fluorine from the water. In the latter instance the facts with respect to the particular case will be controlling.

(Sec. 701, 52 Stat. 1055; 21 U. S. C. 371)

Dated: July 17, 1952.

[SEAL] JOHN L. THURSTON,
Acting Administrator.

[F. R. Doc. 52-8041; Filed, July 22, 1952; 8:50 a. m.]

TITLE 26—INTERNAL REVENUE

Chapter I—Bureau of Internal Revenue, Department of the Treasury

Subchapter C—Miscellaneous Excise Taxes

[T. D. 5920; Regs. 132]

PART 325—EXCISE AND SPECIAL TAX ON WAGERING

REGISTRY, RETURN AND PAYMENT OF TAX

Regulations 132 amended to require persons liable for special (occupational) wagering tax to file returns and pay tax before commencing taxable activity and to file supplemental returns advising of all agents or employees engaged to receive wagers or with respect to all persons for whom wagers are received.

On June 3, 1952, notice of proposed rule making regarding amendment of § 325.50 of Regulations 132 was published in the FEDERAL REGISTER (17 F. R. 4988). No objection to the rules proposed having been received, § 325.50 of Regulations 132 is amended to read as follows:

§ 325.50 *Registry, return, and payment of tax.* (a) No person shall engage in the business of accepting wagers subject to the 10 percent excise tax imposed by section 3285 of the Internal Revenue Code (see § 325.24) until he has filed a return on Form 11-C and paid the special tax imposed by section 3290. Likewise, no person shall engage in receiving wagers for or on behalf of any person engaged in such business until he has filed a return on Form 11-C and paid the special tax imposed by section 3290 of the Internal Revenue Code. Filing of successive applications and payment of tax by such persons are required on or before July 1 of each year thereafter during which taxable activity continues. The return, with remittance, shall be filed with the collector of internal revenue for the district in which is located the taxpayer's office or principal place of business. If such taxpayer resides in the United States, but has no office or principal place of business in the United States, the return shall be filed with the collector of internal revenue for the district in which he resides. If the taxpayer has no office, residence, or principal place of business in the United States, the return shall be filed with the Collector of Internal Revenue, Baltimore, Maryland. The collector, upon request, will furnish the taxpayer proper forms which shall be filled out and signed as indicated therein.

(b) Each return shall show the taxpayer's full name. A person doing business under an alias, style, or trade name shall give his true name, followed by his alias, style, or trade name. In the case of a partnership, association, firm,

B 23

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Recodification Docket No. 9]

SUBCHAPTER C—DRUGS: GENERAL

Reorganization and Republication

The Commissioner of Food and Drugs, for the purposes of establishing an orderly development of informative regulations for the Food and Drug Administration, furnishing ample room for expansion of such regulations in years ahead, and providing the public and affected industries with regulations that are easy to find, read, and understand, has initiated a recodification program for Chapter I of Title 21 of the Code of Federal Regulations.

This is the ninth document in a series of recodification documents that will eventually include all regulations administered by the Food and Drug Administration.

This recodification document represents a reorganization of material remaining in Subchapter C—Drugs that has general applicability, rather than strictly human or animal use. In addition certain related sections under Parts 1 and 3 have been redesignated as part of the revised Subchapter C—Drugs: General.

The following table shows the relationship of the CFR section numbers under the former Subchapters A and C to their redesignation reflected in the new Parts 200 through 299:

Old Section	New Section	Old Section	New Section
1.100	299.5	3.21	250.102
1.101	201.6	3.22	200.101
1.101a	201.60	3.27	250.203
1.102	201.50	3.28	200.50
1.102a	201.61	3.29	201.307
1.102b	201.1	3.30	201.308
1.102c	201.51	3.35	201.303
1.102d	201.62	3.36	250.103
1.103	201.15	3.37	201.309
1.104	201.10	3.40	250.201
1.105	202.1	3.43	201.310
1.106(a)	201.5	3.44	201.311
1.106(b)	201.100	3.45	200.30
1.106(c)	201.105	3.48	250.106
1.106(d)	201.109	3.50	250.104
1.106(f)	201.110	3.52	250.107
1.106(g)	201.115	3.53	250.10
1.106(h)	201.116	3.56	201.405
1.106(i)	201.117	3.61	200.18
1.106(j)	201.119	3.62	299.4
1.106(k)	201.120	3.63	250.11
1.106(l)	201.122	3.64	250.12
1.106(m)	201.125	3.67	201.305
1.106(n)	201.127	3.71	250.100
1.106(o)	201.128	3.74	201.56
1.107	201.150	3.76	200.10
1.108(a) & (b)	201.16	3.77	299.35
1.108(c)	299.6	3.81	201.200
1.109	299.5	3.84	201.410
1.110	299.10	3.90	250.300
1.115	200.15	3.91	250.250
3.3	201.300	3.94	250.109
3.4	201.302	3.95	250.110
3.7	250.108	3.501	200.5
3.8	250.101	3.502	201.19
3.11	201.301	3.503	201.312
3.12	201.304	3.505	201.313
3.15	201.306	3.506	200.11
3.16	200.100	3.507	201.17
		3.508	201.18

Old Section	New Section	Old Section	New Section
3.509	201.314	133.11	211.58
3.510	201.315	133.12	211.110
3.512	200.31	133.13	211.60
3.513	200.7	133.14	211.62
3.514	201.55	133.15	211.115
3.515	201.160	133.100	225.1
3.516	250.105	133.101	225.20
3.518	201.161	133.102	225.30
132.1	207.3	133.103	225.10
132.2	207.20	133.104	225.42
132.3	207.21	133.105	225.102
132.4	207.22	133.106	225.40
132.5	207.25	133.107	225.80
132.6	207.30	133.108	225.58
132.7	207.31	133.109	225.110
132.8	207.35	133.110	225.115
132.9	207.37	133.200	226.1
132.10	207.26	133.201	226.20
132.11	207.39	133.202	226.30
132.31	207.40	133.203	226.10
132.51	207.65	133.204	226.42
133.1	210.3	133.205	226.102
133.2	211.1	133.206	226.40
133.3	211.20	133.207	226.80
133.4	211.30	133.208	226.58
133.5	211.10	133.209	226.110
133.6	211.42	133.210	226.115
133.7	211.101	133.300	229.25
133.8	211.40	138.1	299.3
133.9	211.55	138.2	299.20
133.10	211.80		

The changes being made are nonsubstantive in nature and for this reason notice and public procedure are not prerequisites to this promulgation. For the convenience of the user, the entire text of Parts 200, 201, 202, 207, 210, 211, 225, 226, 229, 250, 290, and 299 of Subchapter C is set forth below.

Dated: March 21, 1975.

SAM D. FINE,
Associate Commissioner for Compliance.

Therefore, 21 CFR is amended by redesignating portions of Parts 1 and 3 of Subchapter A and Parts 132, 133, and 138 of Subchapter C as Parts 200, 201, 202, 207, 210, 211, 225, 226, 229, 250, 290, and 299 of Subchapter C—Drugs: General, and republished to read as follows:

SUBCHAPTER C—DRUGS: GENERAL

Part

200—General

201—Labeling

202—Prescription Drug Advertising

207—Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution

210—Current Good Manufacturing Practices in Manufacturing, Processing, Packing, or Holding of Drugs: General

211—Current Good Manufacturing Practice for Finished Pharmaceuticals

225—Current Good Manufacturing Practice for Medicated Feeds

226—Current Good Manufacturing Practice for Medicated Premixes

229—Current Good Manufacturing Practice for Certain Other Drug Products

250—Special Requirements for Specific Human Drugs

290—Controlled Drugs

299—Drugs; Official Names and Established Names

PART 200—GENERAL

Subpart A—General Provisions

Sec.

Subpart B—Manufacturing Procedures Affecting New Drug Status

Subpart C—Requirements for Specific Classes of Drugs

Subpart D—Suitability of Specific Drug Components

AUTHORITY: Sec. 701, 52 Stat. 1055; 21 U.S.C. 371, unless otherwise noted.

Subpart A—General Provisions

§ 200.5 Mailing of important information about drugs.

Manufacturers and distributors of drugs and the Food and Drug Administration occasionally are required to mail important information about drugs to physicians and others responsible for patient care. In the public interest, such mail should be distinctive in appearance so that it will be promptly recognized and read. The Food and Drug Administration will make such mailings in accordance with the specifications set forth in this section. Manufacturers and distributors of drugs are asked to make such mailings as prescribed by this section and not to use the distinctive envelopes for ordinary mail.

(a) Use first class mail and No. 10 white envelopes.

(b) The name and address of the agency or the drug manufacturer or distributor is to appear in the upper left corner of the envelope.

(c) The following statements are to appear in the far left third of the envelope front, in the type and size indicated, centered in a rectangular space approximately 3 inches wide and 2¼ inches high with an approximately ⅛-inch-wide border in the color indicated:

(1) When the information concerns a significant hazard to health, the statement:

IMPORTANT
DRUG
WARNING

The statement shall be in three lines, all capitals, and centered. "Important" shall be in 36 point Gothic Bold type. "Drug" and "Warning" shall be in 36 point Gothic Condensed type. The rectangle's

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code of federal regulations

Food and Drugs

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PARTS 200 TO 299

Revised as of April 1, 1995

CONTAINING
A CODIFICATION OF DOCUMENTS
OF GENERAL APPLICABILITY
AND FUTURE EFFECT

AS OF APRIL 1, 1995

With Ancillaries

Published by
the Office of the Federal Register
National Archives and Records
Administration

as a Special Edition of
the Federal Register

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ing of section 503(b) of the Federal Food, Drug, and Cosmetic Act unless it is labeled with the legend "Caution—Federal law prohibits dispensing without prescription."

(e) Any drug for oral ingestion intended, represented, or advertised for the prevention or treatment of pernicious anemia or which purports to contain any substance or mixture of substances described in paragraph (d) of this section (other than diagnostic drugs containing radioactive cyanocobalamin) will be regarded as misbranded under sections 502(f)(2) and (j) of the act unless its labeling bears a statement to the effect that some patients afflicted with pernicious anemia may not respond to the orally ingested product and that there is no known way to predict which patients will respond or which patients may cease to respond to the orally ingested products. The labeling shall also bear a statement that periodic examinations and laboratory studies of pernicious anemia patients are essential and recommended.

(f) Under section 409 of the Federal Food, Drug, and Cosmetic Act, intrinsic factor and intrinsic factor concentrate are regarded as food additives. No food additive regulation nor existing extension of the effective date of section 409 of the act authorizes these additives in foods, including foods for special dietary uses. Any food containing added intrinsic factor or intrinsic factor concentrate will be regarded as adulterated within the meaning of section 402(a)(2)(C) of the act.

(g) Regulatory action may be initiated with respect to any article shipped within the jurisdiction of the act contrary to the provisions of this policy statement after the 180th day following publication of this statement in the FEDERAL REGISTER.

§250.203 Status of fluoridated water and foods prepared with fluoridated water.

(a) The program for fluoridation of public water supplies recommended by the Department of Health and Human Services, through the Public Health Service (Centers for Disease Control), contemplates the controlled addition of fluorine at a level optimum for the prevention of dental caries.

(b) Public water supplies do not ordinarily come under the provisions of the Federal Food, Drug, and Cosmetic Act. Nevertheless, a substantial number of inquiries have been received concerning the status of such water under the provisions of the act and the status, in interstate commerce, of commercially prepared foods in which fluoridated water has been used.

(c) The Department of Health and Human Services will regard water supplies containing fluorine, within the limitations recommended by the Environmental Protection Agency, as not actionable under the Federal Food, Drug, and Cosmetic Act. Similarly, commercially prepared foods within the jurisdiction of the act, in which a fluoridated water supply has been used in the processing operation, will not be regarded as actionable under the Federal law because of the fluorine content of the water so used, unless the process involves a significant concentration of fluorine from the water. In the latter instance the facts with respect to the particular case will be controlling.

[40 FR 14033, Mar. 27, 1975, as amended at 48 FR 11426, Mar. 18, 1983]

Subpart D—Requirements for Drugs and Cosmetics

§250.250 Hexachlorophene, as a component of drug and cosmetic products.

(a) *Antibacterial component.* The use of hexachlorophene as an antibacterial component in drug and cosmetic products has expanded widely in recent years. It is used in such products because of its bacteriostatic action against gram-positive organisms, especially against strains of staphylococcus; however, hexachlorophene offers no protection against gram-negative infections. In addition, the antibacterial activity depends largely on repeated use. A notice published in the FEDERAL REGISTER of April 4, 1972 (37 FR 6775), invited data on OTC antimicrobial ingredients, including hexachlorophene, for review by an OTC Drug Advisory Review Panel to be convened under the procedures set forth in the FEDERAL REGISTER of May 11, 1972

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List of substances	Limitations
Monochlorobenzene Monochlorobenzene.	Not to exceed 500 parts per million as residual solvent in finished basic resin in paragraph (a)(1) of this section.
N-methyl-2-pyrrolidone.	Not to exceed 0.01 percent (100 parts per million) as residual solvent in finished basic resin in paragraph (a)(2) of this section.

* * * * *

Dated: May 17, 1996.

Fred R. Shank,

Director, Center for Food Safety and Applied Nutrition.

[FR Doc. 96-14697 Filed 6-10-96; 8:45 am]

BILLING CODE 4160-01-F

Food and Drug Administration

21 CFR Parts 200, 250, and 310

[Docket No. 95N-0310]

Revocation of Obsolete Regulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revoking certain regulations that are obsolete or are no longer necessary to achieve public health goals. These regulations were among those identified for revocation in a page-by-page review conducted in response to the Administration's "Reinventing Government" initiative, which seeks to streamline government to ease the burden on regulated industry and consumers.

EFFECTIVE DATE: July 11, 1996.

FOR FURTHER INFORMATION CONTACT: Christine F. Rogers, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of October 13, 1995 (60 FR 53480), FDA published a proposed rule to revoke certain regulations. This was done in response to the President's order to all Federal agencies to conduct a page-by-page review of all their regulations and to "eliminate or revise those that are outdated or otherwise in need of reform." The proposed rule contained a section-by-section analysis of all the regulations (21 CFR parts 100, 101, et al.) that FDA intended to revoke. This final rule pertains only to those regulations (21 CFR parts 200, 250, and 310) pertaining exclusively to the Center for Drug Evaluation and Research. No comments were received in response to the proposal to revoke these regulations.

II. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule, which is the revocation of certain regulations that are obsolete or are no longer necessary, is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this final rule is the revocation of certain regulations that are obsolete or are no longer necessary, the agency is not aware of any adverse impact this final rule will have on any small entities, and the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

III. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(9) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects

21 CFR Part 200

Drugs, Prescription drugs.

21 CFR Part 250

Drugs.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 *et seq.*) and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 200, 250, and 310 are amended as follows:

PART 200—GENERAL

1. The authority citation for 21 CFR part 200 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 515, 701, 704, 705 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360e, 371, 374, 375).

2. Sections 200.100 and 200.101 are removed and the heading for subpart D is reserved.

PART 250—SPECIAL REQUIREMENTS FOR SPECIFIC HUMAN DRUGS

3. The authority citation for 21 CFR part 250 continues to read as follows:

Authority: Secs. 201, 306, 402, 502, 503, 505, 601(a), 602(a) and (c), 701, 705(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 336, 342, 352, 353, 355, 361(a), 362(a) and (c), 371, 375(b)).

§ 250.104 [Removed]

4. Section 250.104 *Status of salt substitutes under the Federal Food, Drug, and Cosmetic Act* is removed.

§ 250.203 [Removed]

5. Section 250.203 *Status of fluoridated water and foods prepared with fluoridated water* is removed.

PART 310—NEW DRUGS

6. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512-516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b-360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b-263n).

§ 310.101 [Removed]

7. Section 310.101 *FD&C Red No. 4; procedure for discontinuing use in new drugs for ingestion; statement of policy* is removed.

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ENVIRONMENTAL PROTECTION AGENCY

[OW-FRL-3410-1]

Drinking Water Technical Assistance; Termination of the Federal Drinking Water Additives Program

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA), Office of Drinking Water (ODW), has operated an advisory program that gives technical assistance to concerned parties on the use of drinking water additives. On May 17, 1984, EPA proposed to terminate major elements of this Federal program and to assist in the establishment of a private-sector program which would offer assistance in evaluating drinking water additives. 49 FR 21004. EPA solicited proposals from qualified nongovernmental, nonprofit organizations for assistance under a cooperative agreement to establish a credible and efficient program in the private sector.

On September 17, 1985, EPA selected a consortium consisting of the National Sanitation Foundation (NSF), the American Water Works Association Research Foundation (AWWARF), the Conference of State Health and Environmental Managers (COSHEM), and the Association of State Drinking Water Administrators (ASDWA) to receive funds under a cooperative agreement to develop the private-sector program. EPA believes that the NSF-led program has proceeded satisfactorily. NSF Standard 60, covering many direct additives, was adopted on December 7, 1987; and NSF Standard 61, covering indirect additives, was adopted on June 3, 1988. Other standards are forthcoming. The NSF-led program has begun offering testing, certification, and listing services, as described in 49 FR 21004, for certain classes of products covered by these standards. Accordingly, as the NSF-led program becomes operational, EPA will phase out its activities in this area, as described in this notice.

DATE: Any written comments on implementing this notice should be submitted to the address below by September 6, 1988.

ADDRESSES: Submit comments to: Mr. Arthur H. Perler, Chief, Science and Technology Branch, Office of Drinking Water (WH-550D), U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460. A copy of all comments will be available for review during normal business hours at the U.S. Environmental Protection Agency, Criteria and Standards Division, Science and Technology Branch, Room 931ET, 401 M Street, SW., Washington, DC 20460. For further information on the NSF-led private-sector program, including standards development and testing, certification, and listing services, contact: Director, Drinking Water Additives Program, National Sanitation Foundation, P.O. Box 1468, Ann Arbor, MI 48106; or call (313) 769-8010. For information on alternative testing, certification, and listing programs, contact individual State regulatory authorities or the American Water Works Association, Technical and Professional Department, 6666 Quincy Avenue, Denver CO, 80235, or call (303) 794-7711. For information on the directory of products certified as meeting the criteria in a NSF standard, contact the American Water Works Association Research Foundation, 6666 Quincy Avenue, Denver CO, 80235, or call (303) 794-7711.

FOR FURTHER INFORMATION CONTACT: Mr. Arthur H. Perler, Chief, Science and Technology Branch, Office of Drinking Water (WH-550D), U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460, or call (202) 382-2022.

I. Introduction

The Safe Drinking Water Act (SDWA) (42 U.S.C. 300f *et seq.*) provides for enhancement of the safety of public drinking water supplies through the establishment and enforcement of national drinking water regulations. The Environmental Protection Agency (EPA) has the primary responsibility for establishing the regulations, and the States have the primary responsibility for enforcing such regulations. The regulations control contaminants in drinking water which may have any adverse effect on public health. Section 1412, 42 U.S.C. 300g-1. The regulations include maximum contaminant levels (MCLs) or treatment techniques and monitoring requirements for these contaminants. Sections 1401 and 1412; 42 U.S.C. 300f and 300g-1. EPA also promulgates monitoring requirements for unregulated contaminants. Section 1445; 42 U.S.C. 300j-4. In addition, EPA has broad authorities to provide technical assistance and financial assistance (e.g., grants, cooperative agreements) to States and to conduct research. Sections 1442, 1443, 1444; 42 U.S.C. 300j-1, 300j-2, 300j-3.

The Agency has established MCLs for a number of harmful contaminants that occur naturally or pollute public drinking water supplies. In addition to such contaminants, there is a possibility that drinking water supplies may be contaminated by compounds "added" to drinking water, either directly or indirectly, in the course of treatment and transport of drinking water. Public water systems use a broad range of chemical products to treat water supplies and to maintain storage and distribution systems. For instance, systems may directly add chemicals such as chlorine, alum, lime, and coagulant aids in the process of treating water to make it suitable for public consumption. These are known as "direct additives." In addition, as a necessary function of maintaining a public water system, storage and distribution systems (including pipes, tanks, and other equipment) may be fabricated from or painted, coated, or treated with products which may leach into or otherwise enter the water. These products are known as "indirect additives." Except to the extent that direct or indirect additives consist of ingredients or contain contaminants for which EPA has promulgated MCLs, EPA does not currently regulate the levels of additives in drinking water.

In 1979, EPA executed a Memorandum of Understanding (MOU) with the U.S. Food and Drug Administration (FDA) to establish and clarify areas of authorities with respect to control of additives in drinking water. 44 FR 42775, July 20, 1979. FDA is authorized to regulate "food additives" pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA). (21 U.S.C. 301 *et seq.*). Both agencies acknowledged in the MOU that "passage of the SDWA in 1974 repealed FDA's authority under the FFDCA over water used for drinking water purposes." The MOU stated that FDA would continue to have authority for taking regulatory action under the FFDCA to control additives in bottled drinking water and in water used in food and for food processing. The MOU went on to say that EPA had authority to control additives in public drinking water supplies.

While the SDWA does not require EPA to control the use of specific additives in drinking water, EPA has provided technical assistance to States and public water systems on the use of additives through the issuance of advisory opinions on the acceptability of many additive products. EPA has provided this technical assistance pursuant to its discretionary authority in section 1442(b)(1) to "collect and make available information pertaining to research, investigations and demonstrations with respect to

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providing a dependable safe supply of drinking water together with appropriate recommendations in connection therewith." EPA has additional authorities under the Toxic Substances Control Act (TSCA) (15 U.S.C. 2601 *et seq.*) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136 *et seq.*) that could be used to control additives in drinking water. TSCA authorizes EPA to regulate a new chemical substance before it is manufactured or any existing chemical substance before it is manufactured or processed for a use that EPA has determined to be a "significant new use." Although an additive product might come within the jurisdiction of TSCA, EPA has never invoked this authority. EPA has used its authority under FIFRA to control the use of pesticides, disinfectants, and certain other additives. For a more complete discussion of these authorities, see the MOU. 44 FR 42776.

In 1980, EPA declared a moratorium on the issuance of new advisory opinions on additives pending a review of past advisory opinions and the establishment of uniform test protocols and decision criteria. However, between 1980 and 1984, EPA continued to issue advisory opinions in cases where the new additive products were virtually identical to products previously reviewed. Resource constraints and the need to implement mandatory provisions of the SDWA precluded the Agency from implementing the comprehensive program originally envisioned for the issuance of additives advisory opinions. Thus, the Agency was not able to review the technical data supporting previous submissions (approximately 2,300 products from 525 manufacturers) nor was it able to develop test protocols or decision criteria for the consistent evaluation of new products. The result has been long delays in processing manufacturer petitions, inability to review and accept completely new products, and acceptance of products simply because they were virtually identical to older products. Hence, few products have been thoroughly evaluated for the safety of their formulations based on the latest scientific information.

Recognizing the need for continuing technical assistance in evaluating additive products and for providing advice to States and public water systems on the toxicological aspects of additive products, the Agency proposed to terminate its attempts to institute a formal advisory program, and to solicit proposals from nongovernmental, nonprofit organizations to establish such a program in the private sector. The Agency believed that the proposal to assist in the establishment of a private-sector program was consistent with, and would best serve the goals of, the SDWA.

On May 17, 1984, EPA formally announced its intention to transfer the program to the private sector, which would function as to many other voluntary product-standard programs. 49 FR 21004. This was accomplished by requesting proposals from qualified organizations or consortia of organizations for the competitive award of a cooperative agreement designed to provide incentive for the establishment of a private-sector program. The 1984 notice stated that:

- EPA expected the activity to be self-supporting.
- EPA would maintain an active interest in the development of the program, without assuming responsibility for or directing its approach.
- EPA would continue to establish regulations under the SDWA, FIFRA, and/or TSCA, as needed, for chemicals in treated, distributed drinking water that may originate as additives.
- Establishment of such a program would be consistent with the Administration's initiatives in the area of regulatory reform and offered an opportunity for an innovative alternative to regulation.

The May 1984 notice requested public comments on the proposal and solicited applications from qualified nongovernmental, nonprofit organizations for partial funding of the developmental phase of the program under a cooperative agreement. The response to the solicitation for comments indicated strong public support for the proposed approach. EPA received 106 public comments on the proposal. All but six supported this "third-party" approach. However, despite the Agency's open competition, EPA received only one application for financial assistance. The applicant was a consortium, led by the National Sanitation Foundation, which included the American Water Works Association Research Foundation, the Conference of State Health and Environmental Managers, and the Association of State Drinking Water Administrators. This single proposal met all of the basic criteria articulated in the May 1984 notice. Furthermore, EPA believed that the single applicant was very likely to succeed, because it represented an organization experienced in private-sector consensus standard-setting, State regulators, and water utilities.

EPA awarded the cooperative agreement to the NSF consortium on September 17, 1985, and committed funding of $185,000 to NSF over a three-year period. The non-Federal (consortium and participating industry) contribution during the first three years of the program was projected to be approximately $1.4 million.

The NSF program has the following major objectives:

- To develop systematic, consistent, and comprehensive voluntary consensus standards for public health safety evaluation of all products (previously EPA-accepted as well as new) intended for use in drinking water systems.
- To obtain broad-based participation in the standard-setting program from industry, States, and utilities.
- To provide for regular periodic review, update, and revision of the standards.
- To undertake needed research, testing, evaluation, and inspections and to provide the followup necessary to maintain the program.
- To establish a separate program for testing, evaluation, certification, and listing of additive products.
- To widely disseminate information about the program, and to make information about conforming products available to users.
- To maintain the confidentiality of all proprietary information.
- To fully establish the third-party program on a self-supporting basis.

NSF's established standard-setting process utilizes a tiered structure. Each standard is drafted by a task group and then presented to a Joint Committee, which includes 12 industry, 12 user, and 12 regulatory members. Following successful Joint Committee balloting, standards are reviewed by the Council of Public Health Consultants, which is a high level advisory group consisting of technical and policy experts from regulatory agencies and academia.

NSF has established task groups to develop standards for the product categories listed below. Each task group includes a member representing the regulatory agencies and a member representing the utilities. All manufacturers expressing interest in a particular product task group may participate as members of that group. Therefore, task group membership is predominately manufacturers. In addition, a group of health effects consultants is addressing the toxicological and risk considerations for various product categories. NSF's role in the standard-setting process is administrative, that is, to bring together experts from government, industry,

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utilities, users, and other relevant groups so that a standard which reflects a consensus of these interests can be developed. In addition, NSF staff provide technical leadership and laboratory support. Product categories and correspoding task groups are:

- Protective Materials.
- Chemicals for Corrosion and Scale Control, Softening, Precipitation, Sequestering, and pH Adjustment.
- Coagulation and Flocculation Chemicals.
- Miscellaneous Treatment Chemicals.
- Joining and Sealing materials.
- Process Media.
- Pipes and Related Products.
- Disinfection and Oxidation Chemicals.
- Mechanical Devices.

All of the task groups have made satisfactory progress during the term of the cooperative agreement. In addition, the health effects consultants have endorsed the bases of the standards. Standards have been drafted for all product categories, and final standards were published and implemented as follows:

Standard 60, December 1987

- Chemicals for Corrosion and Scale Control, Softening, Precipitation, Sequestering, and pH Adjustment.
- Disinfection and Oxidation Chemicals.
- Miscellaneous Treatment Chemicals (selected).

Standard 61, June 1988

- Process Media.

Development of the remaining standards is on schedule, and publication and implementation are expected on the following schedule:

Standards 60 and 61, expected October 1988

- Protective Materials.
- Coagulation and Flocculation Chemicals.
- Miscellaneous Treatment Chemicals (additional).
- Joining and Sealing Materials.
- Pipes and Related Products.
- Mechanical Devices.

EPA believes that the NSF program is successfully pursuing all of its objectives. Furthermore, the program is strongly supported by user and regulatory sectors. AWWARF, COSHEM, ASDWA, the Great Lakes Upper Mississippi River Board, the American Water Works Association (AWWA) (including the Utilities and Standards Councils and the Regulatory Agencies Division), and the Association of Metropolitan Water Agencies, among others, have voiced strong support for the third-party program. The AWWA recently joined the NSF-led consortium and urged EPA to support national uniform accreditation of certifying entities for additives products. To date, more than 60 manufacturers are full participants in the standard-setting program.

The cooperative agreement between EPA and the consortium requires NSF to establish both a standard-setting program and a service for testing, certification, and listing. These are completely separate activities. EPA's intent is to support the development of a widely accepted uniform standard for each category of products while encouraging the development of competing sources for testing, certification, and listing. The cooperative agreement assures that at least one sound and reliable product-evaluation service will be available to manufacturers, i.e., the consortium. However, the consortium's standards will allow for entities other than NSF to be evaluators of products.

EPA recognizes the authority and responsibility of the individual States to determine the acceptability of drinking water additives. Hence, it is up to the States and utilities to determine the suitability of any "third-party" certification. AWWARF will maintain a directory of products approved by all organizations claiming to conduct evaluations under Standards 60 and 61. However, AWWARF will not judge the competence or reliability of these organizations.

II. Announcement of Phase-Down of EPA's Additives Program

During the developmental phase of the NSF consortium's program, EPA has continued to review products and process requests for advisory opinions on a limited basis. The May 1984 notice stated that, "EPA does not intend to develop further interim administrative procedures, testing protocols or decision criteria for future evaluation of additive products. The use of existing informal criteria will continue until a third-party or alternative program is operational * * *. EPA may not be able to process all requests for opinions on additive products before the establishment of a cooperative agreement with a third party. The large volume of currently pending requests makes it unlikely that additional requests will be completely processed by that date." Likewise, EPA, in its acknowledgment letters to manufacturers requesting opinions on new products, explains that the Agency is, "* * * making a concerted effort to process petitions as quickly as possible. However, EPA may not be able to process your request for an opinion on an additive product before the establishment of an alternative program as described in the Federal Register, Vol. 49, No. 97, 21003–8, May 17, 1984." Product reviews and issuance of advisory opinions have been limited to:

- Products composed entirely of other products which EPA had previously determined to be acceptable;
- Products composed entirely of ingredients which have been determined to be acceptable by EPA or the FDA, or other Federal agencies, for addition to potable water or aqueous foods;
- Products composed entirely of ingredients listed in the "Water Chemicals Codex," National Academy of Sciences, November 1982, and in the "Water Chemicals Codex: Supplementary Recommendations for Direct Additives," National Academy of Sciences, 1984;
- Certain other products of particular interest to EPA or to other Federal agencies; and
- Products which, if effectively excluded from the marketplace by lack of approval, might jeopardize public health or safety.

Continued processing of petitions during the development of the private-sector program minimized disruption of the marketplace from the viewpoint of manufacturers whose business depended in part on EPA acceptance of products, users who required water treatment products for the production of safe drinking water, and State officials who rely on the advice of EPA.

EPA believes that NSF is moving expeditiously and on schedule toward the full establishment of a third-party program covering products intended for use in drinking water systems. Priorities for standards development and implementation of a testing, certification, and listing program for various product categories have been based upon need, interest, complexity, and availability of information for developing standards. Direct drinking water additives were assigned high priority for the following reasons: (1) Use of direct additives is widespread in drinking water systems, so there are large population exposures to these chemicals; (2) as direct additives to drinking water, they present greater potential for water contamination than indirect mechanisms (e.g., migration from protective paints in pipes and storage tanks); and (3) the National Academy of Sciences' *Water Chemicals Codex* provided a good starting point for development of standards.

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As originally planned, EPA is beginning to phase out the Agency's additives evaluation program. Thus, EPA will not accept new petitions or requests for advisory options after the date of this notice. While EPA will continue to process requests which are pending and those received on or before July 7, 1988, petition evaluations not completed by October 4, 1988, will be returned to the submitter. After that date, EPA will no longer evaluate additive products.

Petitions which are completely evaluated by October 5, 1988, will be added to the quarterly list of acceptable products published shortly after that date. That quarterly list will be the last such list issued by EPA. On April 7, 1990, EPA will withdraw its list of acceptable products, and the list and the advisories on these additives will expire. This means that: (1) The various lists published by EPA under the titles *Report on Acceptable Drinking Water Additives, Report on Coagulant Aids for Water Treatment, Report on Concrete Coatings/Admixture for Water Treatment, Report on Detergents, Sanitizers and Joint Lubricants for Water Treatment, Report on Evaporative Suppressants for Water Treatment, Report on Liners/Grouts/Hoses and Tubings for Water Treatment, Report on Miscellaneous Chemicals for Water Treatment, Report on Protectivce Paints/Coatings for Water Treatment,* and any and all other lists of drinking water products issued by EPA or its predecessor agencies regarding drinking water additives will be invalid after April 7, 1990; and (2) advisory opinions on drinking water additives issued by EPA and predecessor agencies will be invalid after that date.

EPA believes that, while in the past every effort has been made to provide the best possible evaluations, all products should be evaluated against carefully developed and considered nationally uniform standards. Many of the currently listed products were evaluated and accepted up to 20 years ago and have not been reevaluated since that time. Numerous products have been accepted because they were virtually identical to or were repackagings of older products. The result is that few products have been completely evaluated for the safety of their original or current formulations vis-a-vis the latest toxicological, chemical, and engineering information. A uniform evaluation of all products, old and new, will result in consistent quality of products, and will assure fair and equitable treatment to all manufacturers and distributors.

Henceforth, parties desiring to have existing or new products evaluated against the NSF standards should contact NSF or other organizations offering such evaluations. To contact NSF about the drinking water additives program write to: David Gregorka, National Sanitation Foundation, P.O. Box 1468, Ann Arbor, MI 48106, or call (313) 769-8010. Information on alternatives to NSF evaluation may be obtained by contacting State regulatory agencies or the AWWA, Technical and Professional Department, 6666 Quincy Avenue, Denver Co, 80235, or call (303) 794-7711, which is addressing certifier accreditation.

EPA believes that the 21 months between today and the expiration date of EPA's last list is sufficient time for manufacturers to submit their products to NSF or other certification entities for evaluation. The first NSF list will be published prior to April 7, 1990, thereby preventing any disruption in the marketplace. Furthermore, NSF had indicated that it will consider current EPA and other regulatory evaluations when evaluating products in order to ensure a smooth transition. States may choose to rely on the last EPA quarterly list of products until their individual programs for accepting private-sector certification are fully implemented.

Parties desiring to market drinking water additive products are reminded that the individual States have the authority to regulate the sale and/or use of specific products as they see fit. Thus, reliance upon a particular standard or organization to certify that a product complies with a particular standard must be acceptable to the State in which the supplier wishes to do business.

Discontinuation of the additives program at EPA does not relieve the Agency of its statutory responsibilities. If contamination resulting from third-party sanctioned products occurs or seems likely, EPA will address that issue with appropriate drinking water regulations or other actions authorized under the SDWA. EPA is a permanent member of the NSF program Steering Committee, and senior EPA staff and management will continue to participate in this and other programs designed to assure that high-quality products are employed in the treatment of public drinking water. Also, the Agency will continue to sponsor research on contaminants introduced in public water supplies during water treatment, storage, and distribution.

III. Comments

Although this notice does not include a proposed or final regulation, EPA welcomes comments and suggestions that would assist the Agency in implementing the additives program phasedown. Please address all comments and suggestions to: Mr. Arthur H. Perler, Chief, Science and Technology Branch, Office of Drinking Water (WH-550D), U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460.

Date: June 16, 1988.

William Whittington,

Acting Assistant Administrator for Water.

[FR Doc. 88-15232 Filed 7-6-88; 8:45 am]

BILLING CODE 6560-50-M

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Federal facilities. Prior to making a final recommendation to the Administrator, U.S. EPA, the Regional Administrator, Region V, is providing opportunity for public comment on the State of Wisconsin request. Any interested person may comment upon the State request by writing to the U.S. EPA, Region V Office, 230 South Dearborn Street, Chicago, Illinois 60604, Attention: Permit Branch. Such comments will be made available to the public for inspection and copying. All comments or objections received by August 22, 1979, will be considered by U.S. EPA before taking final action on the Wisconsin request for authority to issue permits to Federal facilities.

The State's request, related documents, and all comments received are on file and may be inspected and copied (@ 20 cents/page) at the U.S. EPA, Region V Office, in Chicago.

Copies of this notice are available upon request from the Enforcement Division of U.S. EPA, Region V, by contacting Dorothy A. Price, Public Notice Clerk (312–353–2105), at the above address.

Dated: July 13, 1979.

John McGuire,
Regional Administrator.

[FR Doc. 79-22872 Filed 7-19-79; 8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

ENVIRONMENTAL PROTECTION AGENCY

[FRL 1275–4]

Drinking Water Technical Assistance; Implementation Plan for Control of Direct and Indirect Additives to Drinking Water and Memorandum of Understanding Between the Environmental Protection Agency and the Food and Drug Administration

AGENCY: Environmental Protection Agency and Food Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) have executed a memorandum of understanding (MOU) with regard to the control of direct and indirect additives to and substances in drinking water. The purpose of the MOU is to avoid the possibility of overlapping jurisdiction between EPA and FDA with respect to control of drinking water additives. The agreement became effective on June 22, 1979.

ADDRESS: Submit comments to: Victor J. Kimm, Deputy Assistant Administrator for Drinking Water, Environmental Protection Agency (WH–550), Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: David W. Schnare, Ph.D., Office of Drinking Water (WH–550), Environmental Protection Agency, Washington, D.C. 20460, (202) 755–5643; or Gary Dykstra, Enforcement Policy Staff (HFC–22), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, (301) 443–3470.

SUPPLEMENTARY INFORMATION: In the spirit of interagency cooperation and to avoid the possibility of overlapping jurisdiction over additives and other substances in drinking water, FDA and EPA have entered into a memorandum of understanding to avoid duplicatve and inconsistent regulation. In brief, the memorandum provides that EPA will have primary responsibility over direct and indirect additives and other substances in drinking water under the Safe Drinking Water Act, the Toxic Substances Control Act, and the Federal Insecticide, Fungicide and Rodenticide Act. FDA will have responsibility for water, and substances in water, used in food and for food processing and for bottled water under the Federal Food, Drug and Cosmetic Act.

Pursuant to the notice published in the Federal Register of October 3, 1974, (39 FR 35697) stating that future memoranda of understanding, and agreements between FDA and others would be published in the Federal Register, the following memorandum of understanding is issued:

Memorandum of Understanding Between the Environmental Protection Agency and the Food and Drug Administration

I. Purpose

This Memorandum of Understanding establishes an agreement between the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) with regard to the control of direct and indirect additives to and substances in drinking water.

EPA and FDA agree:

(1) That contamination of drinking water from the use and application of direct and indirect additives and other substances poses a potential public health problem;

(2) That the scope of the additives problem in terms of the health significance of these contaminants in drinking water is not fully known;

(3) That the possibility of overlapping jurisdiction between EPA and FDA with respect to control of drinking water additives has been the subject of Congressional as well as public concern;

(4) That the authority to control the use and application of direct and indirect additives to and substances in drinking water should be vested in a single regulatory agency to avoid duplicative and inconsistent regulation;

(5) That EPA has been mandated by Congress under the Safe Drinking Water Act (SDWA), as amended, to assure that the public is provided with safe drinking water;

(6) That EPA has been mandated by Congress under the Toxic Substances Control Act (TSCA) to protect against unreasonable risks to health and the environment from toxic substances by requiring, *inter alia*, testing and necessary restrictions on the use, manufacture, processing, distribution, and disposal of chemical substances and mixtures;

(7) That EPA has been mandated by Congress under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, to assure, *inter alia*, that when used properly, pesticides will perform their intended function without causing unreasonable adverse effects on the environment; and,

(8) That FDA has been mandated by Congress under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended, to protect the public from, *inter alia*, the adulteration of food by food additives and poisonous and deleterious substances.

It is the intent of the parties that;

(1) EPA will have responsibility for direct and indirect additives to and other substances in drinking water under the SDWA, TSCA, and FIFRA; and,

(2) FDA will have responsibility for water, and substances in water, used in food and for food processing and responsibility for bottled drinking water under the FFDCA.

II. Background

(A) *FDA Legal Authority.* "Food" means articles used for food or drink for man or other animals and components of such articles. (FFDCA § 201(f)). Under Section 402, *inter alia*, a food may not contain any added poisonous or deleterious substance that may render it injurious to health, or be prepared, packed or handled under unsanitary conditions. Tolerances may be set, under Section 403, limiting the quantity of any substance which is required for the production of food or cannot be avoided in food. FDA has the authority under Section 409 to issue food additive regulations approving, with or without conditions, or denying the use of a "food additive." That term is defined in Section 201(s) to include any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, if such substance is not generally recognized as safe.

In the past, FDA has considered drinking water to be a food under Section 201(f). However, both parties have determined that the passage of the SDWA in 1974 implicitly repealed FDA's authority under the FFDCA over water used for drinking water purposes. Under the express provisions of Section 410

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of the FFDCA. FDA retains authority over bottled drinking water. Furthermore, all water used in food remains a food and subject to the provisions of the FFDCA. Water used for food processing is subject to applicable provisions of FFDCA. Moreover, all substances in water used in food are added substances subject to the provisions of the FFDCA, but no substances added to a public drinking water system before the water enters a food processing establishment will be considered a food additive.

(B). *EPA Legal Authority.* The SDWA grants EPA the authority to control contaminants in drinking water which may have any adverse effect on the public health, through the establishment of maximum contaminant levels (MCLs) or treatment techniques, under Section 1412, which are applicable to owners and operators of public water systems. The expressed intent of the Act was to give EPA exclusive control over the safety of public water supplies. Public water systems may also be required by regulation to conduct monitoring for unregulated contaminants under Section 1445 and to issue public notification of such levels under Section 1414(c).

EPA's direct authority to control additives to drinking water apart from the existence of maximum contaminant levels or treatment techniques is limited to its emergency powers under Section 1431. However, Section 1442(b) of the act authorizes EPA to "collect and make available information pertaining to research, investigations, and demonstrations with respect to providing a dependably safe supply of drinking water together with appropriate recommendations therewith."

TSCA gives EPA authority to regulate chemical substances, mixtures and under some circumstances, articles containing such substances or mixtures. Section 4 permits EPA to require testing of a chemical substance or mixture based on possible unreasonable risk of injury to health or the environment, or on significant or substantial human or environmental exposure while Section 8 enables EPA to require submission of data showing substantial risk of injury to health or the environment, existing health and safety studies, and other data. For new chemical substances, and significant new uses of existing chemical substances, Section 5 requires manufacturers to provide EPA with premanufacturing notice. Under Section 6 the manufacture, processing, distribution, use, and disposal of a chemical substance or mixture determined to be harmful may be restricted or banned. Although Section 3(2)(B) of TSCA excludes from the definition of "chemical substance" food and food additives as defined under FFDCA, the implicit repeal by the SDWA of FDA's authority over drinking water enables EPA to regulate direct and indirect additives to drinking water as chemical substances and mixtures under TSCA.

The FIFRA requires EPA to set restrictions on the use of pesticides to assure that when used properly, they will not cause unreasonable adverse effects on the environment. EPA may require, *inter alia*, labeling which specifies how, when, and where a pesticide may be legally used. In addition, EPA has, under Section 409 of the FFDCA, required FIFRA registrants at times to obtain a food additive tolerance before using a pesticide in or around a drinking water source. Such tolerances establish further restrictions on the use of a pesticide which are enforceable against the water supplier as well as the registrant of the pesticide.

III. Terms of Agreement

(A) EPA's responsibilities are as follows:

(1) To establish appropriate regulations, and to take appropriate measures, under the SDWA and/or TSCA, and FIFRA, to control direct additives to drinking water (which encompass any substances purposely added to the water), and indirect additives (which encompass any substances which might leach from paints, coatings or other materials as an incidental result of drinking water contact), and other substances.

(2) To establish appropriate regulations under the SDWA to limit the concentrations of pesticides in drinking water; the limitations on concentrations and types of pesticides in water are presently set by EPA through tolerances under Section 409 of the FFDCA.

(3) To continue to provide technical assistance in the form of informal advisory opinions on drinking water additives under Section 1442(b) of the SDWA.

(4) To conduct and require research and monitoring and the submission of data relative to the problem of direct and indirect additives in drinking water in order to accumulate data concerning the health risks posed by the presence of these contaminants in drinking water.

(B). FDA's responsibilities are as follows:

(1) To take appropriate regulatory action under the authority of the FFDCA to control bottled drinking water and water, and substances in water, used in food and for food processing;

(2) To provide assistance to EPA to facilitate the transition of responsibilities, including:

(a) To review existing FDA approvals in order to identify their applicability to additives in drinking water.

(b) To provide a mutually agreed upon level of assistance in conducting literature searches related to toxicological decision making.

(c) To provide a senior toxicologist to help EPA devise new procedures and protocols to be used in formulating advice on direct and indirect additives to drinking water.

IV. Duration of Agreement

This Memorandum of Understanding shall continue in effect unless modified by mutual consent of both parties or terminated by either party upon thirty (30) days advance written notice to the other.

This Memorandum of Understanding will become effective on the date of the last signature.

Dated: June 13, 1979.

Douglas M. Costle,

Administrator, Environmental Protection Agency.

Dated: June 22, 1979.

Donald Kennedy,

Administrator, Food and Drug Administration.

Implementation Plan

EPA is concerned that direct and indirect additives may be adding harmful trace chemical contaminants into our Nation's drinking water during treatment, storage and distribution. Direct additives include such chemicals as chlorine, lime, alum, and coagulant aides, which are added at the water treatment plant. Although these chemicals themselves may be harmless, they may contain small amounts of harmful chemicals if their quality is not controlled. Indirect additives include those contaminants which enter drinking water through leaching, from pipes, tanks and other equipment, and their associated paints and coatings. This notice is being published in the Federal Register to solicit public comment on EPA's implementation plan to assess and control direct and indirect additives in drinking water.

Legal Authorities

EPA and the Food and Drug Administration (FDA) signed a Memorandum of Understanding which recognizes that regulatory control over direct and indirect additives in drinking water is placed in EPA. The two agencies agreed that the Safe Drinking Water Act's passage in 1974 implicitly repealed FDA's jurisdiction over drinking water as a 'food' under the Federal Food, Drug and Cosmetic Act (FFDCA). Under the agreement, EPA now retains exclusive jurisdiction over drinking water served by public water supplies, including any additives in such water. FDA retains jurisdiction over bottled drinking water under Section 410 of the FFDCA and over water (and substances in water) used in food or food processing once it enters the food processing establishment.

In implementing its new responsibilities, EPA may utilize a variety of statutory authorities, as appropriate. The authorities are identified in Appendix A.

Under the Safe Drinking Water Act, EPA has authority to set and enforce maximum contaminant levels and treatment techniques in drinking water for ubiquitous contaminants, to conduct research, to offer technical assistance to States and to protect against imminent

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hazards should such situations arise. Under the Toxic Substances Control Act, EPA has authority to review all new chemicals proposed for use related to drinking water, to mandate toxicological testing of existing and new chemicals where there is evidence that such materials may pose an unreasonable risk to health and the environment as well as authority to limit some or all uses of harmful chemicals. Pesticide use is regulated by EPA under the Federal Insecticide, Fungicide and Rodenticide Act. Thus, EPA believes it has adequate authority to deal with additives to drinking water where they may pose a problem.

Past Actions

For more than ten years, the Public Health Service and other organizations which have become part of EPA have provided advisory opinions on the toxicological safety of a variety of additives to drinking water. These historical informal opinions reflect a variety of information provided by manufacturers and reflect changing toxicological concerns over the years. As such, they will require detailed review over the next few years.

General Approach

EPA intends to begin its responsibility over additives to drinking water with a series of analytical studies to determine the composition and significance of the health risks posed by contaminants related to direct and indirect additives to drinking water. A first step in this process will be monitoring studies of the contaminants actually getting into drinking water from generic categories of additives like bulk chemicals, paints and coatings, pipes and equipment.

In the initial six to twelve months, EPA will develop interim administrative procedures, testing protocols, and decision criteria for future toxicological advisories to the States. These will be distributed for public comment once they are developed. All existing opinions will remain in effect until a general review of past opinions can be undertaken using the new procedures. During this development phase, no new opinions will be rendered unless a proposed product can be shown to be virtually identical to a product for which an opinion has already been rendered, on the basis of chemical formulation and production process. New products or new uses of existing products which are proposed for use in drinking water will be subject to the pre-manufacture notice procedures of TSCA.

A more detailed outline of the steps to be taken by EPA follows.

1. *Problem Definition.*—EPA will contract for *in situ* monitoring to determine use patterns and the contribution of trace contaminants to drinking water from:

a. bulk chemicals.

b. generic classes of paints and coatings.

c. pipes and equipment.

d. coagulant aids.

EPA has already contracted with the National Academy of Sciences to develop a CODEX system of quality control standards for chemicals (direct additives) used in the treatment of drinking water. This effort will take about three years to complete. When finished, the CODEX system, modeled on the existing FDA-inspired CODEX system for chemicals used in processing food, will be largely self-enforcing.

For the indirect additives listed in items b and c above, considerable effort will be expended to identify the trace contaminants involved before the related health risks can be fully evaluated and appropriate recommendations for future use can be assessed.

2. *Review of Past Advisories.*—The same data base derived from *in situ* monitoring will serve as a basis for a structured reassessment of past toxicological advisories which will be conducted by generic classes of use e.g., paints, coagulant aides, etc. Past opinions will be reviewed to insure conformance with and satisfaction of new test protocols and decision criteria that will be developed.

3. *Future Toxicological Advisories.*—Once initial procedures, test protocols and decision criteria are developed, EPA will resume offering toxicological opinions to the States.

General Policy

In assessing additives to drinking water, EPA will be guided by a policy of reducing public health risks to the degree it is feasible to do so. In such determinations, EPA will evaluate the risks and benefits associated with the materials of concern and their substitutes. Economic impacts of agency actions will also be analyzed.

Notwithstanding these procedures, EPA would use its authorities to protect against any direct or indirect additive to drinking water when data and information indicate that the use of any additive may pose an undue risk to public health.

Implementation

To fulfill this program, resources from the Office of Drinking Water, the Office of Research and Development, and the Office of Toxic Substances will be used. In addition, EPA looks forward to the cooperation of FDA and other Federal regulatory bodies. EPA intends to involve interested industry groups, independent testing groups, State regulatory bodies, interested members of the public, and industry standards groups, in a continued effort to ensure the safety of the Nation's drinking water.

Finally, EPA may recommend specialized legislative authority to regulate additives to drinking water should a situation arise for which legal authorities prove inadequate.

Lead responsibility for this new Federal initiative will be in EPA's Office of Drinking Water. Public comments on any or all aspects of the proposed program are requested, and should be directed to the address given in the opening sections of this notice.

Dated: July 13, 1979.

Thomas C. Jorling,

Assistant Administrator for Water and Waste Management.

Appendix A

Safe Drinking Water Act

Section 1412—establishment of national primary drinking water regulations applicable to public water systems to control contaminants in drinking water which may have any adverse effect on human health. This may include maximum contaminant levels, treatment techniques, monitoring requirements, and quality control and testing procedures.

Section 1431—use of emergency powers where a contaminant which is present in water, or is likely to enter a public water system, may present an imminent and substantial endangerment to the health of persons.

Section 1445—establishment of monitoring and reporting requirements applicable to public water systems.

Section 1450—authority to prescribe such regulations as are necessary or appropriate to carry out the Administrator's functions under the Act.

Toxic Substances Control Act

Section 4—testing of chemical substances and mixtures.

Section 5—pre-manufacture notice required for new chemicals or significant new uses.

Section 6—regulation of hazardous chemical substances and mixtures which pose an unreasonable risk of injury to health or the environment, including restrictions on manufacture, processing, distribution, and use.

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Section 7—imminent hazards authority including seizure and other relief through civil court action.

Section 8—reporting and retention of information as required by the Administrator, including health and safety studies and notice to the Administrator of substantial risks.

Section 10—research and development. Development of systems for storing, retrieving and disseminating data.

Section 11—inspections and subpenas and other enforcement and general administration provisions therein.

Federal Insecticide, Fungicide and Rodenticide Act

Section 3—registration of pesticides, including imposition of restrictions and labeling requirements.

Section 6—suspension and cancellation procedures.

[FR Doc. 79-22222 Filed 7-18-79; 8:45 am]

BILLING CODE 6560-01-M

BILLING CODE 4110-03-M

FEDERAL COMMUNICATIONS COMMISSION

[Report No. A-1a]

FM Broadcasting Applications Accepted for Filing and Notification of Cut-off Date; Erratum

Released: July 12, 1979.

The FM Application listed below was inadvertently included on the acceptance/cut-off notice, Report No. A-1, BC Mimeo No. 18676, released on June 25, 1979.

BPH-790108AE (New): Creston, Pennsylvania, Sherlock-Hart Broadcasting, Inc.
Req.: 94.3 MHz, Channel 232A
ERP: 0.600 kW, HAAT: 600 feet.

Accordingly, the application is removed from the acceptance/cutoff list and the August 8, 1979, cutoff date is deleted.

Federal Communications Commission.

William J. Tricarico,

Secretary.

[FR Doc. 79-22422 Filed 7-19-79; 8:45 am]

BILLING CODE 6712-01-M

FEDERAL LABOR RELATIONS AUTHORITY

Official Time of Employees Involved in Negotiating Collective Bargaining Agreements

AGENCY: Federal Labor Relations Authority.

ACTION: Notice Relating to Official Time.

SUMMARY: This notice principally relates to the interpretation of section 7131 of the Federal Service Labor-Management Relations Statute (92 Stat. 1214) on the questions of whether employees who are on official time under this section while representing an exclusive representative in the negotiation of a collective bargaining agreement are entitled to payments from agencies for their travel and per diem expenses, and whether the official time provisions of section 7131(a) of the Statute encompass all negotiations between an exclusive representative and an agency, regardless of whether such negotiations pertain to the negotiation or renegotiation of a basic collective bargaining agreement. The notice further invites interested persons to address the impact, if any, of section 7135(a)(1) of the Statute (92 Stat. 1215) on such interpretation, and to submit written comments concerning these matters.

DATE: Written comments must be submitted by the close of business on August 24, 1979, to be considered.

ADDRESS: Send written comments to the Federal Labor Relations Authority, 1900 E Street, NW., Washington, D.C. 20424.

FOR FURTHER INFORMATION CONTACT: Harold D. Kessler, Deputy Executive Director, 1900 E Street, NW., Washington, D.C. 20424, (202) 632-3920.

SUPPLEMENTARY INFORMATION: The Federal Labor Relations Authority was established by Reorganization Plan No. 2 of 1978, effective January 1, 1979 (43 FR 36037). Since January 11, 1979, the Authority has conducted its operations under the Federal Service Labor-Management Relations Statute (92 Stat. 1191).

Upon receipt of requests and consideration thereof, the Authority has determined, in accordance with 5 CFR 2410.3(a) (1978) and sections 7105 and 7135(b) of the Statute (92 Stat. 1196, 1215), that an interpretation is warranted concerning section 7131 of the Statute (92 Stat. 1214). Interested persons are invited to express their views in writing on this matter, as more fully explained in the Authority's notice set forth below:

To Heads of Agencies, Presidents of Labor Organizations and Other Interested Persons

The Authority has received a request from the American Federation of Government Employees (AFGE) for a statement of policy and guidance concerning whether employees representing an exclusive representative in the negotiation of a collective bargaining agreement are entitled to payments from agencies for their travel and per diem expenses under the official time provisions of section 7131 of the Federal Service Labor-Management Relations Statute (92 Stat. 1214). Additionally, the National Federation of Federal Employees (NFFE) has requested a major policy statement as to the application of the official time provisions of section 7131(a) of the Statute (92 Stat. 1214) to all negotiations between an exclusive representative and an agency, regardless of whether such negotiations pertain to the negotiation or renegotiation of a basic collective bargaining agreement. AFGE has raised a similar issue in its request.

The Authority hereby determines, in conformity with 5 CFR 2410.3(a) (1978) and section 7135(b) of the Statute (92 Stat. 1215), as well as section 7105 of the Statute (92 Stat. 1196), that an interpretation of the Statute is warranted on the following:

(1) Whether employees who are on official time under section 7131 of the Statute while representing an exclusive representative in the negotiation of a collective bargaining agreement are entitled to payments from agencies for their travel and per diem expenses.

(2) Whether the official time provisions of section 7131(a) of the Statute encompass all negotiations between an exclusive representative and an agency, regardless of whether such negotiations pertain to the negotiation or renegotiation of a basic collective bargaining agreement.

Before issuing an interpretation on the above, the Authority, pursuant to 5 CFR 2410.6 (1978) and section 7135(b) of the Statute (92 Stat. 1215), solicits your views in writing. You are further invited to address the impact, if any, of section 7135(a)(1) of the Statute (92 Stat. 1215) on the above matters and to submit your views as to whether oral argument should be granted. To receive consideration, such views must be submitted to the Authority by the close of business on August 24, 1979.

Issued, Washington, D.C., July 13, 1979.

Federal Labor Relations Authority.

Ronald W. Haughton,

Chairman.

Henry B. Frazier III,

Member.

[FR Doc. 79-22440 Filed 7-19-79; 8:45 am]

BILLING CODE 6325-01-M

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MOU number: 225-79-2001

Memorandum of Understanding

Between
The Environmental Protection Agency

and

The Food and Drug Administration

I. Purpose:

This Memorandum of Understanding establishes an agreement between the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) with regard to the control of direct and indirect additives to and substances in drinking water.

EPA and FDA agree:

A. That contamination of drinking water from the use and application of direct and indirect additives and other substances poses a potential public health problem;

B. That the scope of the additives problem in terms of the health significance of these contaminants in drinking water is not fully known;

C. That the possibility of overlapping jurisdiction between EPA and FDA with respect to control of drinking water additives has been the subject of Congressional as well as public concern;

D. That the authority to control the use and application of direct and indirect additives to and substances in drinking water should be vested in a single regulatory agency to avoid duplicative and inconsistent regulation;

E. That EPA has been mandated by Congress under the Safe Drinking Water Act (SDWA), as amended, to assure that the public is provided with safe drinking water;

F. That EPA has been mandated by Congress under the Toxic Substances Control Act (TSCA) to protect against unreasonable risks to health and the environment from toxic substances by requiring, inter alia, testing and necessary restrictions on the use, manufacture, processing, distribution, and disposal of chemical substances and mixtures;

G. That EPA has been mandated by Congress under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, to assure, inter alia, that when used properly, pesticides will perform their intended function without causing unreasonable adverse effects on the environment; and,

H. That FDA has been mandated by Congress under the Federal Food, Drug, and

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Cosmetic Act (FFDCA), as amended, to protect the public from, inter alia, the adulteration of food by food additives and poisonous and deleterious substances.

It is the intent of the parties that:

A. EPA will have responsibility for direct and indirect additives to and other substances in drinking water under the SDWA, TSCA, and FIFRA; and,

B. FDA will have responsibility for water, and substances in water, used in food and for food processing and responsibility for bottled drinking water under the FFDCA.

II. Background:

A. FDA Legal Authority

"Food" means articles used for food or drink for man or other animals and components of such articles. (FFDCA Section 201(f)). Under Section 402, inter alia, a food may not contain any added poisonous or deleterious substance that may render it injurious to health, or be prepared, packed or handled under unsanitary conditions. Tolerances may be set, under Section 406, limiting the quantity of any substance which is required for the production of food or cannot be avoided in food. FDA has the authority under Section 409 to issue food additive regulations approving, with or without conditions, or denying the use of a "food additive." That term is defined in Section 201(s) to include any substance the intended use of which results or may reasonable be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, if such substance is not generally recognized as safe.

In the past, FDA has considered drinking water to be a food under Section 201(f). However, both parties have determined that the passage of the SDWA in 1974 implicitly repealed FDA's authority under the FFDCA over water used for drinking water purposes. Under the express provisions of Section 410 of the FFDCA, FDA retains authority over bottled drinking water. Furthermore, all water used in food remains a food and subject to the provisions of the FFDCA. Water used for food processing is subject to applicable provisions of FFDCA. Moreover, all substances in water used in food are added substances subject to the provisions of the FFDCA, but no substances added to a public drinking water system before the water enters a food processing establishment will be considered a food additive.

B. EPA Legal Authority

The SDWA grants EPA the authority to control contaminants in drinking water which may have any adverse effect on the public health, through the establishment of maximum contaminant levels (MCLs) or treatment techniques, under Section 1412, which are applicable to owners and operators of public water systems. The expressed intent of the Act was to give EPA exclusive control over the safety of public water supplies. Public water systems may also be required by regulation to conduct monitoring for unregulated contaminants under Section 1445 and to issue public notification of such levels under Section 1414(c).

EPA's direct authority to control additives to drinking water apart from the existence of maximum contaminant levels or treatment techniques is limited to its emergency powers under Section 1431. However, Section 1442(b) of the Act authorizes EPA to "collect and make available information pertaining to research, investigations, and demonstrations with respect to providing a dependably safe supply of drinking water together with appropriate recommendations therewith."

TSCA gives EPA authority to regulate chemical substances, mixtures and under some circumstances, articles containing such substances or mixtures. Section 4 permits EPA

to require testing of a chemical substance or mixture based on possible unreasonable risk of injury to health or the environment, or on significant or substantial human or environmental exposure while Section 8 enables EPA to require submission of data showing substantial risk of injury to health or the environment, existing health and safety studies, and other data. For new chemical substances, and significant new uses of existing chemical substances, Section 5 requires manufacturers to provide EPA with pre-manufacturing notice. Under Section 6 the manufacture, processing, distribution, use, and disposal of a chemical substance or mixture determined to be harmful may be restricted or banned. Although Section 3(2)(B) of TSCA excludes from the definition of "chemical substance" food and food additives as defined under FFDCA, the implicit repeal by the SDWA of FDA's authority over drinking water enables EPA to regulate direct and indirect additives to drinking water as chemical substances and mixtures under TSCA.

The FIFRA requires EPA to set restrictions on the use of pesticides to assure that when used properly, they will not cause unreasonable adverse effects on the environment. EPA may require, inter alia labeling which specifies how, when, and where a pesticide may be legally used. In addition, EPA has, under Section 409 of the FFDCA, required FIFRA registrants at times to obtain a food additive tolerance before using a pesticide in or around a drinking water source. Such tolerances establish further restrictions on the use of a pesticide which are enforceable against the water supplier as well as the registrant of the pesticide.

III. Terms of Agreement:

A. EPA's responsibilities are as follows:

1. To establish appropriate regulations, and to take appropriate measures, under the SDWA and/or TSCA, and FIFRA, to control direct additives to drinking water (which encompass any substances purposely added to the water), and indirect additives (which encompass any substance which might leach from paints, coatings or other materials as an incidental result of drinking water contact), and other substances.

2. To establish appropriate regulations under the SDWA to limit the concentrations of pesticides in drinking water; the limitations on concentrations and types of pesticides in water are presently set by EPA through tolerances under Section 409 of the FFDCA.

3. To continue to provide technical assistance in the form of informal advisory opinions on drinking water additives under Section 1442(b) of the SDWA.

4. To conduct and require research and monitoring and the submission of data relative to the problem of direct and indirect additives in drinking water in order to accumulate data concerning the health risks posed by the presence of these contaminants in drinking water.

B. FDA's responsibilities are as follows:

1. To take appropriate regulatory action under the authority of the FFDCA to control bottled drinking water and water, and substances in water, used in food and for food processing.

2. To provide assistance to EPA to facilitate the transition of responsibilities, including:

a) To review existing FDA approvals in order to identify their applicability to additives in drinking water.

b) To provide a mutually agreed upon level of assistance in conducting literature searches related to toxicological decision making.

c) To provide a senior toxicologist to help EPA devise new procedures and protocols to be used in formulating advice on direct and indirect additives to drinking water.

IV. Duration of Agreement:

This Memorandum of Understanding shall continue in effect unless modified by mutual consent of both parties or terminated by either party upon thirty (30) days advance written notice to the other.

This Memorandum of Understanding will become effective on the date of the last signature.

Approved and Accepted for the Environmental Protection Agency

Signed by: Douglas P. Costle
Administrator
Environmental Protection Agency

Date: June 12, 1979

Approved and Accepted for the Food and Drug Administration

Signed by: Donald Kennedy
Administrator
Food and Drug Administration

Date: June 22, 1979

Domestic MOUs

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FDA Website Management Staff

§ 321. Definitions; Generally.

Archive

United States Statutes

Title 21. Food and Drugs

Chapter 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT

Subchapter II. DEFINITIONS

Current through P.L. 111-290

§ 321. Definitions; Generally

For the purposes of this chapter-

(a) (1) The term "State", except as used in the last sentence of section **372 (a)** of this title, means any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico.

(2) The term "Territory" means any Territory or possession of the United States, including the District of Columbia, and excluding the Commonwealth of Puerto Rico and the Canal Zone.

(b) The term "interstate commerce" means

(1) commerce between any State or Territory and any place outside thereof, and

(2) commerce within the District of Columbia or within any other Territory not organized with a legislative body.

(c) The term "Department" means Department of Health and Human Services.

(d) The term "Secretary" means the Secretary of Health and Human Services.

(e) The term "person" includes individual, partnership, corporation, and association.

(f) The term "food" means

(1) articles used for food or drink for man or other animals,

(2) chewing gum, and

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(3) articles used for components of any such article.

(g) (1) The term "drug" means

(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

(D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections **343 (r)(1)(B)** and **343 (r)(3)** of this title or sections **343 (r)(1)(B)** and **343 (r)(5)(D)** of this title, is made in accordance with the requirements of section **343 (r)** of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section **343 (r)(6)** of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.

(2) The term "counterfeit drug" means a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor.

(h) The term "device" (except when used in paragraph (n) of this section and in sections **331 (i)**, **343 (f)**, **352 (c)**, and **362 (c)** of this title) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is-

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended

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(dd) For purposes of sections **335a** and **335b** of this title, the term "drug product" means a drug subject to regulation under section **355**, **360b**, or **382** of this title or under section **262** of title 42.

(ee) The term "Commissioner" means the Commissioner of Food and Drugs.

(ff) The term "dietary supplement"-

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;

(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

(2) means a product that-

(A)

(i) is intended for ingestion in a form described in section **350 (c)(1)(B)(i)** of this title; or

(ii) complies with section **350 (c)(1)(B)(ii)** of this title;

(B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and

(C) is labeled as a dietary supplement; and

(3) does-

(A) include an article that is approved as a new drug under section **355** of this title or licensed as a biologic under section **262** of title 42 and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section **342 (f)** of

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this title; and

(B) not include-

(i) an article that is approved as a new drug under section **355** of this title, certified as an antibiotic under section **357** of this title, or licensed as a biologic under section **262** of title 42, or

(ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public,

which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter.

Except for purposes of paragraph (g) and section 350f of this title, a dietary supplement shall be deemed to be a food within the meaning of this chapter.

(gg) The term "processed food" means any food other than a raw agricultural commodity and includes any raw agricultural commodity that has been subject to processing, such as canning, cooking, freezing, dehydration, or milling.

(hh) The term "Administrator" means the Administrator of the United States Environmental Protection Agency.

(ii) The term "compounded positron emission tomography drug"-

(1) means a drug that-

(A) exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon positron emission tomographic diagnostic images; and

(B) has been compounded by or on the order of a practitioner who is licensed by a State to compound or order compounding for a drug described in subparagraph (A), and is compounded in accordance with that State's law, for a patient or for research, teaching, or quality control; and

(2) includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of such a drug.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 21 2000

The Honorable Ken Calvert
Chairman
Subcommittee on Energy and Environment
Committee on Science
House of Representatives
Washington, D.C. 20515-6301

Dear Mr. Chairman:

Thank you for the letter of May 8, 2000, to Dr. Jane E. Henney, Commissioner of Food and Drugs, regarding the use of fluoride in drinking water and drug products. We apologize for the delay in responding to you.

We have restated each of your questions, followed by our response.

1. **If health claims are made for fluoride-containing products (e.g. that they reduce dental caries incidence or reduce pathology from osteoporosis), do such claims mandate that the fluoride-containing product be considered a drug, and thus subject the product to applicable regulatory controls?**

Fluoride, when used in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animal, is a drug that is subject to Food and Drug Administration (FDA) regulation. FDA published a final rule on October 6, 1995, for anticaries drug products for over-the-counter (OTC) human use (copy enclosed). This rule establishes the conditions under which OTC anticaries drug products are generally recognized as safe and effective and not misbranded. The rule has provisions for active ingredients, packaging conditions, labeling, and testing procedures that are required by manufacturers in order to market anticaries products. A new drug application (NDA) may be filed for a product containing fluoride that does not meet the provisions stated in the final rule. As you know, the Environmental Protection Agency regulates fluoride in the water supply.

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2. Are there any New Drug Applications (NDA) on file, that have been approved, or that have been rejected, that involve a fluoride-containing product (including fluoride-containing vitamin products) intended for ingestion with the stated aim of reducing dental caries? If any such NDA's have been rejected, on what grounds were they rejected? If any such NDA have been approved, please provide the data on safety and efficacy that FDA found persuasive.

No NDAs have been approved or rejected for fluoride drugs meant for ingestion. Several NDAs have been approved for fluoride topical products such as dentifrices and gels. Fluoride products in the form of liquid and tablets meant for ingestion were in use prior to enactment of the Kefauver-Harris Amendments (Drug Amendments of 1962) to the Food, Drug, and Cosmetic Act in which efficacy became a requirement, in addition to safety, for drugs marketed in the United States (U.S.). Drugs in use prior to 1962 are being reviewed under a process known as the drug efficacy study implementation (DESI). The DESI review of fluoride-containing products has not been completed.

3. Does FDA consider dental fluorosis a sign of over exposure to fluoride?

Dental fluorosis is indicative of greater than optimal ingestion of fluoride. In 1988, the U.S. Surgeon General reported that dental fluorosis, while not a desirable condition, should be considered a cosmetic effect rather than an adverse health effect. Surgeon General M. Joycelyn Elders reaffirmed this position in 1994.

4. Does FDA have any action-level or other regulatory restriction or policy statement on fluoride exposure aimed at minimizing chronic toxicity in adults or children?

The monograph for OTC anticaries drug products sets acceptable concentrations for fluoride dentifrices, gels and rinses (all for topical use only). This monograph also describes the acceptable dosing regimens and labeling including warnings and directions for use. FDA's principal safety concern regarding fluoride in OTC drugs is the incidence of fluorosis in

children. Children under two years of age do not have control of their swallowing reflex and do not have the skills to expectorate toothpaste properly. Young children are most susceptible to mild fluorosis as a result of improper use and swallowing of a fluoride toothpaste. These concerns are addressed in the monograph by mandating maximum concentrations, labeling that specifies directions for use and age restrictions, and package size limits.

Thanks again for contacting us concerning this matter. If you have further questions, please let us know.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

Enclosure
"Final Rule/Federal Register - October 6, 1995
Over-the-Counter Anticaries Drug Products"

Web site administrator's note:
To perform query to access this document
Enter: http://www.access.gpo.gov/su_docs/aces/aces140.html
Enter: checkmark for 1995 Volume 60
Enter: On: 10/06/95
Enter: Search terms: anticaries

Fluorosilicic Acid

Fluorosilicic Acid (Hydrofluorosilicic Acid, HFS, FSA)

Technical Data Sheet

CHEMICAL ANALYSIS	SPECIFICATION	TYPICAL ANALYSIS
H_2SiF_6, %	23-25	23.5
Heavy Metals (as Pb), %		< 0.02
HF, %	1.0 max	0.5
Color, APHA	100 max	< 20
P_2O_5, %		< 0.2

Product meets ANSI/AWWA Standard B703-06, and is certified by NSF International or Classified by UL to ANSI/NSF Standard 60. Maximum use level for potable water treatment is 6.0 mg/L.

PHYSICAL PROPERTIES

Physical Description	Aqueous solution, water white to straw-yellow, corrosive acid, irritating to skin and having pungent odor.
Molecular Weight	144.08
Specific Gravity 23% solution @ 75°F	1.212
Boiling Point of Aqueous 23% Solution	221°F (Decomposes)
Freezing Point of Aqueous 23% Solution	5°F (approx.)
Freezing Point of Aqueous 25% Solution	-4°F
pH of 1%, H_2SiF_6	1.2

CONTAINERS

Tank truck, rubber or plastic-lined	40,000 lb (approx.)
Tank car, rubber or plastic-lined	196,000 lb net (approx.)

DOT AND FREIGHT DESCRIPTION

Hazardous Material Description	Fluorosilicic acid
Haz. Mat. Class, I.D.#, Packaging Group	8, UN 1778, PG II
Freight Classification	Hydrofluorosilicic Acid
Principal CAS Number	16961-83-4
RQ	None
Placard	Corrosive
Label	Corrosive

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SOLVAY Fluorides

SOLVAY

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Fluorosilicic Acid

Fluorosilicic Acid (Hydrofluorosilicic Acid, HFS, FSA)

Technical Data Sheet

Use in public Water Treating Plants:

The reduction in dental caries by adjusting the fluoride content of public water supplies is a matter of common knowledge today, half a century following the first installation in Grand Rapids, Michigan. Approximately 170 million people in over three thousand communities are now drinking fluoride-treated water from water purification plants where fluoridation is currently practiced. Fluoridation is concerned with the controlled introduction to water of the fluoride ion. Other materials in the fluoride compound simultaneously introduced into the water with the fluoride ions are carriers which provide no benefits and are nontoxic. The addition of one part per million of fluoride requires that the product be soluble, of definite concentration and have high purity standards. In conformity with the American Water Works Association standard B703-94, the term fluorosilicic acid has replaced the more technical designation of hydrofluosilicic acid. After the original work with sodium fluoride proved the effectiveness of fluoride on tooth health and a broad fluoridation program was envisaged, new sources of fluoride and economics of their use were investigated. Fluorosilicic acid is a high purity source of fluoride. It is simpler to use than any other chemical approved for water fluoridation purposes, primarily because it is a liquid and can therefore be accurately measured and fed with a minimum of equipment. In contrast to powdered or granular chemicals, it presents no dust problems, no measuring problems and handling requires a minimum of labor. Today most of the large cities and many small ones are fluoridating with fluorosilicic acid. It is readily available in tank cars or tank trucks and can also be supplied in 15-gallon carboys and 55-gallon drums. The addition of fluorosilicic acid to a water supply can be readily controlled to give a total fluoride (F) level of one part per million which has been established as effective for reducing tooth decay. It should be used in accordance with procedures approved by each state's department of health.

Acid Characteristics:

Fluorosilicic acid is a transparent, clear to straw-colored, corrosive liquid having the chemical formula of H_2SiF_6. It is manufactured in modern rubber-lined equipment producing an acid of high commercial purity. Commercial water solutions of the acid are available, having concentration of between 23% and 25% H_2SiF_6. Fluorosilicic acid is generally believed not to exist in the vapor phase, but only in solution. Upon vaporizing, it decomposes into hydrofluoric acid (HF) and silicon tetrafluoride. This equilibrium exists at the surface of strong solutions of fluorosilicic acid and if stored in glass containers, the small concentration of hydrofluoric acid may very slowly attack the glass above the solution level. For this reason, it is generally shipped in polyethylene containers rather than glass carboys. A 23% fluorosilicic acid-water solution weighs 10.1 pounds per gallon at 75°F, and has a fluoride (F) content of 18.20%.

CGR#3323 HFS-0205 Revised 0707

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Fluorosilicic Acid (Hydrofluorosilicic Acid, HFS, FSA)

Technical Data Sheet

Installation:
In a typical large plant installation, rubber-lined vented storage tanks are usually mounted outside the building with the tanks ranging in size from 4,500 to 6,500 gallon capacities. These tanks, equipped with recording level gauges, feed the acid through plastic piping or tubing to the dosage unit. Feeding is regulated by controlled volume pumps. Metering is used for accurate flow records. Fluorosilicic acid may be handled in rubber-lined, saran or other available corrosive-resistant equipment as suggested below:

Pipes and lines	-	rubber, saran or polyethylene
Pumps	-	Lucite, saran or Hastelloy
Valves	-	rubber-lined or polyethylene-lined
Tanks	-	rubber-lined, saran or polyethylene-lined

Acid should be pumped by positive diaphragm proportioning pumps.

Operation procedure:
The drum or drums of fluorosilicic acid should be mounted on a platform of sufficient size and capacity to permit weighing the amount used each day. Proportioning pumps deliver an accurate volume, but for small pumping rates, the dosage may be more satisfactorily regulated by periodic weighing of the drum. Whenever a drum of fluorosilicic acid is replaced on the scale, the time and weight should be recorded in the daily operating log. Whenever dosage is changed to a varying pumpage, the time and feeder setting should be recorded in the daily log.

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SHANGHAI MINTCHEM DEVELOPMENT CO., LTD

Specification Sheet

Sodium Fluoride

Physical Properties:

Formula	**Na F**	**Molecular Weight**	**41.99**	**CAS NO**	**7681-49-4**
U.N-NO	**1690**	**Class**	**6.1**	**H.S-NO**	**2826110010**

Character: White crystal or powder. Relative Density 2.558. It's odorless. Soluble in water and HF. Insoluble in ethanol. Mellting point 993ºC and boiling point 1695ºC. Non flammable but toxic.

Chemical Parameters:

NO.	Technological Specification	Granular Standard%		Powder Standard%	
1	NaF purity	98.5%min		98.5%min	
2	Sodium Carbonate	0.5%max.		0.5%max.	
3	Na2SiF6	1.5%max		1.5%max	
4	Silicon Dioxide	0.5%max.		0.5%max.	
5	Sulphate	0.3%max.		0.3%max.	
6	HF	0.1%max,		0.1%max,	
7	H2O(moisture)	0.5%max.		0.5%max.	
8	Heavy Metal(As Pb)	0.04%max.		0.04%max.	
9	Available Fluoride	43.8%min.		43.8%min.	
10	Water Insoluble matter	0.6%max.		0.6%max.	
11	Particle Size	-20 mesh	98%min	+80 mesh	4 % max
12		+100 mesh	50%min	+200 mesh	25 % max
13		-325 mesh			

APPLICATION: It is mainly used as fluxing agent, timber preservative and water treatment etc.

PACKAGE: Packing in plastic weaved bag 25kg each. TRANSPORTATION: DG, Class 6.1, UN 1690

MANUFACTURER: SHANGHAI MINTCHEM DEVELOPMENT CO., LTD

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mid 1980's[7] (Evans R.W, Stamm JW., 1991). Across all age groups more than 90% of fluorosis cases were very mild or mild. (Evans R.W, Stamm JW., 1991). The study did not include measures of fluoride intake. Concurrently, dental caries prevalence did not increase. (Lo ECM *et al,* 1990). Although not fully generalizable to the current U.S. context, these findings, along with those from the 1986–87 survey of U.S. schoolchildren, suggest that risk of fluorosis can be reduced and caries prevention maintained toward the lower end (*i.e.,* 0.7 mg/L) of the 1962 USPHS recommendations for fluoride concentrations for community water systems.

Relationship of fluid intake and ambient temperature among children and adolescents in the United States:

The 1962 USPHS recommendations stated that community drinking water should contain 0.7–1.2 mg/L [ppm] fluoride, depending on the ambient air temperature of the area. These temperature-related guidelines were based on studies conducted in two communities in California in the early 1950's. Findings indicated that a lower fluoride concentration was appropriate for communities in warmer climates because children drank more tap water on warm days (Galagan DJ, 1953; Galagan DJ and Vermillion JR, 1957; Galagan DJ *et al,* 1957). Social and environmental changes, including increased use of air conditioning and more sedentary lifestyles, have occurred since the 1950's, and thus, the assumption that children living in warmer regions drink more tap water than children in cooler regions may no longer be valid.

Studies conducted since 2001 suggest that fluid intake in children does not increase with increases in ambient air temperature (Sohn W, *et al,* 2001; Beltrán-Aguilar ED, *et al,* 2010b). One study conducted among children using nationally representative data from 1988 to 1994 did not find an association between fluid intake and ambient air temperature (Sohn W, *et al,* 2001). A similar study using nationally representative data from 1999 to 2004 also found no association between fluid intake and ambient temperature among children or adolescents (Beltrán-Aguilar ED, *et al,* 2010b). These recent findings demonstrating a lack of an association between fluid intake among children and adolescents and ambient temperature support use of a single target concentration for community water fluoridation in all temperature zones of the United States.

Conclusions

HHS recommends an optimal fluoride concentration of 0.7 mg/L for community water systems based on the following information:

- Community water fluoridation is the most cost-effective method of delivering fluoride for the prevention of tooth decay;
- In addition to drinking water, other sources of fluoride exposure have contributed to the prevention of dental caries and an increase in dental fluorosis prevalence;
- Significant caries preventive benefits can be achieved and risk of fluorosis reduced at 0.7 mg/L, the lowest concentration in the range of the USPHS recommendation.
- Recent data do not show a convincing relationship between fluid intake and ambient air temperature. Thus, there is no need for different recommendations for water fluoride concentrations in different temperature zones.

Surveillance Activities

CDC and the National Institute of Dental and Craniofacial Research (NIDCR), in coordination with other Federal agencies, will enhance surveillance of dental caries, dental fluorosis, and fluoride intake with a focus on younger populations at higher risk of fluorosis to obtain the best available and most current information to support effective efforts to improve oral health.

Process

The U.S. Department of Health and Human Services (HHS) convened a Federal inter-departmental, inter-agency panel of scientists (Appendix A) to review scientific evidence related to the 1962 USPHS Drinking Water Standards related to recommendations for fluoride concentrations in drinking water in the United States and to update these proposed recommendations. Panelists included representatives from the Centers for Disease Control and Prevention, the National Institutes of Health, the Food and Drug Administration, the Agency for Healthcare Research and Quality, the Office of the Assistant Secretary for Health, the U.S. Environmental Protection Agency, and the U.S. Department of Agriculture. The panelists evaluated existing recommendations for fluoride in drinking water, systematic reviews of the risks and benefits from fluoride in drinking water, the epidemiology of dental caries and fluorosis in the U.S., and current data on fluid intake in children, aged 0 to 10 years, across temperature gradients in the U.S. Conclusions were reached and are summarized along with their rationale in this proposed guidance document. This guidance will be advisory, not regulatory, in nature. Guidance will be submitted to the **Federal Register** and will undergo public and stakeholder comment for 30 days, after which HHS will review comments and consider changes.

Dated: January 7, 2011.

Kathleen Sebelius,

Secretary.

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Beltrán-Aguilar ED, Barker L, Sohn W. Daily temperature and children's water intake in the United States. Accepted for publication, CDC's Division of Oral Health, 2010b. *http://www.cdc.gov/fluoridation/fact_sheets/totalwaterintake.htm.*

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[7] Fluorosis prevalence ranged from 64% (SE = 4.1) to 47% (SE = 4.5) based on the upper right central incisor only.

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STATE OF WASHINGTON

WASHINGTON STATE BOARD OF HEALTH

PO Box 47990 • Olympia, Washington 98504-7990

November 16, 2010

Mr. William Osmunson, DDS, MPH, President
Washington Action for Safe Water
1418 – 112th Ave NE, Suite 200
Bellevue, WA 98004

Dear Dr. Osmunson:

This letter provides formal notice that the Washington State Board of Health has denied your petition for rule making received on October 7, 2010 to add an intent statement in two places in WAC 246-290-460, regarding water fluoridation. The suggested statement was "with the intent to prevent dental caries." This was the fifth petition for rule making you submitted to the Board this year regarding this rule.

The Board's intent for setting an "optimal" fluoride concentration in WAC 246-290-460 is part of its requirement to "adopt rules for group A public water systems...to assure safe and reliable public drinking water and to protect the public health" under RCW 43.20.050(2)(a). The Board follows guidelines of the Centers for Disease Control and Prevention (CDC) regarding setting an appropriate level of fluoride in drinking water if the directors of a water system decide to fluoridate under the authority of RCW 57.08.012. The CDC promotes community water fluoridation as one of the ten great public health achievements of the twentieth century. It says fluoridation is the single most effective public health measure to prevent tooth decay. The Board supports this and other positions of the CDC. The Board considers it self evident that the purpose of water fluoridation is to help prevent tooth decay. The Board does not consider it efficient use of public resources to initiate and complete a rule making process to add to the rule the language requested by the petitioner.

The Board handled your request as a petition for rule making under RCW 34.05.330 and Board Policy 2005-001, Responding to Petitions for Rule Making. The statute requires the Board to respond within 60 days of receipt. RCW 34.05.330(3) allows a person to appeal a petition's denial to the Governor within 30 days. The Board's policy allows the Board Chair to respond to a petition for rule making without the petition being placed on a meeting agenda for full Board consideration. If you have questions about this decision, please contact Craig McLaughlin, Executive Director of the Board, at 360-236-4106 or craig.mclaughlin@doh.wa.gov.

Sincerely,

Keith Higman
Chair

cc: Michelle Davis, Department of Health
Gregg Grunenfelder, Department of Health
State Board of Health Members

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CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

August 17, 2001 / Vol. 50 / No. RR-14

MMWR™
MORBIDITY AND MORTALITY
WEEKLY REPORT

Recommendations and Reports

Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, GA 30333

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Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States

Summary

Widespread use of fluoride has been a major factor in the decline in the prevalence and severity of dental caries (i.e., tooth decay) in the United States and other economically developed countries. When used appropriately, fluoride is both safe and effective in preventing and controlling dental caries. All U.S. residents are likely exposed to some degree to fluoride, which is available from multiple sources. Both health-care professionals and the public have sought guidance on selecting the best way to provide and receive fluoride. During the late 1990s, CDC convened a work group to develop recommendations for using fluoride to prevent and control dental caries in the United States. This report includes these recommendations, as well as a) critical analysis of the scientific evidence regarding the efficacy and effectiveness of fluoride modalities in preventing and controlling dental caries, b) ordinal grading of the quality of the evidence, and c) assessment of the strength of each recommendation.

Because frequent exposure to small amounts of fluoride each day will best reduce the risk for dental caries in all age groups, the work group recommends that all persons drink water with an optimal fluoride concentration and brush their teeth twice daily with fluoride toothpaste. For persons at high risk for dental caries, additional fluoride measures might be needed. Measured use of fluoride modalities is particularly appropriate during the time of anterior tooth enamel development (i.e., age <6 years).

The recommendations in this report guide dental and other health-care providers, public health officials, policy makers, and the public in the use of fluoride to achieve maximum protection against dental caries while using resources efficiently and reducing the likelihood of enamel fluorosis. The recommendations address public health and professional practice, self-care, consumer product industries and health agencies, and further research. Adoption of these recommendations could further reduce dental caries in the United States and save public and private resources.

INTRODUCTION

Dental caries (i.e., tooth decay) is an infectious, multifactorial disease afflicting most persons in industrialized countries and some developing countries (*1*). Fluoride reduces the incidence of dental caries and slows or reverses the progression of existing lesions (i.e., prevents cavities). Although pit and fissure sealants, meticulous oral hygiene, and appropriate dietary practices contribute to caries prevention and control, the most effective and widely used approaches have included fluoride use. Today, all U.S. residents are exposed to fluoride to some degree, and widespread use of fluoride has been a major factor in the decline in the prevalence and severity of dental caries in the United States and other economically developed countries (*1*). Although this decline is a major public

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Fluoridated Drinking Water and Processed Beverages and Food

Fluoridated drinking water contains a fluoride concentration effective for preventing dental caries; this concentration can occur naturally or be reached through water fluoridation, which is the controlled addition of fluoride to a public water supply. When fluoridated water is the main source of drinking water, a low concentration of fluoride is routinely introduced into the mouth. Some of this fluoride is taken up by dental plaque; some is transiently present in saliva, which serves as a reservoir for plaque fluoride; and some is loosely held on the enamel surfaces (*76*). Frequent consumption of fluoridated drinking water and beverages and food processed in fluoridated areas maintains the concentration of fluoride in the mouth.

Estimates of fluoride intake among U.S. and Canadian adults have ranged from ≤1.0 mg fluoride per day in nonfluoridated areas to 1–3 mg fluoride per day in fluoridated areas (*77–80*). The average daily dietary fluoride intake for both children and adults in fluoridated areas has remained relatively constant for several years (*11*). For children who live in optimally fluoridated areas, this average is approximately 0.05 mg/kg/day (range: 0.02–0.10); for children who live in nonfluoridated areas, the average is approximately half (*11*). In a survey of four U.S. cities with different fluoride concentrations in the drinking water (range: 0.37–1.04 ppm), children aged 2 years ingested 0.41–0.61 mg fluoride per day and infants aged 6 months ingested 0.21–0.54 mg fluoride per day (*81,82*).

In the United States, water and processed beverages (e.g., soft drinks and fruit juices) can provide approximately 75% of a person's fluoride intake (*83*). Many processed beverages are prepared in locations where the drinking water is fluoridated. Foods and ingredients used in food processing vary in their fluoride content (*11*). As consumption of processed beverages by children increases, fluoride intake in communities without fluoridated water will increase whenever the water source for the processed beverage is fluoridated (*84*). In fluoridated areas, dietary fluoride intake has been stable because processed beverages have been substituted for tap water and for beverages prepared in the home using tap water (*11*).

A study of Iowa infants estimated that the mean fluoride intake from water during different periods during the first 9 months of life, either consumed directly or added to infant formula or juice, was 0.29–0.38 mg per day, although estimated intake for some infants was as high as 1.73 mg per day (*85*). As foods are added to an infant's diet, replacing some of the formula prepared with fluoridated water, the amount of fluoride the infant receives typically decreases (*86*). The Iowa study also reported that infant formula and processed baby food contained variable amounts of fluoride. Since 1979, U.S. manufacturers of infant formula have voluntarily lowered the fluoride concentration of their products, both ready-to-feed and concentrates, to <0.3 ppm fluoride (*87*).

Drinking Water

Community Water. During the 1940s, researchers determined that 1 ppm fluoride was the optimal concentration in community drinking water for climates similar to the Chicago area (*88,89*). This concentration would substantially reduce the prevalence of dental caries, while allowing an acceptably low prevalence (i.e., 10%–12%) of very mild and mild enamel fluorosis and no moderate or severe enamel fluorosis. Water fluoridation for caries control began in 1945 and 1946, when the fluoride concentration was

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U.S. Food and Drug Administration

Regulatory Information

Significant Amendments to the FD&C Act

Significant Amendments to the FD&C Act:

Since 1980, listed chronologically; date shown is when the Public Law was approved. "Summary" indicates link to a summary of the law; other links are to full text. Provisions of these Public Laws are incorporated into the FD&C Act.

- Infant Formula Act of 1980 (summary)[1]
  Public Law (PL) 96-359 (Oct. 26, 1980)
- Orphan Drug Act[2]
  PL 97-414 (Jan. 4, 1983)
- Drug Price Competition and Patent Term Restoration Act of 1984 (summary)[3]
  PL 98-417 (Sept. 24, 1984)
- Prescription Drug Marketing Act of 1987[4]
  PL 100-293 (Apr. 22, 1988)
- Generic Animal Drug and Patent Term Restoration Act of 1988 (summary)[5]
  PL 100-670 (Nov. 16, 1988)
- Nutrition Labeling and Education Act of 1990 (summary)[6]
  PL 101-535 (Nov. 8, 1990)
- Safe Medical Devices Act of 1990 (summary)[7]
  PL 101-629 (Nov. 28, 1990)
- Medical Device Amendments of 1992 (summary)[8]
  PL 102-300 (June 16, 1992)
- Prescription Drug Amendments of 1992; Prescription Drug User Fee Act of 1992[9]
  PL 102-571 (Oct. 29, 1992)
- Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994[10]
  PL 103-396 (Oct. 22, 1994)
- Dietary Supplement Health and Education Act of 1994[11]
  PL 103-417 (Oct. 25, 1994)
- FDA Export Reform and Enhancement Act of 1996[12]
  PL 104-134 (April 26, 1996)
- Food Quality Protection Act of 1996[13]
  PL 104-170 (Aug. 3, 1996)
- Animal Drug Availability Act of 1996[14]
  PL 104-250 (Oct. 9, 1996)
- Food and Drug Administration Modernization Act (FDAMA) of 1997[15]
  PL 105-115 (Nov. 21, 1997)
- Best Pharmaceuticals for Children Act[16]
  PL 107-109 (Jan. 4, 2002)
- Medical Device User Fee and Modernization Act (MDUFMA) of 2002[17]
  PL 107-250 (Oct. 26, 2002)
- Animal Drug User Fee Act of 2003[18]
  PL 108-130 (Nov. 18, 2003)
- Pediatric Research Equity Act of 2003[19]
  PL 108-155 (Dec. 3, 2003)
- Minor Use and Minor Species Animal Health Act of 2004[20]
  PL 108-282 (Aug. 2, 2004)
- Dietary Supplement and Nonprescription Drug Consumer Protection Act[21]
  PL 109-462 (Dec. 22, 2006)
- Food and Drug Administration Amendments Act (FDAAA) of 2007[22]
  PL 110-85 (Sept. 27, 2007)
- Family Smoking Prevention and Tobacco Control Act (Public Law 111-31)[23]
  PL 111-31 (June 22, 2009)
- FDA Food Safety Modernization Act[24]
  PL 111-353 (Jan. 4, 2011)

Links on this page:

1. http://thomas.loc.gov/cgi-bin/bdquery/z?d096:HR06940:@@@L|TOM:/bss/d096query.html|#summary
2. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/OrphanDrugAct/default.htm

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3. http://thomas.loc.gov/cgi-bin/bdquery/z?d098:SN01538:@@@D&summ2=m&|TOM:/bss/d098query.html|
4. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/PrescriptionDrugMarketingActof1987/default.htm
5. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm147135.htm
6. http://thomas.loc.gov/cgi-bin/bdquery/z?d101:HR03562:@@@D&summ2=3&|TOM:/bss/d101query.html|
7. http://thomas.loc.gov/cgi-bin/bdquery/z?d101:HR03095:@@@D&summ2=1&|TOM:/bss/d101query.html|
8. http://thomas.loc.gov/cgi-bin/bdquery/z?d102:SN02783:@@@D&summ2=m&|TOM:/bss/d102query.html|
9. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/PrescriptionDrugAmendmentsof1992PrescriptionDrugUserFeeActof1992/default.htm
10. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/AnimalMedicinalDrugUseClarificationActAMDUCAof1994/default.htm
11. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148003.htm
12. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148005.htm
13. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148008.htm
14. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=104_cong_public_laws&docid=f:publ250.104
15. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/default.htm
16. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148011.htm
17. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/MedicalDeviceUserFeeandModernizationActMDUFMAof2002/default.htm
18. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/AnimalDrugUserFeeActof2003/default.htm
19. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ155.108
20. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/MinorUseandMinorSpeciesAnimalHealthActof2004/default.htm
21. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148035.htm
22. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm
23. http://www.gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf
24. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm244718.htm

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NOV 21 2014

Dear Ms. McElheney:

Thank you for your correspondence concerning fluoridation of drinking water. Your letter requests that I take a number of actions related to fluoridation. These include instructing the Food and Drug Administration (FDA) to advise fluoridation manufacturers to submit New Drug Applications; instructing the Centers for Disease Control and Prevention (CDC) to stop "promotion. . . of any and all drugs, including the ingestion of fluoride products, not FDA CDER approved"; sponsoring a review of fluoride's neurotoxicity by the National Research Council; and supporting a prospective randomized control trial of the effectiveness of ingesting hydrofluorosilicic acid.

For nearly 70 years, community water fluoridation (CWF) has been a safe and healthy way to effectively prevent tooth decay. CDC has recognized water fluoridation as one of ten great public health achievements of the 20th century. CDC works with national partners, states, communities, and water operators to ensure that the U.S. population has access to optimally fluoridated water to prevent tooth decay.

However, fluoride ingestion while teeth are developing can result in a range of visually detectable changes in the tooth enamel, called dental fluorosis. The prevalence of mild to moderate dental fluorosis in the United States has increased in recent years. Fluoride in drinking water is one of several available fluoride sources. In 2011, the Department of Health and Human Services (HHS) proposed that the recommended level of fluoride in drinking water be set at 0.7 mg/L. This will reduce the chance for children's teeth to develop dental fluorosis, while still preventing tooth decay. The previous U.S. Public Health Service recommendations for fluoride levels ranged from 0.7mg/L to 1.2 mg/L, depending on average maximum regional air temperature. The new recommendation is based on recent findings that in the U.S., outdoor temperature does not determine water intake.

HHS expects that the final recommendations to reduce the optimal fluoride level will be publicly available soon. CDC, in collaboration with the National Institute of Dental and Craniofacial Research (NIDCR), will monitor the impact of these changes through enhanced surveillance of dental caries (tooth decay) and dental fluorosis in the National Health and Nutrition Examination Survey (NHANES).

Your specific requests are addressed below.

Instruct FDA CDER to no longer defer regulatory action. FDA CDER to send a letter to fluoridation manufacturers advising them to make FDA CDER NDA (New Drug Application) as required by Congress in the US FD&C Act.

FDA has provided the following information regarding your request:

> *FDA has determined that Congress did not intend for FDA to regulate the addition of fluoride to public drinking water for dental caries prevention as a drug under the FD&C Act. Instead, Congress intended that the U.S. Environmental Protection Agency (EPA) regulate fluoride in public drinking water as a potential contaminant under the Safe Drinking Water Act of 1974 (SDWA), Public Law No. 93-523, 88 Stat. 1660 (codified as amended at 42 U.S.C. 300f et seq.) to protect against adverse health effects, and that within the limits thus set by EPA, state and local governments be permitted, but not required, to fluoridate public drinking water to help prevent dental caries. Thus, FDA does not require NDAs for fluoridated public drinking water.*

Instruct the CDC to stop the promotion (internet and education) of any and all drugs, including the ingestion of fluoride products, not FDA CDER approved.

Section 317M of the Public Health Service Act, codified at 42 U.S.C. § 247b-14, authorizes the Secretary of HHS, acting through the Director of the CDC, to make grants to States and Indian tribes for the purpose of increasing the resources available for community water fluoridation. This includes funds to develop educational materials on the benefits of fluoridation. CDC's Division of Oral Health leads an effort to improve the oral health of the nation and reduce inequalities in oral health. This includes encouraging the use of proven strategies to prevent oral disease, such as the effective use of fluoride products and community water fluoridation.

Sponsor a review of the scientific evidence on fluoride's neurotoxicity by the National Academy of Science's National Research Council. The review should include studies listed at www.FluorideAlert.org/issues/health/brain.

The NRC reviewed the toxicity of fluoride as recently as 2006, when it reviewed the Environmental Protection Agency's drinking water standard for fluoride as a contaminant. (See *Fluoride in Drinking Water: A Scientific Review of EPA's Standards.*) More recently and of more relevance to community water fluoridation is the systematic review undertaken by the Community Preventive Services Task Force (Task Force) in 2013. The Task Force is an independent, nonfederal, unpaid panel of public health and prevention experts that provides evidence-based findings and recommendations about community preventive services, programs, and policies to improve health. Its members represent a broad range of research, practice, and policy expertise in community preventive services, public health, health promotion, and disease prevention. In its report, *Preventing Dental Caries: Community Water Fluoridation*, the Task Force noted, "Overall, the body of evidence indicates that Community Water Fluoridation is an effective intervention for reducing caries at the population level. At the optimal fluoride concentration, associated risks are predominantly the milder forms of fluorosis that are only detectable under clinical examination." The report further stated, "In addition, there is no evidence that CWF (Community Water Fluoridation) results in severe dental fluorosis."

Sponsor a quality published independent prospective randomized controlled trial (RTC), of the effectiveness of ingesting hydrofluorosilicic acid (fluoridation), including blood serum and urine concentrations of fluoride.

As stated above, the effectiveness and safety of community water fluoridation was reaffirmed by the Community Preventive Services Task Force in 2013 following a systematic evidence review. Studies on the effectiveness of adjusting fluoride in community water to the optimal concentration cannot be designed as randomized clinical trials. Random allocation of study subjects is not possible when a community begins to fluoridate the water because all residents receiving community water have access to and are exposed to this source of fluoride. Furthermore, clinical studies cannot be conducted double-blind because both study subjects and researchers usually know whether a community's water has been fluoridated. In addition, it would not be possible to find control subjects with no fluoride exposure because fluorides are ubiquitous in the environment.

Although I am not able to fulfill your requests, I appreciate the information you provided to me and my staff. I will keep your concerns in mind as HHS continues to consider community water fluoridation.

A copy of this response is being shared with Dr. Hirzy, Mr. Nidel, Dr. Connett, Ms. Smith, and Dr. Osmunson.

Sincerely,

Wanda K. Jones, DrPH
Principal Deputy Assistant Secretary for Health

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Jill McElheney
Chris Nidel, Nidel Law 1615 New Hampshire Ave., NW, Washington, DC 20009. 202-558-2030
Bill Hirzy PhD Fluoride Action Network
Paul Connett PhD President, Fluoride Action Network
Bill Osmunson DDS, MPH Comprehensive Cosmetic Dentist 425.466.0100
54 Ponder Point, Sandpoint, Idaho 83864 bill@teachingsmiles.com

September 4, 2014

Wanda Jones
Jonathan Beeton
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
Sandra.Howard@HHS.GOV
202-690-7778

For the health and safety of the public:

1. Instruct FDA CDER to no longer defer regulatory action. FDA CDER to send a letter to fluoridation manufacturers advising them to make FDA CDER NDA (New Drug Application) as required by Congress in the US FD&C Act.

a. In 1975, Drug Digest reported FDA CDER (Center for Drug Evaluation and Research) protected the public by withdrawing NDA (New Drug Application) for fluoride supplements (pills). FDA CDER must do the same for artificial fluoridation drug manufacturers. There is no difference in intent or efficacy between fluoride in pills and fluoridated water. But there is a significant difference in freedom of choice, labeling, and oversight.

b. **HHS** would incur no cost to request FDA CDER to take regulatory action.

c. **FDA CDER** would incur no cost to send a letter to artificial fluoridation drug manufacturers requiring them to gain NDA as required by law.

d. **FD&C Act** protects the public by requiring ***manufacturers*** to gain NDA, not the FDA nor patients. The FDA CDER is to evaluate and regulate substances used with the intent to prevent disease or listed in the official US Pharmacopoeia as a drug. Fluoride is used with intent to prevent disease and listed in the USP. The FDA has testified to Congress and the public that fluoride, when used with the intent to prevent disease, is a drug.

e. **CDC and Surgeon General** actively promote fluoridation for the manufacturers but do not determine scientifically the safety or efficacy of fluoridation or any drugs. Cities and water districts rely on the CDC and Surgeon General assuming they are correct.

f. **EPA** is prohibited by Congress from regulating the addition of any substance to water intended to treat humans. Fluoride is a protected pollutant and the EPA assumes efficacy.

g. **Excess exposure:** Of greatest concern is EPA's confirming in their Dose Response Analysis (DRA) that all infants on formula with fluoridated water are at risk. The DRA reports about a third of children under the age of 7 and all infants on formula made with fluoridated water will be ingesting too much fluoride under the proposed RfD (Reference Dose) and HHS proposed 0.7 ppm artificial fluoridation. Infants and children are being harmed. Excess exposure is confirmed with 41% of children now having dental fluorosis a biomarker of excess fluoride ingestion. An NDA would provide a legend, caution, warnings, and dosage, reducing risks.

h. Over 60 requests and petitions have been made to the FDA CDER since 2009 and the requests, petitions, and complaints have been made. These have been ignored, no answer, or pending for years.

2. **Instruct the CDC to stop the promotion (internet and education) of any and all drugs, including the ingestion of fluoride products, not FDA CDER approved.**

3. **Sponsor a review of the scientific evidence on fluoride's neurotoxicity by the National Academy of Science's National Research Council. The review should include studies listed at www.FluorideAlert.org/issues/health/brain**

Of most concern are the more than 30 human studies finding harm to brains. The question is no longer whether fluoridation causes neurological damage and lower IQ, the question is how much fluoride and at what age damage is caused.

Neurological harm is one of the reasons Israel recently banned fluoridation. Most developed countries have rejected fluoridation due to ethics, lack of efficacy and risks.

4. **Sponsor a quality published independent prospective randomized controlled trial (RCT), of the effectiveness of ingesting hydrofluorosilicic acid (fluoridation), including blood serum and urine concentrations of fluoride.**

a. Quality research is essential and in 60 years of fluoridation, not one published prospective randomized controlled trial of fluoridation has been done. Current reviews of the low quality research available are biased, serious unknowns are not controlled and even known confounding factors are often not controlled.

b. The results of a well-designed RCT could allow HHS to tailor public health policy on fluoridation to optimize benefits and minimize costs. This is in line with the goals of "Obamacare": evidence-based public health policy.

c. Most research on fluoridation have numerous problems which include:

- Not one Randomized Controlled Trial
- Socioeconomic status usually not controlled
- Inadequate size
- Difficulty in diagnosing decay
- Delay in tooth eruption
- Diet: Vitamin D, calcium, strontium, sugar, variables.
- Total exposure of Fluoride and measured blood and/or urine fluoride concentration
- Oral hygiene habits
- Not evaluating life time benefit
- Estimating or assuming subject actually drinks the fluoridated water.
- Dental treatment expenses
- Breast feeding and infant formula
- Fraud or gross errors.
- Genetics

Sincerely,

Jill McElheney
Chris Nidel JD
Bill Hirzy PhD
Paul Connett PhD
Bill Osmunson DDS, MPH

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Gerald Steel PE
Attorney at Law
7303 Young Rd. NW
Olympia WA 98502
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December 23, 2013

Ms. Jill Warner,
Acting Assoc. Commissioner
WO32, Room 5162
10903 New Hampshire Ave
Silver Spring, MD 20993

RE: Request for Review pursuant to 21 CFR 10.75 – Kailin System Public Drinking Water with Sodium Fluoride – Your file: RFD130073

Dear Ms. Warner:

On September 27, 2013, Leigh Hayes sent me the FDA determination (Attachments A-1 to A-3 hereto) wherein FDA states that it has determined that "Congress did not intend for FDA to regulate the addition of fluoride to public drinking water for dental caries prevention as a drug under the Federal Food, Drug, and Cosmetic Act (FD&C Act)." As a consequence, FDA has responded to our Request for Designation (RFD130073) by finding that our proposed fluoridated public drinking water is not a drug under the FD&C Act. On December 4, 2013, Leigh Hayes informed me that we can request review under 21 CFR 10.75. We hereby submit a Request for Review under 21 CFR 10.75 of the determinations regarding RFD130073.

The FDA has a long history of protecting the public from unsafe and ineffective drugs. Generally, state and local governments do not have the capability or staff to determine if articles or substances intended for preventative health care purposes are safe and effective. HHS, generally acting through the FDA, is the only regulatory body that has the authority to implement the FD&C Act in interstate commerce and protect the public from such articles and substances that are not safe and effective. So we ask the FDA to review its determination that our proposed "fluoridated public drinking water" is not a drug under the FD&C Act.

I believe that the FDA has accepted our statement of facts as accurate. Sodium Fluoride, as a water additive certified under industrial ANSI/NSF Standard 60 is intended for use in the prevention of tooth decay disease in man. (RFD130073 – our RFD at pages 1 and A-1.) This chemical with this intended use is square within the literal language included in the definition of a drug by Congress in 21 USC 321(g)(1)(B). (RFD130073 – our RFD at page 6.) When this chemical is added to our public drinking water, this chemical retains its intended use (prevention of tooth decay disease in man). The purpose of adding this chemical to our public drinking water is to deliver this chemical in drinking water for its intended use. As we stated, our "fluoridated public drinking water" is "intended for use in the prevention of dental caries (tooth decay) disease in man." (RFD130073 – our RFD at page 1.) With this statement, our "fluoridated public drinking water" is square within the literal language included in the definition of a drug in 21 USC 321(g)(1)(B).

RFD130073 provided a letter signed by EPA Water Law Office Associate General Counsel Steven M. Neugeboren, which was sent to me in 2013 on behalf of the EPA Administrator, and

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which states the EPA official position that, "The Department of Health and Human Services (HHS) acting through the FDA, remains responsible for regulating the addition of drugs to water supplies for health care purposes." (RFD130073 – our RFD at page A-8 to A-9.) In RFD130073, we also cited to the Federal Supreme Court ruling in *United States v. An Article of Drug . . . Bacto-Unidisk* (*Bacto-Unidisk*), 394 U.S. 784, 793-801, 89 S.Ct. 1410, 22 L.Ed.2d 726 (1969) which found that the definition of "drug" in 21 USC 321(g)(1)(B) is "as broad as its literal language indicates." (RFD130073 – our RFD at page 6.) There can be no doubt that under the facts presented, ANSI/NSF Standard 60 certified Sodium Fluoride alone and our proposed fluoridated public drinking water are within the literal plain language of the definition of a drug in 21 USC 321(g)(1)(B). Therefore we continue to assert that such Sodium Fluoride and the proposed fluoridated public drinking water are drugs under federal law and are under the jurisdiction of FDA CDER.

I think we can assume that in 1974 Congress was aware of the definition of "drug" in 21 USC 321(g)(1)(B) and aware of the 1969 federal Supreme Court ruling in *Bacto-Unidisk*. I find no plain language in the 1974 SDWA (as amended) that seeks to carve out an exemption from the plain language of 21 USC 321(g)(1)(B) for fluoride water additives or fluoridated public drinking water when the intended use is for the prevention of dental caries disease in man. The challenged determination incorrectly claims that the "text" of the SDWA includes such [plain] language. It does not. The challenged determination also incorrectly claims support from the legislative history of the SDWA. The legislative history of the SDWA cannot be used by FDA to modify the plain language definition of "drug" in 21 USC 321(g)(1)(B) or modify the *Bacto-Unidisk* Court's interpretation of that drug definition. We request that you reverse the determination made for RFD130073 because the SDWA does not carve out an exemption from the plain language of 21 USC 321(g)(1)(B).

We claim that the intent of Congress is clear in 21 USC 321(g)(1)(B) as interpreted by *Bacto-Unidisk* that under our facts, ANSI/NSF Standard 60 certified Sodium Fluoride alone and our proposed fluoridated public drinking water are drugs under the FD&C Act. To further support our claim, we cited to 21 USC 321ff ("Dietary Supplement Health and Education Act of 1994") that states that minerals [such as fluoride public water additives] are foods except when they meet the definition of a drug. (RFD130073 – our RFD at page 6.) This 1994 statute did not exempt minerals that meet the definition of a "drug" in 21 USC 321(g)(1)(B) from being drugs just because the minerals were being added to public water supplies. This subsequent Congressional enactment supports our claim.

The federal Supreme Court in *FDA v. Brown & Williamson Tobacco Corp.* (*Tobacco Corp.*), 529 U.S. 120, 120 S.Ct. 1291, 146 L.Ed.2d 121 (2000) further supports our claim and refutes the claim in the determination regarding Congressional intent of 21 USC 321(g)(1)(B). The *Tobacco Corp.* Court found that reading the FD&C Act as a whole, as well as in conjunction with Congress' subsequent tobacco-specific legislation, it is plain that Congress has not given the FDA the authority to regulate tobacco products as customarily marketed. (*Tobacco Corp.* at 120 and 131-61.) "As customarily marketed" means "without manufacturer claims of therapeutic benefit." (*Id.* at 120.) But the *Tobacco Corp.* Court found that while the FDA did not generally have authority to regulate tobacco under the FD&C Act, there was a "well-established exception of when the manufacturer makes express claims of therapeutic benefit." (*Id.* at 158.) Therapeutic benefit refers to uses identified in 21 USC 321(g)(1)(B). We are making an express claim of therapeutic benefit for our proposed fluoridated public drinking water.

In the instant case, Congress has not shown that it has created a distinct regulatory scheme addressing the subject of purposely adding fluoride to public drinking water. But even if it did

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have such a distinct regulatory scheme, FDA still has authority and responsibility under the FD&C Act to regulate fluoride added to public drinking water when it is added for the "therapeutic benefit" of preventing tooth decay disease. Similarly, FDA has authority and responsibility under the FD&C Act to regulate our fluoridated public drinking water because our water is fluoridated with the intent to prevent tooth decay disease. The FDA can point to no relevant federal caselaw where products that are intended for use in the prevention of disease in man are not regulated by the FD&C Act independent of other Congressional enactments.

Therefore under 21 CFR 10.75(a)(3) and 21 CFR 10.75(c)(1) and (2) along with 21 CFR 10.75(d) we request review and if it is concluded that our proposed ANSI/NSF Standard 60 fluoride water additives and our proposed fluoridated public drinking water are drugs, we again request that you designate our proposed fluoridated public drinking as a drug regulated by CDER.

Respectfully submitted,

Gerald Steel, PE, Attorney at Law
geraldsteel@yahoo.com

Attachments: A-1 to A-3

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Office of Combination Products
WO 32, Room 5129
10903 New Hampshire Avenue
Silver Spring, MD 20993

September 27, 2013

Eloise Kailin
Owner and Manager
Gerald Steel
Attorney
Kailin Public Water System
160 Kane Lane
Sequim, WA 98382

Re: Request for Designation
Kailin Public Drinking Water System with Sodium Fluoride
Our file: RFD130073
Dated: July 22, 2013
Received: July 23, 2013
Filed: July 29, 2013

Dear Dr. Kailin and Mr. Steel:

The United States (U.S.) Food and Drug Administration (FDA) has completed its review of the request for designation (RFD) for the Kailin Public Drinking Water System with Sodium Fluoride that you submitted on behalf of Kailin Public Water System. We have determined that Congress did not intend for FDA to regulate the addition of fluoride to public drinking water for dental caries prevention as a drug under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Instead, Congress intended that the U.S. Environmental Protection Agency (EPA) regulate fluoride in public drinking water as a potential contaminant under the Safe Drinking Water Act of 1974 (SDWA) to protect against adverse health effects, and that within the limits thus set by EPA, state and local governments be permitted, but not required, to fluoridate drinking water to help prevent dental caries. Thus, we are not designating your fluoridated public drinking water as a drug under the FD&C Act.

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Description

In your RFD, you seek designation of your specific public fluoridated drinking water as a drug under the FD&C Act. You assert that you will submit a New Drug Application (NDA) for your fluoridated public drinking water that "will be composed of our public drinking water with an added fluoridation product certified to meet ANSI/NSF Standard 60...: Sodium Fluoride with a maximum addition of 2.3 mg/L....The public drinking water system is registered with the Washington State Department of Health as PWS ID# AC982. It is a neighborhood system with multiple approved connections. The source water comes from a well as is typical for public water systems in Washington State and currently there is a transmission pipeline from the well to a tank that maintains water pressure for the system in an acceptable range. A distribution system which starts at the tank serves all of the individual residential and commercial connections. There are pressure zones in the distribution system where pressure reducers are used to lower water pressure for connections at lower elevations. All individual connections to the distribution system are made in a manner approved by the Washington State Department of Health."

The RFD explains that "...the transmission line will be rerouted to a small fluoridation building where fluoridation will occur and the fluoridated water will be transmitted to the tank that maintains water pressure. This public water system is required to meet standard specifications for public water systems in Washington State as established by the Washington State Board of Health." The RFD states that the addition of the fluoridation materials "...will be metered into flowing water in a manner to maintain the specified chemical concentration rates. The Sodium Fluoride will be injected using an up-draft fluoride saturator. The injection rate into the transmission line in the control house will be controlled using a 4 to 20 milliamperes signal from the main water meter so that finished fluoridation levels are close to 0.7 mg/L. Fluoride levels will be manually checked twice daily." Finally, with regard to packaging of the product, the RFD asserts that "[t]his system does not have conventional packaging. [The company proposes] that [it] will negotiate with CDER regarding adequate labeling. For example, [the company] will propose that drug facts and warning approved by CDER will be sent out with each billing for each connection."

You recommend that your fluoridated public drinking water designed to aid in the prevention and prophylactic treatment of dental caries disease be classified as a drug and that it be assigned to FDA's Center for Drug Evaluation and Research (CDER) for premarket review and regulation.

Product Classification

We have considered the information in the RFD and discussed the issues with staff from CDER, the Center for Food Safety and Applied Nutrition, the Department of Health and Human Services, HHS's Office of the General Counsel, and the EPA.

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After careful consideration, we conclude that Congress did not intend for FDA to regulate the addition of fluoride to public drinking water for dental caries prevention as a drug under the FD&C Act. Instead, Congress intended that EPA regulate fluoride in public drinking water as a potential contaminant under the SDWA to protect against adverse health effects, and that within the limits thus set by EPA, state and local governments be permitted, but not required, to fluoridate public drinking water to help prevent dental caries. The SDWA gives EPA certain authorities with respect to the regulation of public drinking water, including the authority to promulgate national primary drinking water regulations that set maximum contaminant levels (MCLs) for contaminants that EPA determines may have an adverse effect on human health. Pursuant to its authority under the SDWA, EPA has codified a primary MCL for fluoride at 40 CFR § 141.62(b)(1) and a secondary MCL for fluoride at 40 CFR § 143.3.

The historical context surrounding the passage of the SDWA indicates that Congress was aware in 1974 that many localities were adding fluoride to public drinking water to help prevent dental caries. They were also aware that FDA had a codified policy of not regulating such fluoride as a drug, so long as the levels were within certain recommended limits. Based on the text and legislative history of the SDWA, we have concluded that Congress did not intend for FDA to regulate fluoride in public drinking water for the purpose of helping to prevent dental caries as a drug under the FD&C Act. Instead, Congress set up a regime under which EPA would set upper limits for fluoride to protect against adverse health effects, and EPA would not have the authority to mandate or ban the use of fluoride to help prevent dental caries. The decision of whether or not to add fluoride to public drinking water to help prevent dental caries (within the limits set by EPA) was left to state and local authorities, as it had been before 1974. Since the passage of the SDWA, this division of federal and state/local oversight has continued.

Conclusion

For the reasons explained above, we have determined that Congress did not intend for FDA to regulate fluoride in public drinking water to help prevent dental caries as a drug under the FD&C Act, and we therefore are not designating your fluoridated public drinking water as a drug.

If you have any other questions about this letter, please feel free to contact me. You may reach us at the above address or by email at combination@fda.gov.

Sincerely,

Leigh Hayes

Leigh Hayes
Product Assignment Officer

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
GENERAL COUNSEL

February 14, 2013

Gerald Steel, PE
7303 Young Road NW
Olympia, WA 98502

Dear Mr. Steel:

This is in response to your letter of December 28, 2012 to EPA Administrator Lisa Jackson in which you asked several questions about the status of an MOU between EPA and the Federal Drug Administration (FDA) published in 1979. I am replying on behalf of her.

Your first question is whether, from the viewpoint of EPA, the purpose of a 1979 Memorandum of Understanding (MOU) between EPA and the Federal Drug Administration (FDA) was "to take away from FDA, and give to EPA, responsibility for regulating public drinking water additives intended for preventative health care purposes and unrelated to contamination of public drinking water?" Your second question is whether, if that was the purpose of the 1979 MOU, the MOU was terminated through a subsequent Federal Register notice.

The answer to your first question is no, so there is no need to address your second question. The purpose of the MOU was not to shift any responsibilities between the Agencies. Rather, it was to help facilitate effective coordination of our respective legal authorities. Under the Safe Drinking Water Act (SDWA), EPA is the lead federal agency with responsibility to regulate the safety of public water supplies. EPA does not have responsibility for substances added to water solely for preventative health care purposes, such as fluoride, other than to limit the addition of such substances to protect public health or to prevent such substances from interfering with the effectiveness of any required treatment techniques. SDWA Section 1412(b)(11); see also A Legislative History of the Safe Drinking Water Act, Committee Print, 97th Cong, 2d Session (February 1982) at 547. The Department of Health and Human Services (HHS), acting through the FDA, remains responsible for regulating the addition of drugs to water supplies for health care purposes.

The 1979 MOU was intended to address contamination of drinking water supplies as a result of direct or indirect additives to drinking water, not to address the addition of substances solely for preventative health purposes. 44 Fed. Reg. 42775 (July 20, 1979) ("EPA and FDA agree: (1) that *contamination* of drinking water from the use and application of direct and indirect additives and other substances poses a potential public health problem...")(emphasis added). It was intended to avoid potentially duplicative regulation of "food", which FDA had, in the past, considered to include drinking water. 44 Fed. Reg. 42775 (July 20, 1979). The MOU did not address drugs or other substances added to water for health care purposes.

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I hope that this has adequately answered your inquiry. Please do not hesitate to contact Carrie Wehling of my staff (202-564-5492) if you have further questions about this.

Sincerely,

Steven M. Neugeboren
Associate General Counsel
Water Law Office

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 10
1200 Sixth Avenue, Suite 900
Seattle, WA 98101-3140

OFFICE OF
WATER AND
WATERSHEDS

NOV 17 2011

Mr. Gerald Steel, PE
Attorney-at-Law
7303 Young Road NW
Olympia, Washington 98502

Dear Mr. Steel:

I am responding to your letter dated November 7, 2011, on behalf of Dennis J. McLerran, Regional Administrator, U S. Environmental Protection Agency (EPA). In your communication you have asked the EPA to send you a letter that answers the question "Are [Washington Administrative Code] WAC 246-290-220(3) and 246-290-460 part of implementation of requirements of the Federal Safe Drinking Water Act in Washington State, or are they unrelated to the requirements of the Federal Safe Drinking Water Act in Washington State?"

A concise answer to your question is that the provisions at WAC 246-290-220(3) and 246-290-460 are not related to the requirements of the Federal Safe Drinking Water Act in Washington State. An explanation as to why this is the case follows.

The requirements for a State drinking water primacy program are spelled out in Section 1413 of the Federal Safe Drinking Water Act (SDWA) (42 U.S.C. § 300g-2). Section 1413(a) specifies that a State has primary enforcement responsibility (primacy) for public water systems during any period for which the EPA Administrator determines that such State:

(1) has adopted drinking water regulations that are no less stringent than the national primary drinking water regulations i.e., the regulations promulgated at 40 CFR Part 141 (see http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?tpl=/ecfrbrowse/Title40/40tab_02.tpl);

(2) has adopted and is implementing adequate procedures for the enforcement of such State regulations as the Administrator may require by regulation;

(3) will keep such records and make such reports with respect to its activities as the Administrator may require by regulation;

(4) if it permits variances and/or exemptions from the requirements of its drinking water regulations, permits such variances and exemptions under conditions and in a manner which is not less stringent than the conditions under, and the manner in which variances and exemptions may be granted under SDWA sections 1415 and 1416;

(5) has adopted and can implement an adequate plan for the provision of safe drinking water under emergency circumstances; and

(6) has adopted authority for administrative penalties, unless the constitution of the State prohibits the adoption of such authority.

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The EPA's role in SDWA section 1413(b) requires the Administrator to promulgate regulations that establish how the States may apply for primacy, how the Administrator will make primacy determinations and the manner in which the Administrator may determine that the primacy agency is no longer meeting the primacy requirements. These primacy implementing regulations can be found at 40 CFR 142.10 – 40 CFR 142.12. (See enclosure and/or website provided above.) 40 CFR Part 142.10 describes the requirements of a State primacy program. 40 CFR Part 142.11 describes the documents a State must submit to the EPA for an initial determination of primacy. 40 CFR 142.12 describes the contents of a State request for approval of a State's revised primacy program. This must take place whenever the EPA adopts a new or revised drinking water rule. As per 40 CFR 142.12(c) a State must submit for EPA approval a copy of their regulations and a document we refer to as a crosswalk. The crosswalk is a side-by-side comparison of the new or revised Federal requirements in 40 CFR Parts 141 and 142 and the corresponding State authorities, including citations to the specific statutes and administrative regulations (see enclosed example of a crosswalk page). EPA will only make a determination that a State's revised drinking water primacy program can be approved if the State's regulations are as stringent as the Federal regulations and the State continues to maintain all required authorities as per SDWA Section 1413.

WAC 246-290-220(3) requires treatment chemicals with the exception of commercially retailed hypochlorite compounds added to water intended for potable use to comply with ANSI/NSF Standard 60 and also specifies that the maximum application dosage recommendation for the product certified by the ANSI/NSF Standard 60 shall not be exceeded in practice. The Department of Health (DOH), which is the State of Washington's drinking water primacy agency has never submitted WAC 246-290-220(3) to the EPA for approval as there is no analogous provision in the National Primary Drinking Water Regulations at 40 CFR Part 141, and neither the other statutory provisions mentioned above, nor the primacy implementing provisions at 40 CFR Part 142 require that language, such as is found in WAC 246-290-220(3), be part of a State primacy program.

WAC 246-290-460 addresses fluoridation practices, should a community choose to provide fluoridation. DOH has never submitted WAC 246-290-460 to the EPA for approval as there are no analogous provisions in the National Primary Drinking Water Regulations at 40 CFR Part 141, and neither the other statutory provisions mentioned above, nor the primacy implementing provisions at 40 CFR Part 142 require that a State primacy program regulate fluoridation practices.

For the reasons stated in the above paragraphs, I can assert that that the provisions at WAC 246-290-220(3) and 246-290-460 were not required to be submitted by the State or approved by the EPA and these provisions are not related to the requirements of the Federal Safe Drinking Water Act.

I hope this response answers your questions satisfactorily. If you have additional questions, please contact Marie Jennings, our Manager for the Drinking Water Unit at (260) 553-1893.

Sincerely,

Michael A. Bussell, Director
Office of Water & Watersheds

Enclosures

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February 2008

NSF Fact Sheet on Fluoridation Chemicals

Introduction

This fact sheet provides information on the fluoride containing water treatment additives that NSF has tested and certified to NSF/ANSI Standard 60: Drinking Water Chemicals - Health Effects. According to the latest Association of State Drinking Water Administrators Survey on State Adoption of NSF/ANSI Standards 60 and 61, 45 states require that chemicals used in treating potable water must meet Standard 60 requirements. If you have questions on your state's requirements, or how the NSF/ANSI Standard 60 certified products are used in your state, you should contact your state's Drinking Water Administrator.

Water fluoridation is the practice of adjusting the fluoride content of drinking water. Fluoride is added to water for the public health benefit of preventing and reducing tooth decay and improving the health of the community. The U.S. Centers for Disease Control and Prevention is a reliable source of information on this important public health intervention. For more information please visit www.cdc.gov/fluoridation/.

NSF certifies three basic products in the fluoridation category:

1. Fluorosilicic Acid (aka Fluosilicic Acid or Hydrofluosilicic Acid).
2. Sodium Fluorosilicate (aka Sodium Silicofluoride).
3. Sodium Fluoride.

NSF Standard 60

Products used for drinking water treatment are evaluated to the criteria specified in NSF/ANSI Standard 60. This standard was developed by an NSF-led consortium, including the American Water Works Association (AWWA), the American Water Works Association Research Foundation (AWWARF), the Association of State Drinking Water Administrators (ASDWA), and the Conference of State Health and Environmental Managers (COSHEM). This group developed NSF/ANSI Standard 60, at the request of the US EPA Office of Water, in 1988. The NSF Joint Committee on Drinking Water Additives continues to review and maintain the standard annually. This committee consists of representatives from the original stakeholder groups as well as other regulatory, water utility and product manufacturer representatives.

Standard 60 was developed to establish minimum requirements for the control of potential adverse human health effects from products added directly to water during its treatment, storage and distribution. The standard requires a full formulation disclosure of each chemical ingredient in a product. It also requires a toxicology review to determine that the product is safe at its maximum use level and to evaluate potential contaminants in the product. The standard requires testing of the treatment chemical products, typically by dosing these in water at 10 times the maximum use level, so that trace levels of contaminants can be detected. A toxicology evaluation of test results is required to determine if any contaminant concentrations have the potential to cause adverse human health effects. The standard sets criteria for the establishment of single product allowable concentrations (SPAC) of each respective contaminant. For contaminants regulated by the U.S. EPA, this SPAC has a default level not to exceed ten-percent of the regulatory level to provide protection for the consumer in the unlikely event of multiple sources of the contaminant, unless a lower or higher number of sources can be specifically identified.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Office of Combination Products
WO 32, Room 5129
10903 New Hampshire Avenue
Silver Spring, MD 20993

September 23, 2015

Mr. Gerald Steel, PE
Attorney-At-Law
7303 Young Road, NW
Olympia, WA 98502

Re: "Submittal of Three Requests for Designation
for Libera Bottled Fluoridated Water each using a Different Fluoridation Chemical"
Dated: September 2, 2015
Received: September 2, 2015

Dear Mr. Steel:

For the reasons discussed below, we disagree that our previous legal reasoning is, as you indicate below, "no longer valid." As we have previously communicated to you, and as stated in the preamble to 21 CFR Part 3, Part 3 "does not apply to foods, veterinary products, or cosmetics" (56 FR 58754), and jurisdictional questions concerning a product that may be within the jurisdiction of the Center for Food Safety and Applied Nutrition (CFSAN) are outside the scope of 21 CFR part 3 and section 563 of the FD&C Act. In contrast to your characterization, the Center for Food Safety and Applied Nutrition's (CFSAN's) recent communication to you (Letter from F. Billingslea dated August 7, 2015, attached) does not state that your proposed bottled water product with the claim discussed below ("this drinking water is intended for use in the prevention of tooth decay disease") is "not a food under their [CFSAN's] jurisdiction." Instead, Ms. Billingslea stated that this proposed labeling statement "is not an authorized claim on food labeling under Section 403(r) of the Act." Ms. Billingslea further recommended that you contact Ms. Barbara Gould in FDA's Center for Drug Evaluation and Research (CDER) if you wished to market a bottled water product with this claim.

Ms. Billingslea recommended contacting CDER because you propose to market your product with a therapeutic claim. Your proposed claim would establish that your product is intended to prevent disease. Therefore, your proposed product (if marketed with your proposed claim) would be a drug as that term is defined in section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

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However, the fact that your proposed product (if marketed with your proposed claim) would be a drug under the Act does not mean that your product is not also a food. To the contrary, the definitions of "food" and "drug" under the Act are not mutually exclusive. *See, e.g., Nutrilab v. Schweiker*, 713 F.2d 335, 336 (7th Cir. 1983). It is commonplace for FDA to take regulatory action with respect to food products that are promoted for conditions that cause the products to be drugs as well as foods.

Accordingly, we believe that our previous legal reasoning continues to apply, and your most recent requests fall outside the scope of the regulation and statutory provisions that authorize requests for designation. As a result, we are not treating your submissions regarding fluoridated bottled water as requests for designation. Instead, we are treating them as informal inquiries.

We hope it is helpful for you to know that your proposed product (if marketed with your proposed claim) would be both a food and a drug under the Act. We note that if you were to remove your proposed claim ("This drinking water is intended for use in the prevention of tooth decay disease"), your product would not be a drug under the Act unless there was other evidence to establish its status as a drug. As Ms. Billingslea discussed in her letter of August 7, your other proposed claim – "fluoride added" – would not render your product a drug. You can also reference Ms. Billingslea's letter for information about a health claim that may be used on certain bottled water products.

As Ms. Billingslea stated in her letter of August 7, we recommend that you contact Ms. Barbara Gould in CDER if you wish to market your bottled water product with your proposed claim about the prevention of tooth decay.

Patricia A. Hansen, Ph.D.

Acting Director
Office of Nutrition, Labeling and Dietary Supplements
CFSAN
FDA

Leigh Hayes

Leigh Hayes

Product Assignment Officer
Office of Combination Products
FDA

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Risk Analysis, Vol. 00, No. 0, 2021 DOI: 10.1111/risa.13767

A Benchmark Dose Analysis for Maternal Pregnancy Urine-Fluoride and IQ in Children

Philippe Grandjean,[1,2,*] Howard Hu,[3] Christine Till,[4] Rivka Green,[4] Morteza Bashash,[3] David Flora,[4] Martha Maria Tellez-Rojo,[5] Peter X.K. Song,[6] Bruce Lanphear,[7] and Esben Budtz-Jørgensen[8]

As a guide to establishing a safe exposure level for fluoride exposure in pregnancy, we applied benchmark dose modeling to data from two prospective birth cohort studies. We included mother–child pairs from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) cohort in Mexico and the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort in Canada. Maternal urinary fluoride concentrations (U-F, in mg/L, creatinine-adjusted) were measured in urine samples obtained during pregnancy. Children were assessed for intelligence quotient (IQ) at age 4 ($n = 211$) and between six and 12 years ($n = 287$) in the ELEMENT cohort, and three to four years ($n = 407$) in the MIREC cohort. We calculated covariate-adjusted regression coefficients and their standard errors to assess the association of maternal U-F concentrations with children's IQ measures. Assuming a benchmark response of 1 IQ point, we derived benchmark concentrations (BMCs) and benchmark concentration levels (BMCLs). No deviation from linearity was detected in the dose–response relationships, but boys showed lower BMC values than girls. Using a linear slope for the joint cohort data, the BMC for maternal U-F associated with a 1-point decrease in IQ scores was 0.31 mg/L (BMCL, 0.19 mg/L) for the youngest boys and girls in the two cohorts, and 0.33 mg/L (BMCL, 0.20 mg/L) for the MIREC cohort and the older ELEMENT children. Thus, the joint data show a BMCL in terms of the adjusted U-F concentrations in the pregnant women of approximately 0.2 mg/L. These results can be used to guide decisions on preventing excess fluoride exposure in pregnant women.

KEY WORDS: Benchmark dose; cognitive deficits; fluoride; neurotoxicity; pregnancy; prenatal exposure

1. INTRODUCTION

The Environmental Protection Agency's maximum contaminant level goal (MCLG) of 4.0 mg/L for fluoride in drinking water was first set in 1985 to protect against chronic fluoride toxicity in the

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[4]Faculty of Health, York University, Ontario, Canada.
[5]Centro de Investigacion en Salud Poblacional, Instituto Nacional de Salud Publica, Cuernavaca, Morelos, Mexico.
[6]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA.
[7]Faculty of Health Sciences, Simon Fraser University, British Columbia, Canada.
[8]Department of Biostatistics, University of Copenhagen, Denmark.
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form of crippling skeletal fluorosis (U.S. Environmental Protection Agency, 1985). In 2006, the U.S. National Research Council (NRC) concluded that fluoride may adversely affect the brain (National Research Council, 2006). Since then, a substantial number of cross-sectional studies, mostly in communities with chronic fluoride exposure, have shown lower cognitive performance in children growing up in areas with higher fluoride concentrations in drinking water, as summarized in meta-analyses (Choi et al., 2015; Duan, Jiao, Chen, & Wang, 2018; Tang, Du, Ma, Jiang, & Zhou, 2008). Support for fluoride neurotoxicity has also emerged from experimental studies (Bartos et al., 2018; Mullenix, Denbesten, Schunior, & Kernan, 1995; National Toxicology Program, 2020). Despite the existence of recent prospective birth cohort studies (Bashash et al., 2017; Green et al., 2019; Valdez Jimenez et al., 2017), no meta-analysis has so far focused on prenatal fluoride exposure.

Fluoride is found in many minerals, in soil and thus also in groundwater (National Research Council, 2006). Since the mid 1940s, fluoride has been added to many drinking water supplies in order to prevent tooth decay (U.S. Environmental Protection Agency, 1985). Community water fluoridation is practiced in the United States, Canada, and several other countries, whereas some, like Mexico, add fluoride to table salt. Fluoridated water accounts for about 40–70% of daily fluoride intake in adolescents and adults living in these communities (U.S. Environmental Protection Agency, 2010). The fluoride concentration in drinking water roughly equals the fluoride concentration in urine (National Research Council, 2006), as also recently shown in the Canadian cohort of pregnant women (Till et al., 2018). In addition to fluoridation, some types of tea, such as black tea, constitute an additional source of exposure (Krishnankutty et al., 2021; Rodríguez et al., 2020; Waugh, Godfrey, Limeback, & Potter, 2017).

Fluoride is readily distributed throughout the body, with bones and teeth as storage depots. During pregnancy, fluoride crosses the placenta and reaches the fetus (National Research Council, 2006; World Health Organization, 2006). As fluoride is rapidly eliminated via urine, the adjusted urine-fluoride (U-F) concentration mainly represents recent absorption (Ekstrand & Ehrnebo, 1983; World Health Organization, 2006). Pregnant women may show lower U-F concentrations than nonpregnant controls, perhaps due to fetal uptake and storage in hard tissues (Opydo-Symaczek & Borysewicz-Lewicka, 2005).

For the purpose of identifying safe exposure levels, regulatory agencies routinely use benchmark dose (BMD) calculations (European Food Safety Authority, 2009; U.S. Environmental Protection Agency, 2012). As long recognized (National Research Council, 1989), fluoride is not an essential nutrient, and dose-dependent toxicity can therefore be considered monotonic. As with lead (Budtz-Jørgensen, Bellinger, Lanphear, & Grandjean, 2013), BMD results can be generated from regression coefficients and their standard errors for the association between maternal U-F concentrations and the child's intelligence quotient IQ score (Grandjean, 2019). The BMD is the dose leading to a specific change (denoted BMR) in the response (in this case, an IQ loss), compared with unexposed children. A decrease of 1 IQ point is an appropriate BMR, as specified by the European Food Safety Authority and also recognized by the U.S. EPA (Budtz-Jørgensen et al., 2013; European Food Safety Authority, 2010; Gould, 2009; Reuben et al., 2017). The present study uses data from two prospective birth cohort studies (Bashash et al., 2017; Green et al., 2019) to calculate the benchmark concentration (BMCs) of U-F associated with a 1-point decrement in Full Scale IQ (FSIQ).

2. METHODOLOGY

2.1. Study Cohorts

In the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project, mother–child pairs were successively enrolled in longitudinal birth cohort studies from the same three hospitals in Mexico City which serve low to moderate income populations. A full description of the cohorts and associated methods is provided in a recent "Cohort Profile" article (Perng et al., 2019). Urinary samples were collected from pregnant women between 1997 and 1999 (Cohort 2A, n = 327) and between 2001 and 2003 (Cohort 3 with calcium intervention and placebo arms, $n = 670$). Cohort 2A was designed as an observational birth cohort of lead toxicodynamics during pregnancy, while Cohort 3 was designed as a randomized double-blind placebo-controlled trial of calcium supplements. Women were included in the current study if they had at least one biobanked urine sample for fluoride analysis, a urinary creatinine

concentration, complete data of adjusted covariates, and their child underwent cognitive testing at age four years ($n = 287$) and/or between ages 6 and 12 years ($n = 211$). Of the 287 participants with data on general cognitive index (GCI) outcomes and other variables, 110 were from Cohort 2A, 93 were from the Cohort 3 calcium intervention arm, and 84 were from the Cohort 3 placebo arm. Among participant in the GCI outcome, U-F data were available for all three trimesters ($n = 25$), two trimesters ($n = 121$), or one trimester ($n = 141$). Of the 211 participants with data on IQ outcomes, 78 were recruited from Cohort 2A, 75 from the Cohort 3 calcium intervention arm, and 58 from the placebo arm; U-F data for IQ outcome were available for all three trimesters ($n = 10$), two trimesters ($n = 82$), or one trimester ($n = 119$).

In the Maternal–Infant Research on Environmental Chemicals (MIREC) program, 2,001 pregnant women were recruited between 2008 and 2011 from 10 cities across Canada. Women were recruited from prenatal clinics if they were at least 18 years old, less than 14 weeks of gestation, and spoke English or French. Exclusion criteria included fetal abnormalities, medical complications, and illicit drug use during pregnancy; further details have been previously described (Arbuckle et al., 2013). A subset of children ($n = 601$) in the MIREC Study was evaluated for the developmental phase of the study (MIREC-Child Development Plus) at three–four years of age from six of the 10 cities included in the original cohort, half of which were fluoridated. Of the 601 children who completed the neurodevelopmental testing in entirety, 526 (87.5%) mother–child pairs had all three U-F samples; of these, 512 (85.2%) had specific gravity measures, while 407 (67.7%) had creatinine data, as well as complete covariate data; 75 (12.5%) women were missing one or more trimester U-F samples, and 14 women (2.3%) were missing one or more covariates.

2.2. Exposure Assessment

All urine samples from the two studies were analyzed by the same laboratory at the Indiana University School of Dentistry using a modification of the hexamethyldisiloxane (Sigma Chemical Co., USA) microdiffusion method with the ion-selective electrode (Martinez-Mier et al., 2011).

In the ELEMENT study, spot (second morning void) urine samples were collected during the first trimester ($M \pm SD$: 13.7 ± 3.5 weeks for Cohort 2A and 13.6 ± 2.1 weeks for Cohort 3), second trimester (24.4 ± 2.9 weeks for Cohort 2A and 25.1 ± 2.3 weeks for Cohort 3), and third trimester (35.0 ± 1.8 weeks for Cohort 2A and 33.9 ± 2.2 weeks for Cohort 3). The samples were collected into fluoride-free containers and immediately frozen at the field site and shipped and stored at −20 °C at the Harvard School of Public Health, and then at −80 °C at the University of Michigan School of Public Health. To account for variations in urinary dilution at time of measurement, the maternal U-F concentration was adjusted for urinary creatinine, as previously described (Thomas et al., 2016). An average of all available creatinine-adjusted U-F concentrations during pregnancy (up to a maximum of three samples) was computed and used as the exposure parameter.

In the MIREC study, urine spot samples were collected at each trimester, that is, first trimester at 11.6 ± 1.6 ($M \pm SD$) weeks of gestation, second trimester at 19.1 ± 2.4 weeks, and third trimester at 33.1 ± 1.5 weeks. Maternal U-F concentrations at each trimester were adjusted for both creatinine and specific gravity, as described previously (Till et al., 2020). For this joint analysis, however, we elected to use the U-F concentrations adjusted for creatinine to keep the urine dilution factor consistent with the adjustment procedure in ELEMENT. For each woman, the average maternal U-F concentration was derived only if a valid U-F value was available for each trimester.

2.3. Assessment of Intelligence

The ELEMENT study (Bashash et al., 2017) used the McCarthy Scales of Children's Abilities (MSCA) Spanish version to measure cognitive abilities at age four years and derive a GCI as a standardized composite score. The MSCA was administered by trained psychometrists or psychologists who were supervised by an experienced clinical child psychologist. For children aged six–12 years, a Spanish-version of the Wechsler Abbreviated Scale of Intelligence (WASI) was administered to derive FSIQ as a measure of global intellectual functioning. In the MIREC study, children's intellectual abilities (Green et al., 2019) were assessed at age three–four years using the FSIQ from the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). A trained research assistant who was supervised by a psychologist administered the WPPSI-III in either English or French. In both studies, examiners were blinded to the children's fluoride exposure. All raw scores were standardized for age.

The GCI shows concurrent validity with intelligence tests, including the Stanford–Binet IQ ($r = 0.81$) and FSIQ ($r = 0.71$) from the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (Kaplan & Sacuzzo, 2010). Similarly, the FSIQ of the WASI (ELEMENT cohort) and WISC-III (MIREC cohort) is strong ($r = 0.81$) (Wechsler, 1991). The high covariance between the various measures of intellectual ability provides justification for pooling IQ scores across the two cohorts.

2.4. Covariate Adjustment

For the ELEMENT study, data were collected from each subject by questionnaire on relevant parameters, gestational age was estimated by registered nurses, and maternal IQ was estimated using subtests of the Wechsler scale standardized for Mexican adults. Covariates included gestational age (weeks), birth weight, sex, age at outcome measurement, and the following maternal characteristics: parity (being first child), smoking history (ever smoked vs. nonsmoker), marital status (married vs. other), age at delivery, IQ, education (years of education), and subcohort (Cohort 2A, Cohort 3 calcium intervention or placebo).

The MIREC study selected similar covariates from a set of established predictors of fluoride metabolism and cognitive development, including sex, city of residence, HOME score, maternal education (dichotomized as bachelor's degree or higher: yes/no), and maternal race/ethnicity (dichotomized as white: yes/no). Covariates included in the original studies (Bashash et al., 2017; Green et al., 2019) were retained in the statistical calculations in the present study. Due to a growing body of epidemiologic studies showing sex-specific effects associated with neurotoxic exposures (Levin, Dow-Edwards, & Patisaul, 2021), including fluoride (Green et al., 2019; Green, Rubenstein, Popoli, Capulong, & Till, 2020), interactions between sex and U-F exposure were examined.

2.5. Benchmark Concentration Calculations

The BMC is the U-F concentration that reduces the outcome by a prespecified level (known as the benchmark response, BMR) compared to an unexposed control with the same covariate profile (Budtz-Jørgensen, Keiding, & Grandjean, 2001; Crump, 1995). We based the benchmark calculations on regression models with p covariates in the following form:

$$\mathrm{IQ} = \alpha_0 + \alpha_1 \times \mathrm{covariate}_1 + \cdots + \alpha_\mathrm{p} \times \mathrm{covariate}_\mathrm{p} + f(c) + \varepsilon$$

where c is the urine-fluoride concentration and f is the concentration–response function, and ε is a normally distributed error term with a mean of 0 (and a variance of σ^2). To assess the linearity of the concentration-response relationship, several models were considered. In addition to the standard linear model, where $f(c) = \beta \mathrm{c}$, we estimated a squared effect, where $f(c) = \beta \mathrm{c}^2$, and two piecewise-linear models (or broken-stick) with breakpoints at 0.5 and 0.75 mg/L. Piecewise-linear models are useful in benchmark calculations because the slope of the concentration-response function is allowed to change linearity at the breakpoint, and in such models, benchmark calculations are less sensitive to exposure-associated effects occurring only at high concentration levels. Furthermore, to allow for the possibility of different exposure effects in boys and girls, each concentration-response model was also fitted with the inclusion of an interaction with sex.

Models were fitted separately in the two cohorts yielding analyses that were similar to those presented in the original publications (Bashash et al., 2017; Green et al., 2019) based on the original raw data and with the covariate adjustments as originally justified. Sensitivity analyses were carried out using the MIREC specific gravity-adjusted U-F values joint with the ELEMENT creatinine-adjusted U-F values as well. The Mexico study controlled for maternal bone lead stores (the primary source of prenatal lead exposure in this cohort) and blood-mercury during pregnancy, although the sample size was reduced by about one-third; the effect estimates for fluoride on child IQ increased and remained statistically significant ($p < 0.01$) (Bashash et al., 2017). Similarly, controlling for lead, mercury, perfluorinated compound, arsenic, and manganese in the MIREC study did not result in any appreciable change of the U-F estimates (Green et al., 2019). Thus, these other neurotoxicants were not included as covariates in the present calculations. Using the regression coefficients, we first calculated BMC results for each cohort and then derived joint BMCs by combining regression coefficients from the two cohorts.

Given that the BMC reduces the outcome by the BMR, a smaller BMR will result in lower BMC and benchmark concentration level (BMCL) results. For the child IQ as the outcome variable, the BMR is

1 IQ point. In our regression model, the IQ difference between unexposed subjects and subjects at the BMC is given by $f(0) - f(\text{BMC})$, and therefore the BMC satisfies the equation $f(0) - f(\text{BMC}) = \text{BMR}$. We use concentration-response functions with $f(0) = 0$, and therefore the BMC is given by

$$\text{BMC} = f^{-1}(-\text{BMR})$$

In a regression model with a linear concentration-response function [$f(c) = \beta c$], we get $\text{BMC} = -\text{BMR}/\beta$. If the estimated concentration–response is increasing (indicating a beneficial effect), the BMC is not defined, and the BMC is then indicated by ∞.

The main result of the BMC analysis is the BMCL, which is defined as a lower one-sided 95% confidence limit of the BMC (Crump, 1995). In the linear model,

$$\text{BMCL} = -\text{BMR}/\beta_{\text{lower}}$$

where β_{lower} is the one-sided lower 95% confidence limit for β (Budtz-Jørgensen et al., 2013). In the other models considered, we calculated the BMCL by first identifying a lower confidence limit for *f(c)* and then finding the concentration (c) where confidence limit is equal to $-\text{BMR}$.

Finally, we derived two sets of joint benchmark concentrations: The MIREC results (FSIQ score) were combined with ELEMENT outcomes using either GCI or FSIQ scores for all subjects where the creatinine-adjusted U-F was available. Joint benchmark concentration results were obtained under the hypothesis that the concentration-response functions were identical in the two studies. Under this hypothesis, the concentration-response function [*f(c)*] was estimated by combining the regression coefficients describing *f(c)*. Again, using the linear model as an example, we estimated the joint regression coefficient by weighing together cohort-specific coefficients. Here we used optimal weights proportional to the inverse of the squared standard error. In a Wald test, we tested whether the exposure effects in the two cohorts were equal. We calculated sex-dependent BMC results from regression models that included interaction terms between sex and *f(c)*. The fit of the regression models was compared by twice the negative log-likelihood [$-2 \log L$] as supplemented by the Akaike Information Criterion (AIC); the latter is provided in the tables. For both measures, a lower value indicates a better fit, but AIC-based differences below four are not considered important. For sex-dependent results, the AIC value for both boys and girls represents the fit of a model that includes an interaction between sex and exposure. As the linear model is nested in the piecewise linear model, the fit of these two models can be directly compared. Thus, we calculated the p-value for the hypothesis that the concentration-response is linear in a test where the alternative was the piecewise linear model. Here a low p-value indicates that the linear model has a poorer fit. As specific-gravity adjusted U-F values were available for an additional 105 MIREC subjects, we carried out sensitivity analyses using these data jointly with ELEMENT's creatinine-adjusted data.

3. RESULTS

Table 1 shows the regression coefficients obtained from the two outcomes (GCI and IQ score) in the ELEMENT study and the IQ score in the MIREC study. As previously reported (Bashash et al., 2017; Green et al., 2019), maternal U-F exposure predicts significantly lower IQ scores in boys and girls in the ELEMENT cohort, while it does not show a statistically significant association for boys and girls combined in the MIREC cohort. However, for the linear association, the difference between the two studies is not statistically significant and the combined data show highly significant U-F regression coefficients (Table 1). A sensitivity analysis using the larger number of observations with specific-gravity adjusted U-F did not show significant differences between the two cohort studies and yielded joint U-F effects that were significant.

Table 2 shows the BMC results obtained from the regression coefficients for each sex and for both sexes. The BMC and BMCL are presented for the MIREC study, the ELEMENT (GCI and IQ) study, and combined across the two cohorts. The AIC results did not reveal any important differences between the model fits, except that the linear slope appeared superior to the squared for the joint results that included the Mexican GCI data. For the linear models, the joint BMCL in terms of U-F (creatinine-adjusted) is approximately equal for the MIREC-ELEMENT IQ model (0.20 mg/L) and MIREC-ELEMENT GCI model (0.19 mg/L). Similarly, for the squared models, the joint BMCL in terms of U-F is approximately equal for the MIREC-ELEMENT IQ model (0.77 mg/L) and MIREC-ELEMENT GCI model (0.81 mg/L). When using the larger number of specific gravity-adjusted U-F results from the MIREC cohort, the joint analysis with the

Table 1. Regression Coefficients Adjusted for Confounders for the Change in the Outcome, for Boys and Girls Combined, at an Increase by 1 mg/L in Creatinine-Adjusted Maternal Urine Fluoride Concentration for IQ in the MIREC Study, GCI (Upper Rows) and IQ (Lower Rows) in the ELEMENT study, and a Joint Calculation. The Column to the Right (p_{diff}) Shows the p-Value for a Hypothesis of Identical Regressions in the two studies. Two Concentration-Response Models are Used, a Linear and one with the Squared Exposure Variable

	MIREC		ELEMENT		Joint MIREC-ELEMENT		
model	beta	p	beta	p	beta	p	p_{diff}
	FSIQ ($n = 407$)		GCI ($n = 287$)				
Linear	−2.01	0.16	−6.29	0.007	−3.20	0.008	0.12
Squared	−0.419	0.40	−2.68	0.02	−0.780	0.09	0.07
	FSIQ ($n = 407$)		IQ ($n = 211$)				
Linear	−2.01	0.16	−5.00	0.01	−3.07	0.01	0.22
Squared	−0.419	0.40	−2.65	0.002	−0.998	0.023	0.025

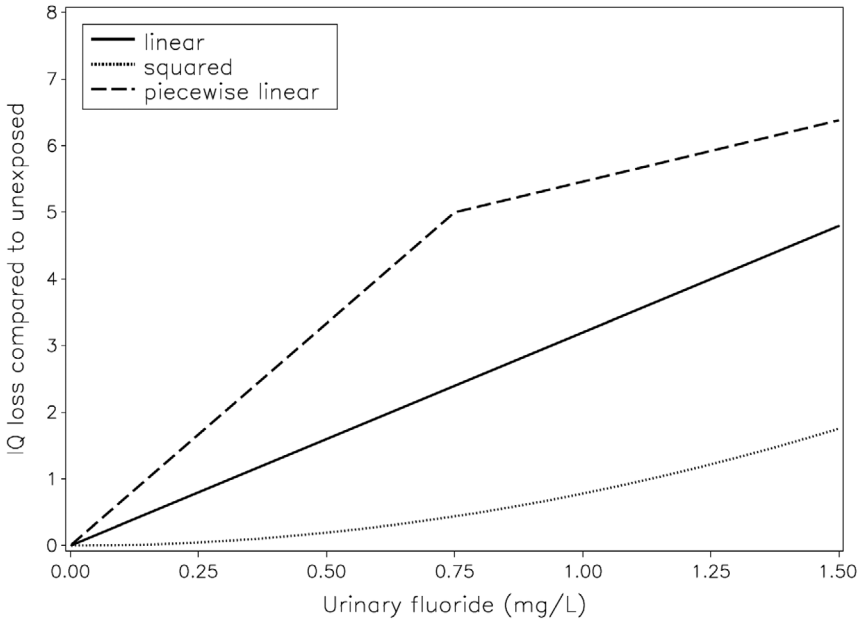

Fig 1. Association between creatinine-adjusted maternal urinary-fluoride (U-F) concentration in pregnancy and child IQ loss for the larger number of children (joint for GCI in ELEMENT and MIREC). Covariate-adjusted models are shown for the linear (solid), squared (dotted), and piecewise (dashed) linear curve with breakpoint 0.75 mg/L. The BMC is the U-F concentration that corresponds to an IQ loss of 1 (numbers shown in Tables 2 and 3).

ELEMENT data yielded results that were very close to those shown in Table 2, that is, with BMC values of about 0.19 mg/L for the linear model and about 0.63 mg/L for the squared model (data not shown).

Linear models allowing for sex-dependent effects showed a slightly better fit in the AIC mainly due to the significant interaction terms in the MIREC cohort. Although the BMCL in the MIREC cohort is clearly higher in girls than boys (0.61 vs. 0.13 mg/L), the overall BMCL for both sexes in the MIREC cohort (0.23 mg/L) is closer to the one for boys than the one for girls (Table 2). Sex-linked differences were not significant in the ELEMENT study.

Table 3 shows results using piecewise linear functions, with one breakpoint at 0.75 mg/L and one at 0.5 mg/L. A piecewise linear model is more flexible than a linear model, but AIC results showed that the joint piecewise linear models in Table 3 did not fit better than the standard linear models in Table 2. Thus, the hypothesis of a linear concentration-response relation could not be rejected: for the joint MIREC-ELEMENT IQ model, p-values for likelihood testing were $p = 0.18$ and $p = 0.15$ when the linear model was tested against models using breakpoints of 0.5 and 0.75 mg/L, respectively. For the joint MIREC-ELEMENT GCI model, the corresponding p-values were $p = 0.83$ and $p = 0.48$.

The shapes of the linear, the squared, and one piecewise concentration-response curves are shown in Fig. 1. In accordance with the BMC values, the Fig. shows that the squared model has a weaker slope

Table 2. Benchmark Concentration Results (mg/L Urinary Fluoride, Creatinine-Adjusted) for a BMR of 1 IQ Point Obtained from the MIREC Study and the Two Cognitive Assessments from the ELEMENT Study as Well as the Joint Results. Two Concentration-Response Models are used, a Linear and One with the Squared Exposure Variable. For both Models, Sex-Specific and joint benchmark Results are Provided. The fit of the Regression models was Compared by the AIC (Where Lower Values Indicate a Better Fit)

Study		MIREC ($n = 407$)		ELEMENT IQ ($n = 211$)		ELEMENT GCI ($n = 287$)		MIREC and ELEMENT IQ ($n = 618$)			MIREC and ELEMENT GCI ($n = 694$)		
Model	Sex	BMC	BMCL	BMC	BMCL	BMC	BMCL	BMC	BMCL	AIC	BMC	BMCL	AIC
Linear	Both	0.497	0.228	0.200	0.122	0.159	0.099	0.326	0.201	4770.1	0.312	0.192	5491.3
Linear	Boys	0.201	0.125	0.275	0.130	0.148	0.084	0.222	0.144	4766.7	0.184	0.125	5488.4
Linear	Girls	∞	0.609	0.160	0.091	0.169	0.087	1.098	0.275	4766.7	2.972	0.315	5488.4
Squared	Both	1.545	0.896	0.614	0.496	0.611	0.467	1.008	0.768	4768.8	1.133	0.807	5493.9
Squared	Boys	0.840	0.622	0.684	0.496	0.581	0.435	0.787	0.619	4769.4	0.761	0.601	5493.7
Squared	Girls	∞	1.262	0.576	0.449	0.642	0.434	1.637	0.866	4769.4	∞	1.040	5493.7

Abbreviations: AIC, Akaike Information Criterion; BMC, benchmark concentration; BMCL, benchmark concentration level; BMR, benchmark response; GCI, Global Cognitive Index; IQ, Intelligence Quotient.

Table 3. Benchmark Concentration (BMC) Results (mg/L Urinary Fluoride, Creatinine-Adjusted) for a BMR of 1 IQ Point Obtained from the MIREC Study and the Two Cognitive Assessments from the ELEMENT study as well as the Joint Results. Two Piecewise Linear Concentration-Response Models (with Urinary Fluoride Breakpoints at 0.5 and 0.75 mg/L) are used. For both Models, Sex-Dependent and Joint Benchmark results are Provided. The fit of the Regression Models was Compared by the AIC (Where Lower Values Indicate a Better Fit)

		MIREC ($n = 407$)		ELEMENT IQ ($n = 211$)		ELEMENT GCI ($n = 287$)		MIREC and ELEMENT IQ ($n = 618$)			MIREC and ELEMENT GCI ($n = 694$)		
Study	Sex	BMC	BMCL	BMC	BMCL	BMC	BMCL	BMC	BMCL	AIC	BMC	BMCL	AIC
Breakpoint 0.5	Both	1.751	0.092	2.688	0.431	1.004	0.042	1.073	0.139	4770.6	0.788	0.104	5495.0
Breakpoint 0.5	Boys	0.086	0.040	2.953	0.135	0.725	0.011	0.156	0.053	4766.7	0.087	0.040	5493.9
Breakpoint 0.5	Girls	∞	0.309	2.363	0.024	1.144	0.046	2.913	0.428	4766.7	3.817	0.385	5493.9
Breakpoint 0.75	Both	0.166	0.081	1.283	0.149	0.115	0.050	0.284	0.112	4769.8	0.150	0.083	5493.8
Breakpoint 0.75	Boys	0.082	0.049	1.379	0.121	0.127	0.035	0.136	0.070	4769.4	0.086	0.052	5493.6
Breakpoint 0.75	Girls	∞	0.125	1.155	0.052	0.109	0.044	1.365	0.140	4769.4	0.413	0.106	5493.6

Abbreviations: AIC, Akaike Information Criterion; BMC, benchmark concentration; BMCL, benchmark concentration level; BMR, benchmark response; GCI, Global Cognitive Index; IQ, Intelligence Quotient.

at low concentrations, while the low-concentration slope for the piece-wise association is steeper.

4. DISCUSSION

Experimental and cross-sectional epidemiology studies have provided evidence of fluoride neurotoxicity, especially when the exposure occurs during early brain development (Grandjean, 2019). As early as 2006, sufficient evidence was available to warrant further consideration of the possible brain toxicity of fluoride exposure with an emphasis on vulnerable populations (National Research Council, 2006). We now have thorough prospective epidemiology evidence on populations exposed to fluoridated water (about 0.7 mg/L) or comparable exposure from fluoridated salt and other sources. The present study is based on data from two prospective birth cohort studies (Bashash et al., 2017; Green et al., 2019) that include detailed assessment of child IQ and urinary fluoride concentrations during pregnancy. In these two studies, the mean U-F concentration (creatinine-adjusted) was similar among pregnant women living in Mexico City (0.89 mg/L) and the pregnant women living in fluoridated cities in Canada (0.84 mg/L).

Due to the brain's continued vulnerability across early development (Grandjean, 2013), early infancy may also be a vulnerable period of exposure for adverse effects from fluoride, especially among bottle-fed infants who receive formula reconstituted with fluoridated water (Till et al., 2019). Still, the effects of fetal exposure (i.e., U-F in pregnancy) in the MIREC Study remained significant when adjusting for exposure occurring in infancy. Similarly, in the ELEMENT study, the effect of maternal U-F was only marginally reduced after controlling for child U-F; fluoride exposure in school-age children showed a weaker and nonstatistically significant association with child IQ (Bashash et al., 2017). Taken together, these findings suggest that fetal brain development is highly vulnerable to fluoride exposure.

The magnitude of the fluoride-associated IQ losses is in accordance with findings in cross-sectional studies carried out in communities where the children examined had likely been exposed to chronic water-fluoride concentrations throughout development (Choi, Sun, Zhang, & Grandjean, 2012). More recent studies have shown similar results (Wang et al., 2020; Yu et al., 2018), and benchmark dose calculations (Hirzy, Connett, Xiang, Spittle, & Kennedy, 2016) relying on a large cross-sectional study (Xiang et al., 2003) showed results on the linear association similar to the ones obtained in the current analysis. These findings provide additional evidence that fluoride is a developmental neurotoxicant (i.e., causing adverse effects on brain development in early life). Given the ubiquity of fluoride exposure, the population impact of adverse effects from fluoride may be even greater than for other toxic elements like lead, mercury, and arsenic (Nilsen et al. 2020). Adverse effects of the latter trace elements are associated with blood concentrations that are about 100-fold lower than the serum-fluoride concentration that corresponds to the benchmark concentration (Grandjean, 2019).

A few retrospective studies have been carried out in communities with elevated fluoride exposure, though with imprecise exposure assessment that mostly relied on proxy variables, and without prenatal fluoride measurements (Aggeborn & Ohman, 2017; Broadbent et al., 2015). In addition to IQ outcome studies, the ELEMENT cohort found that elevated maternal U-F concentrations were associated with higher scores on inattention on the Conners' Rating Scale, an indication of Attention-Deficit/Hyperactivity Disorder (ADHD) behaviors (Bashash et al., 2018). Other studies on attention outcomes found an association between water fluoridation and diagnosis of ADHD in Canada, although data on child U-F did not replicate this association (Riddell, Malin, Flora, McCague, & Till, 2019), which is consistent with the ELEMENT study of child U-F and IQ (Bashash et al., 2017). Similarly, increased risk of ADHD was reported to be associated with water fluoridation at the state level in the United States (Malin & Till, 2015), although inclusion of mean elevation at the residence as a covariate made the association nonsignificant (Perrott, 2018).

Individual vulnerability may play a role in fluoride neurotoxicity. In the original MIREC study, boys were more vulnerable to prenatal fluoride neurotoxicity than girls (Green et al., 2019) suggesting that sex-dependent endocrine disruption may play a role (Bergman et al., 2013), among other sex-differential possibilities. Genetic predisposition to fluoride neurotoxicity may also exist (Cui et al., 2018; Zhang et al., 2015), but has so far not been verified. Other predisposing factors, such as iodine deficiency (Malin, Riddell, McCague, & Till, 2018) may contribute. For such reasons, regulatory agencies routinely use an uncertainty factor to derive safe exposure levels that are lower than the BMCL.

Both prospective studies adjusted for a substantial number of cofactors. Prenatal and early

postnatal lead exposure did not influence the ELEMENT fluoride-associated IQ deficits (Bashash et al., 2017). Adjustment for other neurotoxicants or risk factors, such as arsenic and lead exposure, did not appreciably change the estimates in the MIREC study (Green et al., 2019). While BMC results were calculated for the creatinine-adjusted U-F available from both studies, U-F results adjusted for specific-gravity were available for an additional 105 MIREC women; if using the latter U-F data, slightly lower BMC results were obtained, as compared to those based on creatinine-adjusted data only. Higher results were obtained for the squared, and lower for the broken linear slopes, but neither showed a superior fit to the data when compared to the linear relationship between maternal U-F and child IQ.

The increased precision using the average maternal U-F concentration as an indicator of prenatal fluoride exposure results in stronger statistical evidence of fluoride-associated deficits, compared with using cross-sectional or retrospective studies. Still, the amount of fluoride that reaches the brain during early brain development is unknown, and even the maternal U-F concentration measurements may be considered somewhat imprecise as dose indicators. Such imprecision, likely occurring at random, will tend to underestimate fluoride neurotoxicity (Grandjean & Budtz-Jørgensen, 2010).

The prospective studies offer strong evidence of prenatal neurotoxicity, and the benchmark results should inspire a revision of water-fluoride recommendations aimed at protecting pregnant women and young children. While systemic fluoride exposure has been linked to dental health benefits in early studies (Iheozor-Ejiofor et al., 2015), these benefits occur in the oral cavity after teeth have erupted (Featherstone, 2000), thus suggesting that use of fluoridated toothpaste and other topical treatment should be considered for alternative caries prevention.

5. CONCLUSIONS

Two prospective studies examined concentration-dependent cognitive deficits associated with the maternal U-F during pregnancy; one of the studies (Bashash et al., 2017 measured child IQ at two ages and found similar results, whereas the other study (Green et al., 2019) found a fluoride-IQ effect only in boys. We explored the shape of the concentration-response curve by using a standard linear shape and compared with a squared exposure and a piecewise linear function that allowed a change in steepness at two points within the range of exposures. Comparisons between the models suggest that the standard linear function is a reasonable approximation. All of these estimates have a certain degree of uncertainty, and emphasis should therefore be placed on the joint BMC results from the two studies and involving both sexes. These findings, using a linear concentration dependence, suggest an overall BMCL for fluoride concentrations in urine of approximately 0.2 mg/L. The results of this benchmark analysis should be incorporated when developing strategies to facilitate lowering fluoride exposure among pregnant women.

CONFLICT OF INTEREST

PG has served as an expert on the hazards of environmental chemicals on behalf of the plaintiffs in Food & Water Watch v. US EPA. HH and BL served as nonretained expert witnesses (uncompensated) for the same trial, in which they offered testimony regarding the studies their respective teams on fluoride exposure and neurobehavioral outcomes. All other authors have no interest to declare.

FUNDING

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ACKNOWLEDGMENTS

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geles Martinez-Mier, Christine Buckley, Dr. Frank Lippert and Prithvi Chandrappa for their analysis of urinary fluoride at the Indiana University School of Dentistry; Linda Farmus for her assistance with statistical modeling. This MIREC Biobank study was funded by a grant from the National Institute of Environmental Health Science (NIEHS) (grant #R21ES027044). The MIREC Study was supported by the Chemicals Management Plan at Health Canada, the Ontario Ministry of the Environment, and the Canadian Institutes for Health Research (grant # MOP-81285).

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Dear Ned,

Thank you for your response and here are a few points for your consideration inserted in your email in blue.

From: Therien, Ned (DOH) [mailto:Ned.Therien@DOH.WA.GOV]
Sent: Tuesday, June 28, 2011 9:21 AM
To: bill@teachingsmiles.com
Cc: McLaughlin, Craig D (DOH)
Subject: Response to Rule Making Request

Dr. Osmunson:

The use of additives in food is commonly practiced and widely accepted in this country.
I agree, but fluoride is not a food additive. The absence of fluoride does not cause any disease.

An example is the addition of folic acid to flour and cereal. High-dose folic acid distributed in tablet form for the treatment of disease is a prescription drug.

A. Folic acid LD50 is 10,000 mg/kg bw (*www.sciencelab.com/msds.php?msdsId=9927172)* and fluoride LD50 is 5 to 15 mg/kg. A HUGE difference in toxicity.

B. Folic acid is an approved drug in prescription form (**FDA Application No. (ANDA) 040756**
Fluoride with the intent to prevent dental caries is not approved by the FDA CDER in any form for ingestion.

C. No food additive is defined as toxic (poison) by Washington State law. Substances which cause violent sickness or death with 3,889 mg or less are considered poisons. Fluoride can cause death with 15 mg for children.

Lower doses of folic acid are required to be added to certain foods despite the fact that doing so may pose a threat to a very small number of individuals.
Indeed, the refining of wheat removes folate (as well as many other nutrients) the natural form of folic acid and many other nutrients. My Nutrition Professor used to say something like, "we take out (about) 30 nutrients when refining flour and add back (about) 7 and then call it "Enriched." (I forgot the exact numbers) He would continue, "that is like taking $30 from you and giving you $7 back and calling you Enriched."

Folic acid is required to be returned to the wheat when the wheat has been bleached, refined and stripped of folate. Folic acid is not intended in wheat to be an "addition" to the food but rather a replacement for what has been taken out during refining.

Adding it in this way has saved millions of babies from birth defects and, in many cases, death. The decision to mandate folic acid as an additive came after years of robust debate that carefully considered competing ethical claims. The final decision was significantly influenced by the strength of the science. In Great Britain, there has been greater reluctance to add folic acid to grains because of a greater portion of the public has raised concerns about compulsory treatment.

Yes, I agree. But if we did not refine the wheat, the subject would be almost mute. The processing of the wheat removed the folate. White bread is less bad because we return folic acid to replace the stolen folate.

As you know, fluoridation of drinking water is strongly encourage by the federal government, is explicitly allowed by the state Legislature and has been upheld repeatedly by the courts.

Neither the courts nor the Legislature has approved any unapproved drug. Indeed, the Legislature did not exempt fluoridated water from FDA CDER approval. The courts have been mixed with historic courts more favorable to fluoridation. The strong support is only if agencies, laws and court cases are cherry picked. The FDA CDER has never approved fluoridation of public drinking water and the FDA CDER and Board of Pharmacy have determined fluoride when used with the intent to prevent disease to be a drug. Three court cases finding of fact have agreed fluoride is hazardous.

To expect the public, the patients, the victums of mass medication without consent, those who have been harmed and sick, to use their money to fight for their freedom in court while their taxes are used to fight back is barbaric at best.

By contrast, there is a great deal of history, case law, statutory language, and legislative history around requiring informed consent for any invasive procedure (including a blood draw), use of human subjects for testing, medical privacy, and due process for any mandatory testing.

I fully agree and the fluoridation experiment is not exempt. Informed consent, use of human subjects for experimentation, medical privace and due process are all violated with fluoridation and governments must not violate human subjects, medical privacy or due process. Our petition must strictly protect humans.

Blood testing can only be required when screening newborns for inheritable conditions and when testing people when there is a significant risk of occupational or criminal exposure to HIV. Such testing is done under the authority of the Legislature and we believe that mandating testing is outside the scope of the Board's authority without specific legislative authorization. While you may argue that volunteers will come forward, this process would raise concerns about scientific validity and the Board does not impose requirements on a regulated entity—in this case water districts—it they do not have clear authority to meet them.

You raise some valid concerns. One is legal authority and the other is scientific validity with volunteers.

Let me use examples.

A. The water district would place in their water bill a notice to customers and a request for volunteers who would then be sent to a physician and blood drawn under medical supervision with informed consent and confidentiality. The health care professional would send the fluoride

concentration without the patient's confidential information, name, etc. to the Department of Health and water district.

B. Or a local hospital could be contacted (contracted) requesting fluoride testing of 5 blood samples per month from patients already having blood drawn who volunteer or volunteers. The hospital would gain informed consent from the patient and the private patient identifying information kept confidential with the results sent to the Department of Health and water district.

C. Another possibility would be at autopsy. Informed consent would need to be by next of kin and the coroner would draw blood and send it to the lab identified by number and not name. In turn, the lab would send results to the Department of Health and water district.

The water district is attempting to raise the serum fluoride concentration of individuals, experimenting without their consent and without any testing on nonconsenting competent adults, prisoners, students, children, etc. Certainly the water district can contract with health care providers for volunteers under strict medical privacy, to have their fluoride tested to ensure the fluoride is not too high in their bodies and such testing is within the water districts jurisdiction.

If the Board wants to do a scientific test with scientific validity, a great deal of money, time, controls and effort would need to be put into the study. Such is not the intent of our petition.

Our petition is to protect each person in the water district and not only the mean, median or average individual within one or two standard deviations to any significant confidence.

With limited financial resources, some volunteer testing would be better than nothing.

If fluoridation is safe and effective for everyone or most, then the Board should have confidence the serum fluoride levels are below 0.02 ppm.

While the Board would share your interest in more and better research, turning consumers into research subjects and requiring water districts to conduct invasive procedures is not a viable or appropriate option.

Again, we fully agree and ethically precisely why fluoridation should stop. We have not intent to turn consumers into research subjects as is happening with fluoridation. Our petition is entirely voluntary and is only a method of monitoring what is happening in fluoridated communities.

For these reasons, I believe the proposal is fundamentally flawed and resubmitting the petition with clarifying language would not cause the Board to rethink its decision to deny.

The hypocrasy of using "informed consent and medical privacy" of volunteers as an excuse not to measure the effect of what the water district is doing "without informed consent or medical privacy" should be shouting at the Board.

For protection of the public, the process could be presented to the University of Washington Human Subjects research department for approval.

Sincerely and with respect,

Bill Osmunson

for Craig McLaughlin.
****

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From: Bill Osmunson [mailto:bill@teachingsmiles.com]
Sent: Saturday, June 25, 2011 7:25 PM
To: DOH WSBOH
Subject: RE: Response to Rule Making Request

Dear Honorable Dr. John Austin,

I have just read the Board's denial of our 11th petition for Rule Making. Your comment that both 0.02 and 0.01 mg ppm had been used in the proposed rules made me return to the petition for reconsideration.

Indeed, with further consideration I agree the proposed rule could be confusing to some. Cleaning up the wording would be most acceptable with just one serum fluoride concentration.

The Board's concern for protecting the public health's medical information privacy is in sharp ethical contrast to the Board's position supporting mass medication of an unapproved, misbranded and adulterated drug to everyone without their consent and without the Board knowing how much of the medication is in the person's body or even a typical person's body.

With our rule change proposal to actually test the fluoride blood serum concentration, no patient's name would become public. All patient's would have full privacy under the direction of a licensed physician and laboratory. Only volunteers would be chosen and full individual consent be protected. No medical information privacy laws would be violated and the Board did not list any laws which would be violated because there should be no laws violated.

Apparently our proposed rule change petition was less than clear. Would it be appropriate to polish the wording and be more explicit with the process and resubmit the request?

Sincerely,

Bill Osmunson DDS, MPH, President
Washington Action for Safe Water

From: DOH WSBOH [mailto:WSBOH@DOH.WA.GOV]
Sent: Friday, June 24, 2011 1:54 PM
To: bill@teachingsmiles.com
Subject: Response to Rule Making Request

<<06-24_Response_OsmunsonRulePetition#11_DrinkingWaterFluoridation_Serum Monitoring.pdf>>

Dr. Osmunson:

Included here please find a response to your recent rule making request. Thank you.

Washington State Board of Health
Mailing Address: Post Office Box 47990, Olympia, WA 98504-7990
Physical Address: 101 Israel Road SE, Tumwater, WA 98501
Phone: 360/236-4110 Fax: 360/236-4088
Email: wsboh@doh.wa.gov
Web site: www.sboh.wa.gov

Public Health – Always Working for a Safer and Healthier Washington

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As you know, fluoridation of drinking water is strongly encourage by the federal government, is explicitly allowed by the state Legislature and has been upheld repeatedly by the courts. By contrast, there is a great deal of history, case law, statutory language, and legislative history around requiring informed consent for any invasive procedure (including a blood draw), use of human subjects for testing, medical privacy, and due process for any mandatory testing. Blood testing can only be required when screening newborns for inheritable conditions and when testing people when there is a significant risk of occupational or criminal exposure to HIV. Such testing is done under

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for Craig McLaughlin.

****

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Bill Osmunson DDS, MPH, President
Washington Action for Safe Water

From: DOH WSBOH [mailto:WSBOH@DOH.WA.GOV]
Sent: Friday, June 24, 2011 1:54 PM
To: bill@teachingsmiles.com
Subject: Response to Rule Making Request

<<06-24_Response_OsmunsonRulePetition#11_DrinkingWaterFluoridation_Serum Monitoring.pdf>>

Dr. Osmunson:

Included here please find a response to your recent rule making request. Thank you.

Washington State Board of Health
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Public Health – **Always Working for a Safer and Healthier Washington**

STATE OF WASHINGTON
DEPARTMENT OF HEALTH

June 4, 2009

Bill Osmunson DDS, MPH
Aesthetic Dentistry of Bellevue
1418 112th Avenue NE, Suite 200
Bellevue, Washington 98004

Dear Dr. Osmunson:

This letter is in response to your request at the May 7, 2009 meeting of the Washington Board of Pharmacy for a response to your question about designating fluoride as a poison under chapter 69.38 RCW. RCW 69.38.020 states that "[a]ll substances regulated under chapters 15.58, 17.21, 69.04, and 69.50, and chapter 69.45 RCW are exempt from the provisions [of chapter 69.38 RCW]. Fluoride is a legend drug regulated under chapter 69.41 RCW. RCW 69.41.010 defines a "legend drug" as drugs "which are required by state law or regulation of the state board of pharmacy to be dispensed on prescription only or are restricted to use by practitioners only." In WAC 246-883-020 (2), the Board specified that "legend drugs are drugs which have been designated as legend drugs under federal law and are listed as such in the 2002 edition of the *Drug Topics Red Book.*" Enclosed are copies of pages 169, 342, and 690 of the 2002 edition of the *Drug Topics Red Book.* Page 169 is the key to the products requiring prescription (legend drugs) and page 342 contains the fluoride products. Page 690 contains the listing of over-the-counter fluoride products, primarily toothpaste containing fluoride.

While RCW 69.41.010 restricts the dispensing of prescription drugs to practitioners, the legislature has authorized water districts to fluoridate their water supplies in RCW 57.08.012. This authority was recognized by the Washington Supreme Court in *Parkland Light & Water Company v. Tacoma-Pierce County Board of Health, et al.*, 151 Wn.2d 428 (2004). By adopting a specific statute on the fluoridation of water supplies, the legislature has superseded the more general statutes in the legend drug act requiring a practitioner to dispense fluoride. *Tunstall v. Bergeson*, 141 Wn.2d 201, 211 (2000).

For the above-stated reasons, the Board of Pharmacy will not be considering your request to designate fluoride as a poison under chapter 69.38 RCW.

Sincerely,

Susan Teil Boyer

Susan Teil Boyer, MS, RPh, FASHP
Executive Director
Washington State Board of Pharmacy
PO Box 47852
Olympia WA 98504-7852

KEY TO Rx PRODUCT LISTINGS

How to Find an Rx Product

The layout of *Red Book* product listings allows for easy identification of Rx products, manufacturer names, generic cross-references, and repackagers of pharmaceutical products. It also identifies Federal Upper Limit prices for Medicaid reimbursement from the newly named Centers for Medicare and Medicaid Services (CMS), formerly known as the Health Care Financing Administration or HCFA. Products are listed alphabetically by their prevailing names, as explained below. (For information on how to locate and interpret OTC and non-drug product listings, refer to section 10.)

Product quantities appear in National Council for Prescription Drug Programs (NCPDP) standard billing units (e.g., ea, ml, gm). Please see Section 6, "Drug Reimbursement Information," for an explanation of the NCPDP standard. A conversion table can be found in Section 2, "Clinical Reference Guide."

Trademarked Name: Detailed product information is available under the actual brand name rather than the generic name; i.e., "Valium" product information is listed under "Valium" rather than under diazepam. However, you will find a cross-reference under Roche, the manufacturer of Valium, in the diazepam listing.

```
VALIUM (Roche Labs)
diazepam
TAB, PO, 10 mg,
    100s ea, C-IV ..... 00140-0006-01  108.92  AB
```

Generic Name: In-depth product information on generic products can be found by locating the generic product name, under which the various manufacturers, suppliers, or distributors are listed alphabetically; i.e., diazepam features several dozen generic manufacturers. Manufacturers listed under their trademarked product name feature a cross-reference to that name.

```
DIAZEPAM
FUL
TAB, PO, 2 mg, 100s ea ..... 2.09
(Abbott Hosp)
INJ, IJ (AMP)
    5 mg/ml,
    2 ml 10s, C-IV ..... 00074-3210-01  86.69  AP
(Roche Labs) See VALIUM
```

Single-ingredient generic names are spelled out in full. Multi-ingredient products (two or more) are listed in the alphabetical order of their ingredients using the standard abbreviations listed on the following pages.

Drug Class Symbols

The following descriptive symbols indicate a product's status under the Controlled Substances Act of 1970. They apply to all entries under the product name or dosage form in which they appear. Use these symbols only as a guide. Check the manufacturer's label for definitive information.

C-II High Potential for Abuse. Prescriptions must be written in ink or typewritten and signed by the practitioner. Verbal prescriptions must be confirmed in writing within 72 hours and may be given only in a genuine emergency. No renewals.

C-III Some Potential for Abuse. Prescriptions may be oral or written.
C-IV Up to 5 renewals are permitted within 6 months.
Low Potential for Abuse. Prescriptions may be oral or written.
C-V Up to 5 renewals are permitted within 6 months.
Subject to State and Local Regulation. Abuse potential is low; a prescription may not be required.

Rx Prescription only; not a controlled substance.

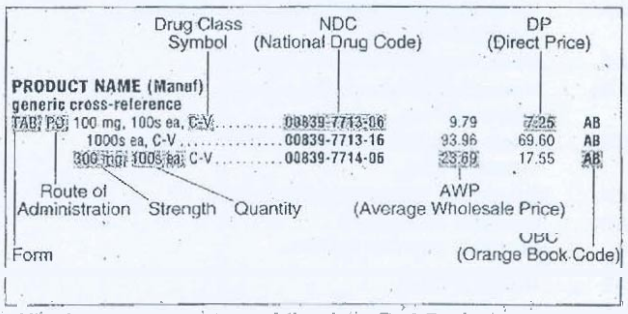
How to Read the Listings

The first line of an entry features the product or generic name. CMS Federal Upper Limit price information is provided for all applicable multi-source product categories. The FUL symbol can be found immediately following the generic product name. A complete listing of Federal Upper Limit prices appears in Section 6 (Drug Reimbursement Information).

Manufacturers are listed alphabetically within generic listings. Repackagers of products feature the REPACK symbol next to their names. For trade name listings, generic cross-references appear in lower case on the following line.

A three-letter abbreviation indicates the form of the drug; i.e., CAP indicates capsules, TAB indicates tablets, etc. For a key to additional abbreviations, refer to the table on the following page.

Route of administration, descriptive information, strength, quantity, and drug class symbol (where applicable) appear next, followed by National Drug Code (NDC) number. The Average Wholesale Price (AWP), Direct Price (DP), and the Orange Book Code (OBC) complete the entry for each product. For more information on Orange Book Codes, refer to the next page.



All prices are current as of the date *Red Book* went to press. However, actual prices paid by retailers may vary, and all prices are subject to change without notice. The prices shown here are based on data obtained from manufacturers, distributors, and other suppliers. While great care has been exercised in compiling this information, the publisher of *Red Book* does not warrant its accuracy. Information may be supplemented by subscribing to the monthly *Red Book UPDATE*, ReadyPrice™, *Red Book* for Windows™, *Red Book* database services, or by obtaining prices published in catalogs or other printed materials disseminated by manufacturers or distributors.

ROUTE OF ADMINISTRATION ABBREVIATIONS

Route of Administration (ROA) refers to the intake or application method of a product. The following abbreviations are used to indicate the ROA:

BC ..... Buccal
DE ..... Dental
EP ..... Epidural
IC ..... Intracavernosal
ID ..... Intradermal
IH ..... Inhalation
IJ ..... Injection
IL ..... Intravesical
IM ..... Intramuscular
IN ..... Intranasal
IP ..... Implantation
IR ..... Irrigation
IU ..... Intrauterine
IV ..... Intravenous
MM ..... Mucous membrane
MR ..... Multiple routes
NA ..... Not applicable
NS ..... Nasal
OP ..... Ophthalmic
OT ..... Otic
PL ..... Intrapleural
PO ..... Oral
PT ..... Intraperitoneal
RC ..... Rectal
SC ..... Subcutaneous
SG ..... Subgingival
SL ..... Sublingual
TD ..... Transdermal
TP ..... Topical
UR ..... Intraurethral
VG ..... Vaginal

ORANGE BOOK CODES

The Orange Book Codes supply the FDA's therapeutic equivalence rating for applicable multi-source categories. Codes beginning with "A" signify that the product is deemed therapeutically equivalentto the reference product for the category. Codes beginning with "B" indicate that bioequivalence has not been confirmed. In certain instances, a number is added to the end of the AB code to make it a three-character code (i.e., **AB1, AB2, AB3, etc.**). Three-character codes are assigned only in situations where more than one reference listed drug of the same strength has been designated under the same heading. "EE" is assigned by *Red Book* to products that have been evaluated by the FDA but for which an equivalence rating is not available.

Products appearing in the Orange Book have historically been limited to those manufacturers holding the original approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA). However, in recognition of the fact that generic products are available from a widespread number of sources, *Red Book* publications and database services extend Orange Book ratingsto distributors and generic labelers other than the holder of the NDA or ANDA. All ratings applied to such labelers have been diredly supplied to *Red Book* through written certification attesting to the accuracy of the codes supplied.

AA.....No bioequivalence problems in conventional dosage forms
AB.....Meets bioequivalence requirements
AB1.....Meets bioequivalence requirements to AB1 rated reference drug
AB2.....Meets bioequivalence requirements to AB2 rated reference drug
AN.....Solution or powder for aerosolization
AO.....Injectable oil solution
AP.....Injectable aqueous solution
AT.....Topical product
BC.....Controlled-release tablet, capsule, or injectable
BD.....Documented bioequivalence problem
BE.....Enteric-coated oral dosage form
BN.....Product in aerosol-nebulizer delivery system
BP.....Potential bioequivalence problem
BR.....Suppository or enema for systemic use
BS.....Testing standards are insufficient for determination
BT.....Topical product with bioequivalence issues
BX.....Insufficient data to confirm therapeutic equivalence
B*.....Requires further FDA investigation and review
EE.....This entry has been evaluated by the FDA, but a rating is not available for in's labeler's product

OTHER DESCRIPTIVE ABBREVIATIONS

The following abbreviations are used to provide additional descriptive information about products:

A.F......Alcohol-free
AMP.....Ampule
D.F......Dye-free
EXT. STR......Extra strength
F.F......Fragrance-free
FR.....French
INSTIT.USE..Institutional use
M.D.V......Multi-dose vial
MAX. STR...Maximum strength
N.B......Nursing Bottle
N.F......National Formulary
P.C......Plastic container
P.F......Preservative-free
R.N.P......Reversed number package
S.D......Single dose
S.D.V......Single-dose vial
S.F......Sugar-free
SRN.....Syringe
TAX INCL..Federal excise tax included
U.S.P......U.S. Pharmacopeia

STANDARD DOSAGE FORM DESCRIPTIONS

The following three-character abbreviations are used to indicate the form in which a product is available.

ACC	Accessory
AER	Aerosol liquid
APP	Medication-filled stick
ARO	Aerosol powder
BAN	Bandage
BAR	Bar
BEA	Beads
C12	Capsule, extended release, 12-hr.
C24	Capsule, extended release, 24-hr.
CAK	Cake
CAP	Capsule
CER	Capsule, extended release
CHI	Chip
CRE	Cream
CRY	Crystal
CTB	Tablet, chewable
CTG	Cartridge
DEV	Device
DRE	Dressing
DSK	Disk
ECC	Capsule, delayed release
ECT	Tablet, enteric-coated
ELI	Elixir
EMU	Emulsion
FDS	Food, solid
FIL	Film
FLA	Flake
FOA	Foam
GAS	Gas
GEF	Powder, effervescent
GEL	Gel/jelly
GER	Granules, extended release
GFS	Gel-forming solution
GRA	Granules
GUM	Gum
ICR	Insert, extended release
IMP	Implant
INJ	Injection
KIT	Kit
LEA	Leaf
LIQ	Liquid
LOT	Lotion
LOZ	Lozenge/troche
LUM	Lump
NMA	Enema
ODT	Tablet, disintegrating
OIL	Oil
OIN	Ointment
PAD	Pad
PAK	Patient pack
PAS	Paste
PDR	Powder for suspension
PDS	Powder for solution
PEL	Pellet
PI1	Powder for suspension, 1-month
PI3	Powder for suspension, 3-month
PI4	Powder for suspension, 4-month
PIH	Powder for Inhalation
PKT	Packet
POD	Pod
POW	Powder
PRO	Prophylactic
PUD	Pudding
SER	Suspension, extended release
SGL	Capsule, liquid-filled
SHA	Shampoo
SOA	Soap
SPE	Suppository, extended release
SOL	Solution
SPG	Sponge
SPR	Spray
STI	Stick
SUP	Suppository
SUS	Suspension
SWA	Swab
SYR	Syrup
T12	Tablet, extended release, 12-hr.
T24	Tablet, extended release, 24-hr.
TAB	Tablet
TAM	Tampon
TAP	Tape
TCP	Tablet, coated particles
TDM	Patch, extended release
TEF	Tablet, effervescent
TER	Tablet, extended release
TES	Test
TIN	Tincture
WAF	Wafer
WAX	Wax

PROD/MFR	NDC	AWP	DP	OBC
(Gallipot)				
POW, NA (MICRONIZED,U.S.P.)				
1 gm	51552-0056-01	52.50		
5 gm	51552-0056-05	236.34		
(Ivax Pharm)				
SOL, TP, 0.05%, 60 ml	00182-5050-68	26.18		AT
(Major) *See FLUOCINONIDE*				
(Major)				
CRE, TP, 0.05%, 15 gm	00904-0770-36	7.30		AB
60 gm	00904-0770-02	16.50		AB
SOL, TP, 0.05%, 60 ml	00904-0769-03	25.45		AT
(Medicis) *See LIDEX*				
(Medicis) *See LIDEX-E*				
(Medisca)				
POW, NA (MICRONIZED, U.S.P.)				
1 gm	38779-0018-06	63.75		
5 gm	38779-0018-03	287.50		
10 gm	38779-0018-01	502.50		
25 gm	38779-0018-04	1125.00		
(NuCare Pharm)				
CRE, TP, 0.05%, 15 gm	66267-0973-15	24.19		EE
(Pharma Pac)				
CRE, TP, 0.05%, 15 gm	52959-0093-01	25.36		EE
30 gm	52959-0093-03	30.35		EE
60 gm	52959-0093-02	43.98		EE
OIN, TP, 0.05%, 15 gm	52959-0315-01	22.15		EE
30 gm	52959-0315-03	30.50		EE
(Phys Total Care)				
CRE, TP, 0.05%, 15 gm	54868-0431-02	4.42		EE
30 gm	54868-0431-03	6.78		EE
60 gm	54868-0431-01	10.71		EE
OIN, TP, 0.05%, 30 gm	54868-3435-00	18.96		EE
OIN, TP, 0.05%, 60 gm	54868-3435-01	44.93		EE
SOL, TP, 0.05%, 60 ml	54868-2451-01	19.14		EE
CRE, TP, 0.05%, 30 gm	54868-3408-00	15.88		EE
60 gm	54868-3408-01	27.76		EE
(Qualitest)				
CRE, TP, 0.05%, 15 gm	00603-7759-74	7.32		AB
30 gm	00603-7759-78	9.68		AB
SOL, TP, 0.05%, 60 ml	00603-7758-89	16.46		AB
(Southwood)				EE
CRE, TP, 0.05%, 15 gm	58016-3121-01	23.28		EE
30 gm	58016-3121-01	24.92		EE
GEL, TP, 0.05%, 60 gm	58016-3274-01	52.55		EE
(Taro)				
CRE, TP, 0.05%, 15 gm	51672-1253-01	13.55		AB
30 gm	51672-1253-02	13.90		AB
60 gm	51672-1253-03	23.72		AB
120 gm	51672-1253-04	81.59		AB
GEL, TP, 0.05%, 15 gm	51672-1279-01	20.87		AB
30 gm	51672-1279-02	28.94		AB
60 gm	51672-1279-03	48.55		AB
OIN, TP, 0.05%, 15 gm	51672-1264-01	21.04		AB
30 gm	51672-1264-02	29.19		AB
60 gm	51672-1264-03	49.00		AB
SOL, TP, 0.05%, 20 ml	51672-1273-02	16.88		AT
60 ml	51672-1273-04	27.00		AT
CRE, TP (EMULSIFIED BASE)				
0.05%, 15 gm	51672-1254-01	19.40		AB
30 gm	51672-1254-02	26.88		AB
60 gm	51672-1254-03	45.06		AB
(Teva)				
CRE, TP, 0.05%, 15 gm	00093-0262-15	8.97		AB
30 gm	00093-0262-30	13.02		AB
60 gm	00093-0262-92	21.84		AB
GEL, TP, 0.05%, 60 gm	00093-0265-92	46.01		AB
OIN, TP, 0.05%, 15 gm	00093-0264-15	19.91		AB
30 gm	00093-0264-30	27.51		AB
60 gm	00093-0264-92	46.01		AB
SOL, TP, 0.05%, 60 ml	00093-0266-39	26.18		AT
CRE, TP (EMULSIFIED BASE)				
0.05%, 15 gm	00093-0263-15	19.90		AB
30 gm	00093-0263-30	27.50		AB
60 gm	00093-0263-92	46.00		AB
(Thames)				
CRE, TP, 0.05%, 15 gm	49158-0212-20	5.04		AB
30 gm	49158-0212-68	8.40		AB
60 gm	49158-0212-24	14.72		AB
SOL, TP, 0.05%, 20 ml	49158-0316-54	10.00		AT
60 ml	49158-0316-48	23.49		AT
CRE, TP, 0.05%, 15 gm	52544-0449-73	16.36		AB
CRE, TP, 0.05%, 15 gm	52544-0449-73	24.08		AB
SOL, TP, 0.05%, 60 ml	52544-0447-06	24.50		AT
60 gm	52544-0447-06			AT
(Watson)				

PROD/MFR	NDC	AWP	DP	OBC
FLUOCINONIDE (Major)				
CRE, TP, 0.05%, 30 gm	00904-0770-31	10.15		AB
FLUOGEN (Phys Total Care)				
REPACK				
influenza virus vaccine (subvirion)				
SOL, IM (M.D.V.,STERI-VIAL,99-00)				
45 mcg/0.5 ml				
5 ml	54868-4124-00	30.96		
FLUOR-A-DAY (Pharmascience Labs)				
sodium fluoride				
CTB, PO (S.F., RASPBERRY)				
0.25 mg, 120s ea	51817-0602-16	7.02		
0.5 mg, 120s ea	51817-0611-16	7.02		
1 mg, 120s ea	51817-0622-16	7.02		
LIQ, PO (DROPS)				
30 ml	51817-0656-61	5.81		
LOZ, PO (S.F., MINT)				
1 mg, 60s ea	51817-0672-16	7.25		
(medvantx)				
REPACK				
CTB, PO (S.F.,RASPBERRY)				
0.25 mg, 30s ea	65116-0164-30	1.83		
FLUOR-I-STRIP (Bausch&Lomb Pharm)				
fluorescein sodium				
TES, OP (STRIP)				
9 mg, 300s ea	24208-0390-83	77.80		
(Allscripts)				
REPACK				
TES, OP (STRIP)				
9 mg, 300s ea	54569-2086-00	77.80		
FLUOR-I-STRIP A.T. (Bausch&Lomb Pharm)				
fluorescein sodium				
TES, OP (STRIP)				
1 mg, 300s ea	24208-0391-83	77.80		
FLUOR-OP (Novartis Ophth)				
fluorometholone				
SUS, OP, 0.1%, 5 ml	58768-0358-05	15.03		AB
10 ml	58768-0358-10	22.86		AB
15 ml	58768-0358-15	28.16		AB
FLUORABON (Perry Med)				
sod fl/vit a/vit c/vit d				
SOL, PO (DROPS, BASIC)				
(Perry Med) 60 ml	11763-0519-26	4.18		
sodium fluoride				
CTB, PO (GRAPE)				
1 mg, 100s ea	11763-0526-01	1.98		
1 mg, 100s ea	11763-0525-01	1.98		
(ORANGE)				
LIQ, PO (DROPS)				
1 mg, 100s ea	11763-0532-01	1.98		
60 ml (0.25 mg/0.6 ml)	11763-0524-20	2.75		
FLUORACAINE (Akorn)				
fluorescein/proparacaine				
SOL, OP (GLASS BOTTLE)				
0.25%-0.5%, 5 ml	17478-0311-10	9.15		
FLUORESCEIN (A-A Spectrum)				
POW, NA (U.S.P.)				
25 gm	49452-3157-01	16.80		
100 gm	49452-3157-02	48.50		
FLUORESCEIN SODIUM (A-A Spectrum)				
POW, NA (U.S.P.)				
25 gm	49452-3160-03	12.70		
100 gm	49452-3160-01	27.40		
1000 gm	49452-3160-02	174.70		
(Akorn) *See AK-FLUOR*				
(Akorn) *See D.E.T. DRY EYE TEST*				
(Akorn) *See FLUORETS*				
(Akorn) *See FUL-GLO*				
(Alcon Ophthalmic) *See FLUORESCITE*				
(Allscripts)				
SOL, OP, 2%, 1 ml,12s	54569-2073-00	35.74		
(Bausch&Lomb Pharm) *See FLUOR-I-STRIP*				
(Bausch&Lomb Pharm) *See FLUOR-I-STRIP A.T.*				
(EyeSupply USA) *See ANGIOSCEIN*				
(Integra)				
POW, NA (U.S.P.,REAGENT)				
100 gm	F5801020	48.90		
(WATER SOLUBLE)				
100 gm	F5805020	22.40		

PROD/MFR	NDC	AWP	DP	OBC
(U.S.P.,REAGENT)				
500 gm	F5801030	97.65		
(WATER SOLUBLE)				
500 gm	F5805030	52.15		
(Novartis Ophth) *See ANGISCEIN*				
(Ocumed) *See OCU-FLUR 10*				
FLUORESCEIN/PROPARACAINE				
(Akorn) *See FLUORACAINE*				
(Ocusoft) *See FLUCAINE*				
FLUORESCITE (Alcon Ophthalmic)				
fluorescein sodium				
SOL, IV (AMP)				
10%, 5 ml (SRN, 10 ML)	00065-0092-05	18.96		
10%, 5 ml (AMP)	00065-0093-05	37.20		
25%, 2 ml	00065-0094-02	22.02		
FLUORETS (Akorn)				
fluorescein sodium				
TES, OP (STRIP)				
1 mg, 100s ea	17478-0400-01	13.50		
FLUORI-METHANE (Gebauer)				
dichloro/trichloromono				
SPR, TP (FINE)				
15%-85%, 103 ml	00386-0003-04	23.70		
(Allscripts)				
REPACK				
SPR, TP (FINE)				
15%-85%, 103 ml	54569-3567-00	24.69		
(Phys Total Care)				
REPACK				
SPR, TP (FINE)				
15%-85%, 103 ml	54868-4156-00	29.16		
FLUORIDE (Vintage)				
sodium fluoride				
LIQ, PO (DROPS)				
60 ml (0.125 mg/drp)	00254-9430-48	5.10		
FLUORINSE (Oral B Lab)				
sodium fluoride				
SOL, PO (A.F.,CINNAMON)				
0.2%, 480 ml	00041-0351-07	7.49		
(A.F.,MINT)				
0.2%, 480 ml	00041-0350-07	7.49		
FLUORO/GLY GEL (Topix)				
glycolic acid				
GEL, TP (OFFICE USE ONLY)				
30%, 120 gm	51326-0025-04	15.00		
50%, 120 gm	51326-0027-04	25.00		
70%, 120 gm	51326-0029-04	35.00		
FLUORO/GLY PADS (Topix)				
glycolic acid				
PAD, TP (OFFICE USE ONLY)				
30%, 30s ea	51326-0006-30	30.00		
50%, 30s ea	51326-0008-30	50.00		
70%, 30s ea	51326-0010-30	70.00		
FLUOROMETH/SULFACET SOD				
(Allergan Inc) *See FML-S LIQUIFILM*				
FLUOROMETHOLONE				
FUL				
SUS, OP, 0.1%, 5 ml		8.30		
(A-A Spectrum)				
POW, NA (U.S.P.)				
0.100 gm	49452-3170-01	46.50		
0.500 gm	49452-3170-02	155.60		
(Allergan Inc) *See FML FORTE LIQUIFILM*				
(Allergan Inc) *See FML LIQUIFILM*				
(Allergan Inc) *See FML S.O.P.*				
SUS, OP, 0.1%, 5 ml	54569-4371-00	13.84		EE
(Allscripts)				
10 ml	54569-4372-00	26.16		EE
15 ml	54569-4373-00	35.20		EE
(Bausch&Lomb Pharm)				
SUS, OP, 0.1%, 5 ml	24208-0288-05	15.80		AB
15 ml	24208-0288-15	35.18		AB
10 ml	24208-0288-10	26.16		AB
(Caremark Inc.)				
SUS, OP, 0.1%, 5 ml	00339-5006-50	15.03		AB
10 ml	00339-5006-51	23.63		AB
15 ml	00339-5006-52	31.30		AB
SUS, OP, 0.1%, 5 ml	61314-0328-05	15.80		AB
(Falcon Ophthalmics)				
10 ml	61314-0328-10	26.20		AB
15 ml	61314-0328-15	35.20		AB

PROD/MFR	HRI, UPC,NDC	AWP	SRP
FLEET PREP KIT 3 (Fleet,C.B.)			
KIT,NA (W/SMALL VO..UME ENEMA)	01320-10	4.87	
FLEET SOF-LAX (Fleet,C.B.)			
TAB,PO (GELCAPLET) 100s ea	01320-7516-00	5.60	
FLEET SOF-LAX OVERNIGHT (Fleet,C.B.)			
TAB,PO (GELCAPLET) 50 mg-100 mg,			
30s ea	01320-7553-00	4.00	
60s ea	01320-7556-00	6.00	
FLETCHER'S CASTORIA (Mentholatum)			
LIQ,PO, 6.5%, 75 ml	10742-0032-10	3.59	
GEL,TP, 7%, 60 gm	41167-1601-10	3.24	
120 gm	41167-1601-30	4.66	
FLEXALL 454 MAXIMUM STRENGTH (Chattem)			
GEL,TP, 45 gm	41167-1602-10	3.24	
P, 45 gm	41167-1602-10	3.24	
90 gm	41167-1602-40	4.66	
FLEXALL ULTRA PLUS (Chattem)			
GEL,TP (GREASELESS) 3.1%-16%-10%,			
60 gm	41167-1603-10	4.06	
120 gm	41167-1603-30	5.88	
FLEXI-SEAL FECAL COLLECTOR (Convatec)			
DEV,NA (W/TA.. C..IPS)			
10s ea	00003-6500-78	78.97	92.91
FLEXI-TRAK ANCHORING (Convatec)			
ACC,NA (LARGE)			
50s ea	00003-0374-49	80.23	94.39
FLEXIBLE FABRIC STRIPS (Chain Drug Marketing)			
BAN,TP (ASSORTED) 30s	63868-0020-30		
FLEXIFIX TRANSPARENT ADHESIVE FILM (Smith & Nephew)			
TAP,TP (2"X11YD ROLL) ea	00223-4151-30	14.84	19.78
(4"X11YD ROLL) ea	00223-4151-40	25.98	34.64
FLEXIFLO III PUMP W/SPIKE (Nestle)			
KIT,NA, ea	00065-9017-99	6.54	
FLEXIFLO QUANTUM COLORMARK PUMP (Ross Nutr)			
KIT,NA (W/PIERC PIN & FLUSH BAG)			
ea	70074-5249-00	15.54	
(W/PIERCING PIN) ea	70074-5248-80	10.64	
(W/TOP-FILL & FLUSH BAGS) ea	70074-5455-10	21.3	
(W/TOP-FILL BAG) ea	70074-5454-90	16.49	
FLEXIFLO QUANTUM ENTERAL PUMP (Ross Nutr)			
DEV,NA, ea	70074-5059-70	1380.00	
KIT,NA (40MM) ea	70074-5060-90	7.88	
FLEXIFLO QUANTUM PUMP (Ross Nutr)			
KIT,NA (W/PIERC PIN & FLUSH BAG)			
ea	70074-5060-50	13.74	
(W/PIERCING PIN) ea	70074-5060-10	8.84	
FLEXIFLO-III COLORMARK PUMP (Ross Nutr)			
KIT,NA (W/PIERCING PIN) ea	70074-5248-40	9.06	
FLEXIFLO-III ENTERAL NUTRITION PUMP (Ross Nutr)			
DEV,NA (REFURBISHED)			
ea	70074-5435-10	838.80	
KIT,NA, ea	70074-0007-70	6.26	
(W/PIERCING PIN) ea	70074-0007-80	7.26	
FLEXITAINER 500 CONTAINER (Ross Nutr)			
KIT,NA (ENTERAL NUTRITION)			
ea	70074-0006-80	5.23	
FLEXITAINER NUTRITION CONTAINER (Ross Nutr)			
ACC,NA, ea	70074-0006-90	6.26	
FLEXOPLAST (Western Medical)			
BAN,TP (3" ELASTIC ADHESIVE)			
12s ea	GL1003	102.99	
(3" REVERSE ADHESIVE) 12s ea	GL1003R	102.99	
(4" ELASTIC ADHESIVE) 12s ea	GL1004	123.31	

PROD/MFR	HRI, UPC,NDC	AWP	SRP
FLEXTEND SKIN BARRIER NON-STERILE (Hollister)			
DEV,NA (4"X4") 5s ea	8665	27.69	32.91
FLEXZAN (Bertek)			
DRE,TP (4"X8" SHEETS) 5s ea	62794-0085-32	36.25	
(8"X8" SHEETS) 5s ea	62794-0085-64	24.50	
(4"X4" SHEETS) 10s ea	62794-0085-18	32.00	
FLEXZAN EXTRA (Bertek)			
DRE,TP (4"X8") 5s ea	62794-0091-32	40.60	
FLINTSTONES (Bayer Cons)			
CTB,PO, 60s ea	16500-0781-60	4.46	
FLINTSTONES COMPLETE (Bayer Cons)			
CTB,PO, 60s ea	16500-0880-60	6.54	
150s ea	16500-0971-30	10.88	
FLINTSTONES PLUS CALCIUM (Bayer Cons)			
CTB,PO, 60s ea	16500-0770-60	5.67	
FLINTSTONES PLUS EXTRA C (Bayer Cons)			
CTB,PO, 60s ea	16500-0861-90	5.67	
100s ea	16500-0861-30	8.23	
FLINTSTONES W/IRON (Bayer Cons)			
CTB,PO, 60s ea	16500-0790-90	5.67	
100s ea	16500-0790-50	7.53	
FLIP-FLO INCONTINENCE VALVE (Bard Medical)			
ea	150419	23.65	29.57
(19 OZ,W/LATEX STRAP) ea	150319	6.42	8.02
(32 OZ,BONUS PACK)			
FLIPPER HOLDER/RACK (Bernell Corp)			
ACC,NA (HOLDS 12 FLIPPERS)		23.65	28.57
FLIPPER W/FOUR CELLS (Bernell Corp)		32.95	
DEV,NA (EMPTY,NO LENSES)			
FLIPPER W/TWO PAIRS OF LENSES (Bernell Corp)		5.50	
DEV,NA (1-/1-.25-2 DIOPTERS)	BC1270	16.95	
(1+/1-,2.25-4 DIOPTERS) ea	BC1270	17.95	
(ANY COMBINATION) ea	BC1270S	29.95	
FLO-GARD PUMP W/SPIKE (Nestle)			
KIT,NA, ea	00065-9600-99	6.54	
FLORICAL (Mericon)			
CAP,PO, 364 mg-8.3 mg,			
100s ea	00394-0102-02	9.90	
500s ea	00394-0102-05	46.85	
TAB,PO, 364 mg-8.3 mg,			
100s ea	00394-0100-02	9.12	
500s ea	00394-0100-05	42.88	
FLORIDA FOAM IMPROVED (Hill Derm)			
LIQ,TP, 240 ml	28105-0069-08	5.31	
FLOW DETECTOR (Abbott Hosp)			
KIT,NA (54")			
ea	00074-1997-25	163.65	
FLU & COLD MEDICINE (Perrigo)			
PDR,PO (LEMON, PACKET)			
650 mg-4 mg-60 mg,			
6s ea	58948-0118-91	2.36	
FLU COLD & COUGH NIGHTTIME (Cardinal Health)			
PKT,PO (MAX. STR.,LEMON)			
6s ea	37205-0331-91	3.52	
(Major)			
PKT,PO (MAX. STR. A.F.,LEMON)			
6s ea	00904-5461-86	3.45	
FLU MULTI-SYMPTOM MAXIMUM STRENGTH (Eckerd)			
TAB,PO (GELCAP,NON-DROWSY)			
500 mg-15 mg-30 mg,			
24s ea	19458-2676-01	4.08	
FLU SOLUTION (Dollsos)			
PEL,SL, 5s ea	00134-0001-11	4.17	6.95

PROD/MFR	HRI, UPC,NDC	AWP	SRP
FLU SOLUTION PLUS (Dollsos)			
TAB,SL, 45s ea	00134-0566-41	4.17	6.95
FLU, COLD & COUGH MEDICINE (Cardinal Health)			
PDR,PO (PACKET,LEMON) 6s ea	37205-0330-91	3.19	
FLU-RELIEF (Pfeiffer)			
TAB,PO, 325 mg-2 mg-30 mg, 36s ea	00927-0324-53	2.94	3.29
FLU/COLD/COUGH MEDICINE (Bergen Brunswig)			
PDS,PO (MAX.STR.,PACKET,LEMON)			
6s ea	24385-0868-91	3.59	4.39
(PACKET,LEMON) 6s ea	24385-0536-91	3.19	3.99
(Perrigo)			
PDS,PO (PACKET,LEMON)			
6s ea	58948-0555-91	2.39	
FLUORIDE TARTAR CONTROL TOOTHPASTE (Perrigo)			
GEL,TP (FRESHMINT)	58948-0278-20	1.74	
PAS,TP (ORIGINAL)			
192 gm	58948-0233-20	1.74	
FLUORIDE TOOTHPASTE (Perrigo)			
PAS,TP (MINT)			
192 gm	58948-0007-20	1.59	
(REGULAR) 192 gm	58948-0016-20	1.59	
FLUORIGARD (Colgate Oral)			
SOL,PO, 0.05%, 473 ml	00126-0220-16	3.65	
FO-TI (Botanical Labs.)			
LIQ,PO, 30 ml	41954-0201-90		
FOAM INVALID RING REPLACEMENT COVER (Hermell)			
ACC,NA (FOR IR7210,12,14)	IR7210/12/14	2.75	
(FOR IR7211,13,15) ea	IR7211/13/15	4.00	
FOAM INVALID RING W/COVER (Hermell)			
DEV,NA (14 1/4"X12 3/4",PLAID)			
ea	IR7080	6.15	
(14 1/4"X12 3/4",POLYCOT) ea	IR7070	5.60	
(16 1/4"X13",PLAID) ea	IR7020	6.85	
(16 1/4"X13",POLYCOT) ea	IR7010	6.25	
(18 1/4"X15 1/4",PLAID) ea	IR7050	8.10	
(18 1/4"X15 1/4",POLYCOT) ea	IR7040	7.40	
FOAM PAD (Torbot)			
ACC,NA (1/16",LARGE,BLACK) ea	433L	1.80	
(1/16",LARGE,WHITE) ea	431L	1.30	
(1/16",REGULAR,BLACK) ea	433R	1.80	
(1/16",REGULAR,WHITE) ea	431R	1.30	
(1/16",SPEC SMALL,BLACK) ea	433S	1.80	
(1/16",SPEC SMALL,WHITE) ea	431S	1.30	
(1/16",VERY LARGE,BLACK) ea	434V	2.25	
(1/16",VERY LARGE,WHITE) ea	432V	1.35	
(1/16",X-LARGE,BLACK) ea	434G	2.25	
(1/16",X-LARGE,WHITE) ea	432G	1.40	
(1/16",X-SMALL,BLACK) ea	433E	1.80	
(1/16",X-SMALL,WHITE) ea	431E	1.30	
(1/8",LARGE,WHITE) ea	731L	1.30	
(1/8",REGULAR,WHITE) ea	731R	1.30	
(1/8",SPEC SMALL,WHITE) ea	731S	1.30	
(1/8",VERY LARGE,WHITE) ea	732V	1.35	
(1/8",X-LARGE,WHITE) ea	732G	1.40	
(1/8",X-SMALL,WHITE) ea	731E	1.30	

PROD/MFR	HRI, UPC,NDC	AWP	SRP
FLEET PREP KIT 3 (Fleet,C.B.)			
KIT,NA (W/SMALL-VOLUME ENEMA)			
ea	01320-2120-10	4.87	
FLEET SOF-LAX (Fleet,C.B.)			
TAB,PO (GELCAPLET)			
100 mg, 60s ea	01320-7516-00	5.60	
FLEET SOF-LAX OVERNIGHT (Fleet,C.B.)			
TAB,PO (GELCAPLET)			
30 mg-100 mg,			
30s ea	01320-7553-00	4.00	
60s ea	01320-7556-00	6.00	
FLETCHER'S CASTORIA (Mentholatum)			
LIQ,PO, 6.5%, 75 ml	10742-0032-10	3.59	
FLEXALL 454 (Chattem)			
GEL,TP, 7%, 60 gm	41167-1601-10	3.24	
120 gm	41167-1601-30	4.86	
240 gm	41167-1601-50	7.68	
FLEXALL 454 MAXIMUM STRENGTH (Chattem)			
GEL,TP, 45 gm	41167-1602-10	3.24	
90 gm	41167-1602-20	4.86	
180 gm	41167-1602-40	7.68	
FLEXALL ULTRA PLUS (Chattem)			
GEL,TP (GREASELESS)			
3.1%-16%-10%,			
60 gm	41167-1603-10	4.06	
120 gm	41167-1603-30	5.88	
FLEXI-SEAL FECAL COLLECTOR (Convatec)			
DEV,NA (W/TAIL CLIPS)			
10s ea	00003-6500-78	78.97	92.91
FLEXI-TRAK ANCHORING (Convatec)			
ACC,NA (LARGE)			
50s ea	00003-0374-49	80.23	94.39
FLEXIBLE FABRIC STRIPS (Chain Drug Marketing)			
BAN,TP (ASSORTED)			
20s ea	63868-0830-30	0.98	
FLEXIFIX TRANSPARENT ADHESIVE FILM (Smith & Nephew)			
TAP,TP (2"X11YD ROLL)			
ea	00223-4151-30	14.84	19.78
(4"X11YD ROLL)			
ea	00223-4151-40	25.98	34.64
FLEXIFLO III PUMP W/SPIKE (Nestle)			
KIT,NA, ea	00065-9017-99	6.54	
FLEXIFLO QUANTUM COLORMARK PUMP (Ross Nutr)			
KIT,NA (W/PIERC PIN & FLUSH BAG)			
ea	70074-5249-00	15.54	
(W/PIERCING PIN)			
ea	70074-5248-80	10.64	
(W/TOP-FILL & FLUSH BAGS)			
ea	70074-5455-10	21.38	
(W/TOP-FILL BAG)			
ea	70074-5454-90	16.49	
FLEXIFLO QUANTUM ENTERAL PUMP (Ross Nutr)			
DEV,NA, ea	70074-5059-70	1380.00	
KIT,NA (40MM)			
ea	70074-5060-30	7.85	
FLEXIFLO QUANTUM PUMP (Ross Nutr)			
KIT,NA (W/PIERC PIN & FLUSH BAG)			
ea	70074-5050-50	13.74	
(W/PIERCING PIN)			
ea	70074-5060-10	8.84	
FLEXIFLO-III COLORMARK PUMP (Ross Nutr)			
KIT,NA (W/PIERCING PIN)			
ea	70074-5248-40	9.06	
FLEXIFLO-III ENTERAL NUTRITION PUMP (Ross Nutr)			
DEV,NA (REFURBISHED)			
ea	70074-5435-10	838.80	
KIT,NA, ea	70074-0007-70	5.26	
(W/PIERCING PIN)			
ea	70074-0007-80	7.26	
FLEXITAINER 500 CONTAINER (Ross Nutr)			
KIT,NA (ENTERAL NUTRITION)			
ea	70074-0006-80	5.23	
FLEXITAINER NUTRITION CONTAINER (Ross Nutr)			
ACC,NA, ea	70074-0006-90	6.26	
FLEXOPLAST (Western Medical)			
BAN,TP (3" ELASTIC ADHESIVE)			
12s ea	GL1003	102.99	
(3" REVERSE ADHESIVE)			
12s ea	GL1003R	102.99	
(4" ELASTIC ADHESIVE)			
12s ea	GL1004	123.31	

PROD/MFR	HRI, UPC,NDC	AWP	SRP
FLEXTEND SKIN BARRIER NON-STERILE (Hollister)			
DEV,NA (8"X8") 3s ea	8801	57.59	65.61
(4"X4") 5s ea	8800	25.24	28.75
FLEXZAN (Bertek)			
DRE,TP (4"X8" SHEETS)			
5s ea	62794-0085-32	36.25	
(8"X8" SHEETS)			
5s ea	62794-0085-64	70.50	
(2"X3" SHEETS)			
10s ea	62794-0085-06	24.00	
(4"X4" SHEETS)			
10s ea	62794-0085-18	32.00	
FLEXZAN EXTRA (Bertek)			
DRE,TP (4"X8")			
5s ea	62794-0091-32	40.60	
(8"X8")			
5s ea	62794-0091-64	77.80	
FLINTSTONES (Bayer Cons)			
CTB,PO, 60s ea	16500-0781-80	4.46	
100s ea	16500-0781-40	6.52	
FLINTSTONES COMPLETE (Bayer Cons)			
CTB,PO, 60s ea	16500-0880-50	6.54	
150s ea	16500-0971-30	10.88	
FLINTSTONES PLUS CALCIUM (Bayer Cons)			
CTB,PO, 60s ea	16500-0770-60	5.67	
FLINTSTONES PLUS EXTRA C (Bayer Cons)			
CTB,PO, 60s ea	16500-0861-90	5.67	
100s ea	16500-0861-30	8.23	
FLINTSTONES W/IRON (Bayer Cons)			
CTB,PO, 60s ea	16500-0790-90	5.67	
100s ea	16500-0790-50	7.53	
FLIP-FLO INCONTINENCE VALVE (Bard Medical)			
ACC,NA (19 OZ,BONUS PACK)			
ea	150419	23.65	29.57
(19 OZ,W/LATEX STRAP)			
ea	150319	6.42	8.02
(32 OZ,BONUS PACK)			
ea	150432	23.65	29.57
FLIPPER HOLDER/RACK (Bernell Corp)			
ACC,NA (HOLDS 12 FLIPPERS)			
ea	BCFH	32.95	
FLIPPER W/FOUR CELLS (Bernell Corp)			
DEV,NA (EMPTY,NO LENSES)			
ea	BC4F	5.50	
FLIPPER W/TWO PAIRS OF LENSES (Bernell Corp)			
DEV,NA (1+/1-,.25-2 DIOPTERS)			
ea	BC1270	16.95	
(1+/1-,2.25-4 DIOPTERS)			
ea	BC1270	17.95	
(ANY COMBINATION)			
ea	BC1270S	29.95	
FLO-GARD PUMP W/SPIKE (Nestle)			
KIT,NA, ea	00065-9600-99	6.54	
FLORICAL (Mericon)			
CAP,PO, 364 mg-8.3 mg,			
100s ea	00394-0102-02	9.90	
500s ea	00394-0102-05	46.85	
TAB,PO, 364 mg-8.3 mg,			
100s ea	00394-0100-02	9.12	
500s ea	00394-0100-05	42.88	
FLORIDA FOAM IMPROVED (Hill Derm)			
LIQ,TP, 240 ml	28105-0069-08	5.31	
FLOW DETECTOR (Abbott Hosp)			
KIT,NA (54")			
ea	00074-1907-25	163.65	
FLU & COLD MEDICINE (Perrigo)			
PDR,PO (LEMON, PACKET)			
650 mg-4 mg-60 mg,			
6s ea	58948-0113-91	2.36	
FLU COLD & COUGH NIGHTTIME (Cardinal Health)			
PKT,PO (MAX. STR.,LEMON)			
6s ea	37205-0331-91	3.52	
(Major)			
PKT,PO (MAX. STR.,A.F.,LEMON)			
6s ea	00904-5461-86	3.45	
FLU MULTI-SYMPTOM MAXIMUM STRENGTH (Eckerd)			
TAB,PO (GELCAP,NON-DROWSY)			
500 mg-15 mg-30 mg,			
24s ea	19458-2676-01	4.08	
FLU SOLUTION (Dolisos)			
PEL,SL, 5s ea	00134-0001-11	4.17	6.95

PROD/MFR	HRI, UPC,NDC	AWP	SRP
FLU SOLUTION PLUS (Dolisos)			
TAB,SL, 45s ea	00134-0566-41	4.17	6.95
FLU, COLD & COUGH MEDICINE (Cardinal Health)			
PDR,PO (PACKET,LEMON)			
6s ea	37205-0330-91	3.19	
FLU-RELIEF (Pfeiffer)			
TAB,PO, 325 mg-2 mg-30 mg,			
36s ea	00927-0324-63	2.94	5.29
FLU/COLD/COUGH MEDICINE (Bergen Brunswig)			
PDS,PO (MAX.STR.,PACKET,LEMON)			
6s ea	24385-0368-91	3.59	4.39
(PACKET,LEMON)			
6s ea	24385-0536-91	3.19	3.99
(Perrigo)			
PDS,PO (PACKET,LEMON)			
6s ea	58948-0555-91	2.39	
FLUORIDE TARTAR CONTROL TOOTHPASTE (Perrigo)			
GEL,TP (FRESHMINT)			
0.15%, 181 gm	58948-0278-20	1.74	
PAS,TP (ORIGINAL)			
192 gm	58948-0233-20	1.74	
FLUORIDE TOOTHPASTE (Perrigo)			
PAS,TP (MINT)			
192 gm	58948-0007-20	1.59	
(REGULAR)			
192 gm	58949-0016-20	1.59	
FLUORIGARD (Colgate Oral)			
SOL,PO, 0.05%, 473 ml	00126-0220-16	3.65	
FO-TI (Botanical Labs.)			
LIQ,PO, 30 ml	41954-0201-90	4.50	8.99
FOAM INVALID RING REPLACEMENT COVER (Hermell)			
ACC,NA (FOR IR7210,12,14)			
ea	IR7210/12/14	2.75	
(FOR IR7211,13,15)			
ea	IR7211/13/15	4.00	
FOAM INVALID RING W/COVER (Hermell)			
DEV,NA (14 1/4"X12 3/4",PLAID)			
ea	IR7080	6.15	
(14 1/4"X12 3/4",POLYCOT)			
ea	IR7070	5.60	
(16 1/4"X13",PLAID)			
ea	IR7020	6.85	
(16 1/4"X13",POLYCOT)			
ea	IR7010	6.25	
(18 1/4"X15 1/4",PLAID)			
ea	IR7050	8.10	
(18 1/4"X15 1/4",POLYCOT)			
ea	IR7040	7.40	
FOAM PAD (Torbot)			
ACC,NA (1/16",LARGE,BLACK)			
ea	433L	1.80	
(1/16",LARGE,WHITE)			
ea	431L	1.30	
(1/16",REGULAR,BLACK)			
ea	433R	1.80	
(1/16",REGULAR,WHITE)			
ea	431R	1.30	
(1/16",SPEC SMALL,BLACK)			
ea	433S	1.80	
(1/16",SPEC SMALL,WHITE)			
ea	431S	1.30	
(1/16",VERY LARGE,BLACK)			
ea	434V	2.25	
(1/16",VERY LARGE,WHITE)			
ea	432V	1.35	
(1/16",X-LARGE,BLACK)			
ea	434G	2.25	
(1/16",X-LARGE,WHITE)			
ea	432G	1.40	
(1/16",X-SMALL,BLACK)			
ea	433E	1.80	
(1/16",X-SMALL,WHITE)			
ea	431E	1.30	
(1/8",LARGE,WHITE)			
ea	731L	1.30	
(1/8",REGULAR,WHITE)			
ea	731R	1.30	
(1/8",SPEC SMALL,WHITE)			
ea	731S	1.30	
(1/8",VERY LARGE,WHITE)			
ea	732V	1.35	
(1/8",X-LARGE,WHITE)			
ea	732G	1.40	
(1/8",X-SMALL,WHITE)			
ea	731E	1.30	

WASHINGTON STATE
Board of Health
ALWAYS WORKING FOR A SAFER AND HEALTHIER WASHINGTON

DATE: June 9, 2010

TO: Washington State Board of Health Members

FROM: Environmental Health Committee:
Karen VanDusen, Keith Higman, and John Austin

SUBJECT: **PETITION FOR RULE MAKING: WATER FLUORIDATION, WAC 246-290-220 AND WAC 246-290-460**

Background and Summary:

On May 11, 2010, the Washington State Board of Health received a petition for rule making in the form of an e-mailed letter from Bill Osmunson, DDS, MPH, president of Washington Action for Safe Water. The petition asks the Board to amend WAC 246-290-460 and WAC 246-290-220, sections in the Board's rules for Group A public water supplies. The first requested amendment would change the allowable concentration of a fluoridation additive from a range specified in rule to a range approved by the U.S. Food and Drug Administration (FDA). The second would change the requirement that drinking water fluoridation additives meet Standard 60 of the National Sanitation Foundation (NSF) and American National Standards Institute (ANSI) to a requirement the additives be approved by FDA under a New Drug Application.

RCW 34.05.330 provides the opportunity for anyone to petition the Board with a request to adopt, amend, or repeal any of its rules. Upon receipt of such a petition, the Board has sixty days to initiate rule making, deny the petition, or address concerns raised by the petitioner by alternate means. Board policy number 2005-001 sets forth the procedures followed by the Board when it receives such a request. According to this policy, the chair may either decide on the request and instruct the executive director to respond or take the request to the full Board for discussion and possible action.

Chair Higman has worked with the Board's Environmental Health (EH) Committee to review the petition and make a recommendation for action. Ned Therien, Board staff, will summarize this rule making petition and EH Committee recommendations for the Board. Please refer to materials behind Tab 16 for additional information.

Recommended Board Action

The Environmental Health Committee recommends the Board adopt the following motion:

> ***Motion**: The Board denies the petition for rule making from Dr. William Osmunson dated May 11, 2010 because the U.S. Food and Drug Administration has a memorandum of understanding with the U.S. Environmental Protection Agency clarifying that the latter agency has authority for regulating tap water.*

Discussion:

The Board has authority under RCW 43.20-050(2) to adopt rules for Group A public water supplies "necessary to assure safe and reliable public drinking water and to protect public health." The Board has further responsibility under RCW 70.142.010 to establish standards for chemical contaminants in public drinking water and "consider the best available scientific information in establishing the standards." The Board has adopted such rules in chapter 246-290 WAC. These rules set both a maximum contaminant level (MCL) for fluoride in drinking water and a lower allowable concentration range if fluoride is added to drinking water. These rules also require that drinking water additives meet NSF/ANSI Standard 60.

RCW 57.08.012 gives each water district the authority to decide whether to ask the electors of the water district to vote on adding fluoride to its tap water. The Board does not appear to have authority to adopt rules related to a water district deciding whether to fluoridate. The Board's authority is to regulate allowable concentration levels and method of approval of water additives.

Dr. Osmunson asked the Board of Pharmacy in 2009 to designate fluoride a poison under chapter RCW 69.38 RCW, Poisons—sales and manufacturing. Dr. Osmunson asserted that fluoridation of public water supplies was the therapeutic administration of fluoride and should be controlled by the laws for legend drugs. The Pharmacy Board's response was that RCW 57.08.012, by being more specific, supersedes the general statutory authority under which it regulates drugs.

For fluoride in drinking water, this Board has adopted the U.S. Environmental Protection Agency (EPA) primary MCL of 4 parts per million (ppm) and secondary MCL of 2 ppm under WAC 246-290-310. These standards are primarily intended for naturally occurring fluoride. The Board has adopted under WAC 246-290-460 an allowable concentration range for artificial fluoridation of public tap water. This range is 0.8–1.3 ppm and is based on the Centers for Disease Control and Prevention (CDC) "optimal" recommended levels to help prevent tooth decay. The Board has adopted under WAC 246-290-220 requirements that drinking water additives meet NSF/ANSI Standard 60. These organizations have developed these standards in association with EPA and the American Water Works Association.

CDC recommends public tap water be fluoridated to an "optimal" target concentration of 0.7–1.2 ppm to help prevent cavities. This is a range of target concentrations and the actual target for a given water supplier would be based on a five-year average of the maximum daily air temperature for the supplier's service area. CDC recommends the concentration be controlled within a range no less than 0.1 ppm below and no more than 0.5 ppm above a supplier's target concentration. For example, if the target concentration is determined to be 0.9 ppm, the control range would be between 0.8 ppm and 1.4 ppm. The Board's standard of 0.8–1.3 ppm in WAC 246-290-460 was set based on different target concentrations across the state, which fall between 0.9 ppm and 1.1 ppm. The allowable range permits a variation of no more than 0.4 above the target concentration for the warmest part of the state. Therefore, the Board's rule is more stringent than the CDC recommendation.

The National Research Council (NRC) Committee on Fluoride in Drinking Water issued a report in 2006 titled *FLUORIDE IN DRINKING WATER: A Scientific Review of EPA's Standards*. It

recommended the MCL for fluoride be lowered from 4 ppm, but did not recommend a new level. It concluded that 2 ppm seemed safe, but might be high enough to cause moderate tooth discoloration (less that 15% of children). It did not specifically address the issue of the CDC-recommended 0.7 - 1.2 ppm concentration range for adding fluoride to a water supply. On March 29, 2010, EPA published in the *Federal Register* an announcement of a six-year review of the MCLs for 71 chemicals, one of which was fluoride. It requested public comments on the reviews by May 28, 2010. EPA's conclusion is that it does not have information at this time that warrants it making a change to the MCL for fluoride, but studies are continuing.

CDC considers drinking water fluoridation one of the top ten great public health achievements of the 20th century. A series of surgeon general statements, the last issued in 2004, have strongly supported fluoridation of community water systems. CDC states that the 2006 National Research Council report supports CDC's recommended "optimal" fluoridation levels as being safe. CDC further states that the most common chemical used for fluoridation, fluorosilicic acid, and related compounds are derived in high purity from the gypsum and phosphate fertilizer manufacturing process. CDC cautions against the overuse of fluoride-containing products to control total intake. In a telephone call between Ned Therien and William Bailey, DDS, MPH, U.S. Public Health Service, on May 21 of this year, Captain Bailey stated that CDC is continually reviewing data regarding the "optimal" level and safety of tap water fluoridation. He also stated that EPA is currently doing risk assessment reviews of dose-response, source contribution, and the potential for carcinogenicity of fluoride.

In 1979, EPA and FDA finalized a memorandum of understanding regarding regulating fluoride levels in drinking water. They concluded the 1974 Safe Drinking Water Act gives EPA authority for regulating chemicals in tap water, while FDA has authority for chemicals in bottled water. Under CFR Title 21, Section 165.110, FDA has set a limit for fluoride added to bottled water in the U.S. of between 0.7 and 1.7 ppm, depending on annual average maximum air temperature for the location where bottled. In a May 21 e-mail exchange between Ned Therien and John V. Kelsey, DDS, MBA, Dental Team Leader, Division of Dermatology and Dental Products, FDA, Dr. Kelsey confirmed that FDA does not have regulatory responsibility for public water supplies, but rather that is the responsibility of EPA. He said if the Board accepted the language proposed in the petition, it effectively would ban public water fluoridation in Washington.

The Washington State Department of Health encourages community water fluoridation as a public health measure. State Health Officer Maxine Hayes, MD, MPH, issued a statement in support of community water fluoridation in 2006. The department's Oral Health Program echoes the recommendations of CDC on community water fluoridation and provides warnings about the overuse of fluoridated products. Many health professional associations support CDC's recommendations on community water fluoridation, including the American Dental Association, American Medical Association, American Academy of Family Physicians, and American Public Health Association.

The EH Committee concludes:

- EPA is the lead federal agency for regulating the maximum levels of contaminants and additives in tap water under the Safe Drinking Water Act.
- FDA has relinquished any authority it might have for regulating fluoride levels in tap water under the memorandum of understanding with EPA.
- The Board cannot direct a federal agency to take action.
- The State Board of Pharmacy has stated it cannot regulate tap water fluoridation under its authority.
- An NRC committee evaluated the scientific evidence of the health effects of fluoride in drinking water and published a report in 2006 that concluded fluoride levels in drinking water below 2 ppm are safe for health.
- EPA announced completion of a review of MCLs in the Federal Register in March 2010 that concluded it did not have evidence to revise the MCL for fluoride.
- EPA will be conducting additional reviews regarding fluoride levels in drinking water.
- EPA recognizes NSF/ANSI Standard 60 as appropriate for the approval of drinking water additives.
- The range of 0.8 ppm to 1.3 ppm fluoride in WAC 246-290-460 is within the control range (0.1 ppm below to 0.5 ppm above) recommended by CDC for target "optimal" concentrations based on average maximum temperatures in various regions of Washington.

The EH Committee recommends the Board deny Dr. Osmunson's petition for rule making on the grounds that FDA has stated it has no intention to regulate fluoride levels or approve additives for tap water. Therefore, adopting the proposed rule changes would, essentially, prohibit all tap water fluoridation in Washington and make Board rules conflict with RCW 57.08.012.

The EH Committee considers much of the discussion in the petition to make points that go beyond the requested rule changes and are not pertinent to its decision. However, the Committee recommends the Department of Health monitor EPA evaluations of safe drinking water levels for fluoride and recommendations from CDC for "optimal" fluoride levels, and that the Department propose rule amendments based on any changes. The Committee further recommends the next time the Department undertakes a major review of chapter 246-290 WAC, it consider proposing the word "optimal" in section 460(3) be changed to a phrase such as "generally regarded as safe." The Committee further recommends the Board continue to review legal points raised in the petition concerning state law and Attorney General opinions.

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Allergic Reactions to Fluoride

G. L. WALDBOTT, M.D.

The capacity of halogens, especially iodides and bromides, to induce allergic reactions has been demonstrated by Yamasaki[1] and by Mitsuteru Ishikawa,[2] who sensitized guinea pigs and rabbits to these halogens. They induced cutaneous sensitivity, anaphylactic shock, positive Dale reactions, and histological and hematological changes indicative of hypersensitivity. Allergic manifestations due to iodides, especially asthmatic attacks, dermatitis and edema of the salivary glands, are not uncommon in an allergist's practice. Nevertheless, allergy to halogens is rarely reported in the medical literature, mainly because clinical and laboratory tests to establish allergy to drugs, especially to simple chemicals, are not always reliable.

Fluoride (F-), by far the most reactive of the halogens and indeed the most reactive of all kations, has received very little attention as a possible sensitizer. This is not surprising because until recently F- has played an insignificant role in everyday life. To this day, it is not generally recognized as an important ingredient of food, water and drugs, or as an air contaminant. Furthermore, because of its unusually strong reactivity, chemical analysis for F- has been fraught with difficulties and subject to wide errors. Even today few hospitals in the U.S.A. are equipped to do F- analyses, and few clinicians have taken cognizance of F-'s role as a reactive electrolyte present in everybody's system. All these factors have retarded clinical research on fluoride's effect.

Saito and Kuratate[3] and Mitsuteru Ishikawa[4] obtained positive skin reactions in guinea pigs and rabbits. Rabbits with a 1:100 aqueous solution of sodium fluoride. Twenty-four hours following the injection, skin-sensitizing antibodies to the fluoride solution were present in blood serum and in liver tissue.

My attention was first drawn to F- as a source of allergic reactions when patients referred to me for allergic studies exhibited evidence of chronic F-intoxication from drinking water.[5, 6, 7, 8] Two distinct groups of manifestations were encountered: 1. Symptoms indicative of subacute and chronic intoxication unrelated to allergy. 2. Allergic reactions, particularly urticaria, dermatitis, stomatitis and allergic nasal disease. These manifestations are recorded in Table 1 which was presented in another publication.[9]

Properties of Fluoride. The element fluorine is a pale yellow gas. It condenses to liquid at 127° C and freezes at −250° C. It rarely remains in pure gaseous form because of its strong tendency to combine with other elements.

The fluoride ion, as a part of F- compounds, is very widespread in nature. It is estimated as the thirteenth in abundance among the elements of the earth. Pharmacologically significant is its strong affinity to calcium and to most metals with which it can enter into highly complex compounds. This accounts for its ability to interfere with the calcium-phosphorus metabolism and with

TABLE I

Manifestations of Fluoride Intoxication (Other than Skeletal and Dental Changes)

Kind	Neuromuscular	Cardiorespiratory	Gastrointestinal	Urinary	Miscellaneous
Acute intoxication*	Paresthesias; muscular pains; pareses; convulsions; muscular fibrillation; myasthenia; cephalgia; carpopedal spasms	Dyspnea; cyanosis; perspiration; shock; conjunctivitis †; rhinitis; pneumonitis †; pulmonary edema	Enteritis; hematemesis; diarrhea; salivation	Acute nephritis	Urticaria; petechial hemorrhage; hypersalivation
Chronic intoxication in cryolite workers*	Cephalgia; vertigo; lethargy; paresthesias	Dyspnea; palpitation; cough; expectoration; tachycardia	Acute and chronic gastric distress; epigastric pain; vomiting; spastic constipation; diarrhea; dysphagia		Dermatitis; cachexia
From Drinking Water* Reported by Others	Paresthesias; muscular pain; paralysis; auditory disturbances; hyperreflexia; cephalgia	Costochondral pain; tachycardia; cardiac damage inhibition of thoracic movement	Spastic pain in upper G.I. tract; anorexia; spastic constipation; diarrhea; hepatomegalie; splenomegalie	Pyelocystitis	Arthritic changes; suffusions; petechal hemorrhages; normocytic hypochromic anemia
Own Data	Cephalgia; paresthesias; paresis; convulsions; muscular fibrillation; vertigo; visual disturbances; mental deterioration	Dyspnea; costochondral pain; perspiration; tachycardia	Vomiting; spastic pain; constipation alternating with diarrhea; colitis; stomatitis; salivation	Pyelitis; cystitis; urethritis; dysuria; polydipsia	Dermatitis; urticaria; petechial hemorrhages; suffusions

* In all categories: Pain and stiffness in joints, especially in lower spine.

† In intoxication from inhaled F^- compounds.

TABLE II

Some Uses of Fluoride Compounds

In Manufacturing	In Drugs	In Other Industries
Aluminum	Steroids	Welding (Flux)
Steel	Tranquilizers	Cleaning
Enamel	Diuretics	Refrigerant
Pottery	Antimetabolites	Preserving Wood
Glass	Anticancer	Hardening Cement
Bricks	Antihistamines	Aerosol Propellant
Phosphate Fertilizer	Anesthetics	Optical
Beryllium	Androgens	Rust Removal
Tantalum	Estrogens	Lubricant
Niobium	Calcium-Phosphorus (Contaminant)	Oil Refining
	Caries prevention	Plastics
		Separation of Uranium Isotopes
		Missile Propulsion

the function of many enzymes. The latter are dependent for their activity on the presence of metals, especially magnesium and manganese.

Uses of Fluoride. Formerly, humans were exposed to fluoride mainly through its extensive use as an insecticide and rodent exterminator. During the past fifty years it has also received attention as an occupational hazard because it is a by-product of many industrial operations. Among the numerous processes in which its compounds have been employed since the beginning of the twentieth century are manufacturing of aluminum, superphosphate fertilizer, steel, magnesium, enamel, pottery, glass, bricks, beryllium, zirconium, tantalum and niobium. Fluorides are also used in welding, in the cleaning industry and as a preservative. During the 1930's, F- compounds began to enter into the refrigerant, aerosol, optical, lubricant and plastic fields. During the last two decades they have been used for separation of uranium isotopes by gaseous diffusion. Currently F- compounds are used as propellants in our missile program and in the manufacture of steroids, tranquilizers, diuretics, antimetabolites, anticancer drugs, antihistaminics, anesthetics, androgens, estrogens and for prevention of dental caries (Table II).

Burning coal and oil liberate F-. Smokestacks of industrial plants which eject both gaseous and particulate F- contribute materially to air contamination in industrial cities. Because of its ubiquitous presence in food[10] (Table III), air, and water (Table IV), F-'s role in human pathology has become increasingly significant.

*Fluoride Metabolism**. When F- is administered orally, it is absorbed through the upper gastrointestinal tract. It reaches the blood stream within a few minutes. When inhaled, it promptly reaches the blood stream through the respiratory tract. It is transported by the albumen portion of the blood

* For additional bibliography, see Reference 17.

TABLE III

Occurrence of Fluoride In Food

From Vegetable Kingdom		From Animal Kingdom		From Air Contaminated Areas	
	p.p.m.		*p.p.m.*		*p.p.m.*
Tea	3.2–400.0	Bone Meal	2.46–770.0	Peach	3.2–21.9
Grain	About 1.0	Meat	0.2–2.0	Apples	2.0–4.5
Vegetables	0.10–0.30	Dry	3.3–7.7	Orange Juice	3.12
Potatoes	0.4 and above	Fish	1.0–8.0	Carrots	5.0
Spinach	0.1–0.44	Dry	Up to 84.5	Spinach	16.0–20.3
Citrus Fruit	0.12–03.6	Milk	0.09–0.35	Celery Leaves	77.0–135.0
Noncitrus	0.12–0.8	Cheese	0.16–1.31	Milk	3.2
Nuts	0.3–1.45	Egg	0.2–0.4		
Wine	0.05–0.3				
Beer	0.2–1.2				

TABLE IV

Occurrence of Fluoride

In Water		In Air‡		In Drugs	
	p.p.m.		*p.p.m.*		*p.p.m.*
Sea water	1.0–1.4	Cincinnati (1957)	Up to 0.0012	Halothane	28.9%
Persian Gulf	8.72	Baltimore (1950)		Halotestin 5 mg	0.290
Great Salt Lake	0.5–2.0	Industrial area	0.018	Kenacort } 4 mg	0.186
Lake Nakura, Kenya	2800	Residential area	0.008	Aristocort }	
Rain water	Up to 3.4	San Francisco	0.0003	Stelazine 5 mg	0.699
Well water	Usually less than 0.5* †	Los Angeles (1948)	0.008	Decadron 0.75 mg	0.035
		Venice, Italy (1956)	Up to 1.158	Alujel 650 mg	0.031
River water	0.0–25 and more			Bone salts:	
				Therazyma-cap§	0.1
				Bone-All§	0.215
				Vio-Bone§	0.286

* Maximum allowable limit: In warm climate 1.4; In cool climate 2.4.

† Higher levels in areas of Western Texas, Arizona, Tennessee, Arkansas and South Dakota.

‡ Much airborne F- is derived from combustion of coal (F- content 50–200 p.p.m.).

§ According to Feltman, R. and Kosel, G.: Northwest Med. 55: 663, 1956.

plasma into the intracellular fluid. Excretion takes place mainly through the kidneys, less through the bowels, salivary and sweat glands.

Numerous factors influence the manner in which F- is metabolized, such as degree of skeletal saturation with F-, age, sex, state of nutrition and state of a person's health, food habits, and especially the channels through which the F- ion enters the system. For instance, less F- is absorbed and stored in the system when F- is present in solid food than when in water;

less when the F- ion is accompanied by calcium, aluminum and phosphates. On the other hand, addition of fat to the diet and the presence of molybdenum in food enhance F- absorption.

During the first ten years of life, most storage of F- takes place in teeth and bones. Once the permanent teeth have developed, bones are the major site of storage. Normally soft tissue organs contain little F-, usually less than 1 ppm. However, under certain conditions relatively large accumulations of F- have been reported in skin, kidneys, bladder[11] and in the gastrointestinal tract.[12] Among soft tissues, the aorta contains the highest concentration.[13] Our studies have shown as much as 158 ppm of F- in calcified blood vessels.[14] There is increasing evidence that storage of F- in the system is progressive throughout life.

In contrast to a wealth of statistical and biochemical data, clinical research on how F- affects the human body is sparse. Among adverse effects from persistent F- intake, the defect of dental enamel called mottling has been most thoroughly explored. It occurs solely in persons who have consumed F- during the tooth-forming ages, namely up to age ten. Other literature deals with acute intoxication due to accidental exposure to airborne F- and to ingestion of F- either accidentally or for homicidal or suicidal purposes. This phase of F- effect was recently reviewed by Waldbott[15].

In 1939 the Danish biochemist and physician, Kaj Roholm, presented a wealth of data in a remarkable book[16] which even today constitutes the most exhaustive source of knowledge on how F- affects humans. It is based mainly on his own studies of industrial fluorosis in cryolite workers. More recently reports on chronic intoxication from drinking water containing 0.8 to 18 ppm (mg/liter) F- in water naturally have issued from India, Argentina, Japan, Italy, North Africa—where the disease is endemic.[9]

Characteristic of this disease are the changes in the bones, namely increased bone density alternating with softening, mainly in the pelvic and vertebral bones. In long bones, there is new growth of bone substance at the periosteal and endosteal surfaces. Eventually this leads to grotesque-appearing osteophytes and to extensive calcification of ligaments, tendons and joints. In the most advanced stage of the disease ankylosis of the spine, impaired expansion of the thoracic cage and crippling arthritis occur. This disease has been described where F- occurs in water naturally at concentrations as low as 0.8 ppm.

Only recently[17] has attention been directed to soft tissue damage indicated by the occurrence of gastritis, colitis and lower urinary tract disease. Paresthesias and paresis in arms and legs, cephalalgia, changes in the retina, and arthritis, especially in the lower spine, have been described.

Although allergists are aware of allergic manifestations in the mouth due to F- dentifrices and locally applied F- solutions, relatively few reports on allergy to F- are available in the literature. These reports concern urticaria, dermatitis and stomatitis.

Urticaria

During acute F- intoxication, urticaria has been reported by Lidbeck, Hill and Beeman,[18] Fischer[19] and Geiger.[20] In 1959 Waldbott[6] reported six cases of urticaria due to fluoridated water. In all these cases urticaria constituted a part of the overall clinical picture of chronic F- intoxication, being accompanied by paresthesias and paresis of hands and legs, cephalalgia, arthritis in the lower spine, gastrointestinal and urinary disturbances. In two patients the hives were accompanied by allergic nasal disease, in another by dermatitis. There was evidence of retention of F- in the system of these patients; the 24-hour urinary excretion following a test dose of F- (6.8 mg) was approxi-

TABLE V

Fluoride in Skin

Date	Name, Age & Sex	Diagnosis	Fluoride in Tissue	
			Normal in ppm	Diseased in ppm
6/7/60	Mrs. D. W. 33 F	Atopic Dermatitis	10.54	17.08
4/16/61	Mr. R. A. 70 M	Contact Dermatitis	0	36.7
4/2/62	Mr. C. B. 41 M	Fixed Drug Eruption	242.4	301.0
12/30/59	Mr. V. M. 43 M	Atopic Dermatitis	—	0
4/14/60	Mrs. W. S. 47 F	Atopic Dermatitis	0	0
2/6/63	Mrs. P. V. 69 F	Atopic Dermatitis	0	0
2/22/63	Mr. J. McI. 51 M	Intraepidermal Carcinoma (Bowen's Disease)	0	0
3/30/60	Mrs. R. B. 65 F	Papilloma*	8.78	78.12
6/5/61	Mrs. R. B. 66 F	Papilloma*	—	3.82
4/26/60	Mr. V. S. 20 M	Acne	—	4.75
5/24/62	Miss M. C. 66 F	Papilloma†	0	9.54
7/12/60	Mrs. D. F. 37 F	Psoriasis	0	0
8/4/60	Miss M. P. 10 F	Scleroderma	0	0
9/21/60	Mr. D. S. 33 M	Psoriasis	0	0
2/22/63	Mr. T. M. 50 M	Psoriasis	0	0

* Case of Hyperostosis Frontalis.

† Bronchial Asthma.

mately one-half of that in eighteen normal individuals who were used as controls.

One case (Mrs. P.O., aged 40) was of particular interest, because during the whole course of her illness the patient was unaware of the presence of F- in drinking water. Upon her moving from one community to another, urticaria either disappeared entirely or recurred in full force, depending on whether or not the community was fluoridated. When her attention was eventually directed to F- in drinking water, avoidance of fluoridated water for cooking and drinking cured the disease permanently. Subsequently the relation of this patient's urticaria to fluoride in water was substantiated by a double blind test:

On 4/26/58 the patient was given three identical bottles* containing water, labelled 1, 2 and 3. Two bottles contained plain distilled water, a third bottle 1 mg of F- (2.2 mg NaF) per tablespoon, the daily dose recommended for teeth. The patient was instructed to take one tablespoon daily before breakfast from bottle №1 for one week, from bottle №2 for the second week and from bottle №3 for the third week. Neither she nor her attending physician (Dr. C.J.S.) was aware which bottle contained F-. The urticaria reappeared on the third day of using the F- solution.

Another case of chronic urticaria due to F- water has recently come under my observation:

Mrs. H.P., 48 years old, consulted me on April 26, 1963, because of persistent generalized urticaria which began within three weeks after she had moved to fluoridated Highland Park, Michigan, in 1959. In recent weeks this condition was accompanied by allergic nasal and conjunctival symptoms. The history revealed a familial, but no personal, background of allergy. The patient had always been in perfect health, except for a small diverticulum in the fundus of the stomach. There was no evidence of focal infection nor of sensitivity to aspirin or penicillin, which are common causes of hives. Intradermal skin tests to foods and inhalants were inconclusive. During the previous summer the urticaria had been aggravated for a few weeks by unusually strong reactions to mosquito bites. This condition was overcome by a short course of hyposensitization with mosquito extract; however, the daily episodes of urticaria persisted. Antihistaminics and steroids provided only temporary relief.

While hospitalized on 12/17/63 at Women's Hospital, where she consumed practically fluoride-free (0.1 ppm) water, the urticaria subsided. C.B.C., blood calcium, phosphorus, liver and kidney function tests, cholecystograms, were unrevealing. Twenty-four-hour urinary F- excretion was 1.15 mg. Within 24 hours after her discharge and resumption of Highland Park drinking water, the urticaria recurred. An intradermal skin test with a 1:100 dilution of a 1% aqueous solution of NaF gave a 3-plus wheal reaction. This was followed by a generalized outbreak of urticaria within ten minutes. Control tests with a 1% solution of sodium bromide and of sodium iodide were negative. The

* Plastic bottles must be used, since silicate in glass bottles and metals in metal containers combine with F-.

patient was advised to use distilled water for cooking and drinking and avoid foods high in F- (tea, seafood). The hives improved promptly and eventually disappeared entirely.

On 2/20/64 she was given a double blind test in the same manner as in the previously described case. Urticaria recurred within two days of taking water from bottle #2 which contained F-. The patient has been symptom-free since that time.

In 1959, Spencer[21] encountered a 38-year-old white female with an acute attack of angioneurotic edema of the lower lip and the gums. This condition was brought on within half an hour after her dentist had applied to her teeth and gums a solution of 8% stannous fluoride. It was promptly relieved by 1 cc of SusPhrin subcutaneously and irrigation of the mouth with saline solution.

Shea[22] observed two cases of chronic urticaria in children which he considered due to fluoride toothpaste.

This type of case must be differentiated from an acute inflammatory reaction, due to F-, of the buccal mucosa, which does not respond to epinephrine.

S.F., a three-year-old girl, was admitted to Le Bonheur Children's Hospital, Memphis, Tennessee, on 8/29/61, because of an unusually severe inflammation of the mucosa of the lips, tongue and mouth. It was accompanied by marked facial edema, fever and pain. The edema extended into the base of the tongue and the throat and was associated with pain. This condition started shortly after application of a solution of stannous fluoride by the dentist. Two physicians, Drs. J.N.E. and E.L.W., and two dentists, Drs. A.J.F. and T.C.P., who attended this patient, concurred in the opinion that this reaction was due to stannous fluoride. The inflammation subsided gradually so that the patient could be discharged on the fourth hospital day. The consulting dentist (Dr. A.J.F.) noted in the hospital record that he had seen two similar cases of gingival edema following the same procedure.

Dermatitis

In 1948 Abelson[23] reported a typical contact dermatitis with vesiculopapular pruritic lesions on the first and second phalanges and the thumb of the right hand of a dentist. It occurred immediately upon application of a 2% solution of NaF to his patient's teeth. I have observed[24] the pattern of dermatitis on the fingers described by Abelson repeatedly in dentists, contact-sensitive to medication applied to teeth. A 4-plus positive patch test reaction to sodium fluoride was obtained. Monocaine applied simultaneously with the F- solution as a patch test gave a negative reaction.

Fregert and Moller[25] reported contact dermatitis on the eyes from F- present in (isopropoxy-phosphoryl) eye drops. A dilution of 1:10,000 in olive oil reproduced the reaction; applications of peanut oil and olive oil as controls failed to induce dermatitis. Among a series of other alkylphosphate compounds, three gave cross-reactions on patch testing. The authors concluded

that the structural requirements for cross-sensitization between the organophosphorus compounds were the F- moiety, the central phosphorus atom, and two symmetric and slightly asymmetric aliphatic chains.

Two Russian clinicians, Nekam and Szeplaki,[26] described contact dermatitis in a nineteen-year-old working woman in a glass factory, due to HF which had dropped on her hand. They considered the resulting dermatitis an allergic response to hydrofluoric acid.

In a Czechoslovakian aluminum factory, Horky et al[27] observed among 138 women workers a 20.7% incidence of dermatitis of the external genitalia. They attributed the lesions to F-, a by-product of aluminum manufacturing.

In the AMA Journal[28] reference is made to dermatitis in magnesium workers due to F- (borofluoride) which is used in the smelting process. Magnesium itself was not held responsible for the lesions.

In a 3½-year-old girl, Homan[29] reported a contact dermatitis on the left cheek. It developed shortly after the child had played with fluoridated toothpaste and had covered the involved area with the paste. The child has also experienced stomatitis from the same toothpaste. Patch tests with this and a nonfluoride toothpaste as control, as well as a 2% aqueous solution of stannous fluoride, incriminated the F- in the toothpaste.

Feltman and Kosel[30] noted atopic dermatitis, urticaria, epigastric distress, emesis and headache in 1% of 672 pregnant women and children to whom they had administered F- tablets as a preventive of dental caries.

Waldbott[7] reported a scaly, erythematous, pruritic lesion of 3½ months' duration on both thighs extending into the suprapubic areas in a twenty-year-old woman. The dermatitis was associated with systemic manifestations of chronic fluoride intoxication, namely headaches, visual disturbances, vertigo, arthritis in the lower spine, and paresthesias in arms and legs. It subsided without treatment while the patient was under observation in nonfluoridated Detroit. After she had been symptom-free the dermatitis recurred at the same site with papulous, vesicular lesions and intense pruritus within an hour after the patient had received 6.8 mg of F- in 300 cc of water as a test dose. A placebo test consisting of 300 cc of distilled water given prior to the test had produced no ill effect.

In assessing these cases it is evident that F- can induce different kinds of allergic dermatitis. Abelson's case represents a typical instance of contact dermatitis whereas the cases reported by Feltman and Kosel conform with the description of atopic dermatitis. The above-described case must be classified as a drug eruption of the bromoderma and iododerma type.

Since some ingested F- is excreted through the sweat glands, the skin must be considered a potential site of lesions in susceptible persons. I was unable to obtain biopsy material of the skin for F- analyses in the above case. However, skin biopsy specimens from other individuals who had experienced no adverse effects from F- intake were analyzed for F- according to the Official Methods of Analysis of the Association of Agricultural Chemists,

Eighth Edition, 1955*, (Table IV). This table reveals that usually the skin contains little or no F-. Under certain conditions, however, F- levels can be extraordinarily high, as much as 301 ppm as in Case C.B. The highest F-level in the skin recorded previously in the literature by Herman et al[11] was 290 ppm in a person with nephrolithiasis. The factors responsible for such unusually high accumulation of F- in the skin are currently not known.

Stomatitis

In my practice aphthous stomatitis and ulcers of the mouth are not uncommon in persons using fluoride dentifrices and in children whose dentists apply sodium fluoride (2%) or stannous fluoride (8%) in an aqueous solution to the teeth. Inhalation of fluoride fumes, especially among welders and persons inbibing fluoridated water, may induce stomatitis.

Experimentally, stomatitis has been produced in guinea pigs, rats and rabbits by Stokinger[31] and by Machle[32] following exposure to fluoride fumes.

Douglas[33] presented an account of stomatitis in 133 cases from F- containing dentifrices. The patients' ages ranged from 3½ to 92 years. His series included one family of six and another of four, every member of which was adversely affected by fluoride toothpaste. Several of these patients had gastrointestinal disturbances. All were refractory to antibiotic therapy and to local medication. The lesions cleared up upon their changing to a nonfluoride toothpaste. In 32 patients the stomatitis was reproduced by applying the F- dentifrice, in some as often as six times.

In a given case it is difficult to determine whether the lesions are allergic in nature or due to the irritation by F- compounds. In the following case of stomatitis, eosinophilia present in the lesions suggested an allergic origin:

Mrs. L.C.H., 62 years old, white, developed an ulcer in the mouth within three days after she started using stannous fluoride toothpaste. During the following ten days, additional lesions developed throughout the oral mucosa accompanied by severe spastic pains throughout the whole abdomen, flatulence, diarrhea and dryness in mouth, nose and throat. These symptoms persisted for several weeks and were followed by a febrile colitis. Diagnostic studies including gastrointestinal x-rays by an internist (Dr. R.J.E.) were unrevealing. Elimination of fluoride toothpaste on the advice of her dentist (Dr. W.H.P.) caused the condition to gradually disappear.

Patch tests with a 1% aqueous solution of NaF and several toothpastes, including one containing stannous fluoride, were negative. On 9/14/56 the patient was given an intradermal test with 1/10 cc of a 1% aqueous solution of NaF. Within 15 minutes, an erythema developed at the site of injection extending along the lymph channels toward the axilla. It was associated with paresthesias in mouth and both arms and followed by severe pains in the lower abdomen.

* Fluoride is separated from tissue by the Willard-Winter double distillation technique. H. H. Willard and O. B. Winter, *Anal. Chem. 5:*7 (1933) and titrated by the Williams procedure H. A. Williams, *Analyst 71:*175 (1946), as modified by Smith and Gardner (F. A. Smith and D. E. Gardner, *Journ. Dent. Research 30:*182, (1951).

On 12/13/56, saline solution was applied with a cotton swab beneath her tongue without ill effect. Thirty minutes later a cotton swab soaked in a 1% aqueous solution of NaF was applied in the same manner. Within five minutes a hyperemic, edematous, intensely pruritic lesion developed in the test area which extended into a large portion of the oral mucosa. A smear of the mucus from the area showed marked eosinophilia.

Several allergists have related similar experiences to me without recording details. Spencer,[34] for instance, encountered two instances of aphthous stomatitis and ulceration of the tongue due to stannous fluoride toothpaste. The lesions subsided upon using nonfluoride toothpaste. In one of them, a 37-year-old male, a test application of fluoride toothpaste reproduced a recurrence of a lesion one year after its use had been discontinued. Prompt abandonment of the experiment upon the initial sign of inflammation prevented ulceration.

Stomatitis from industrial hazards due to inhalation of F- is rarely recognized by the medical profession. The proof of the relation to F- is difficult because at the time when the lesions are at their height they may no longer show F- in the biopsy specimen.

Judging by my own experience and by reports of others, it seems that patch tests are not necessarily positive in these cases. On the other hand, a local application of the material to the buccal mucosa for only a few minutes results in irritation of the mucous membranes, occasionally in ulceration. Whether or not the lesions are related to the magnitude of F- excreted by the salivary glands is not known at present.

Van Hoogenhuize[35] related the case of a 45-year-old welder with periodic skin eruptions and ulcers of the mouth of twelve years' duration. The skin lesions were suggestive of erythema multiforme. The fluxes used in welding contained F-. A patch test caused a severe local reaction with subsequent ulcerations. This case is undergoing further studies.

A remarkable similarity in the description of this case is noted with one related in the J.A.M.A. *188*:836, June 1, 1964, by an anonymous physician, in a welder exposed for twelve years to fumes from welding flux. He exhibited stomatitis and erythema multiforme.

TABLE VI

Data on F Analyses obtained in Case V. E.

	p.p.m.
Dust from place of work	89.2
Welding flux	2.1
Tartar of teeth	43.9
Wall tile adhesive	62.5
Biopsy specimen of buccal mucosa	0*
Saliva (single specimen)	0*
Urine	0.25*

* Specimens of saliva, buccal mucosa and 24-hour urine could not be obtained during or shortly after the acute episode. These values were 0 during a symptom-free interval.

The following case of stomatitis due to fluoride was encountered in my practice:

Mr. V.E., aged 52, an automobile metal finisher seen on 10/2/59, presented a history of recurrent ulcers of the mouth which began in 1956. The episodes started with localized swelling and soreness of the tongue, lips or buccal mucosa, involving at times the whole oral cavity. They were associated with such constitutional symptoms as general malaise, paresthesias in arms and legs and severe unilateral cephalalgia of the migraine type. On one occasion there was evidence of an acute nephritis with hyaline and coarse granular casts in the urine, and white counts up to 15,000. The onset and recurrences of the condition were identified with inhalation of welding fumes and, on one occasion, with inhalation of dust upon tearing down wall tile which contained 62.5 p.p.m. of F-.

Histologically the ulcers showed granulation tissue which could not be identified with any specific disease. Cultures and smears of the lips and tongue revealed no unusual bacterial flora, especially no Vincent's organism. Allergic studies were unrevealing. Other data on this case are presented in table 6.

Intradermal skin tests on 10/2/59 with a 1% sodium fluoride solution showed a 4-plus wheal reaction. Control tests with 1% sodium bromide and 1% sodium iodide were negative. On 4/2/60 the skin test was repeated with the same result. On both occasions, the tests reproduced the above systemic symptoms and the lesions in the mouth. Patch tests with sodium fluoride, sodium bromide and sodium iodide were negative.

Discussion

Some F- compounds are very irritating. In contact with fluids in an acid medium such as gastric juice they tend to induce HF[16] which has a corrosive action. In appraising reactions to F-, therefore, it is necessary to distinguish between the toxic action of F- and allergic sensitivity. The degree of tissue damage from the toxic action of F- depends on numerous factors, principally the dose of the fluoride ion, the duration of the contact with the involved tissue, the pH of the intracellular and extracellular fluids, the presence of calcium, magnesium and other metals. True allergic reactions, on the other hand, can result from relatively insignificant doses and from short exposures. The presence of such allergic symptoms as urticaria, vasomotor rhinitis, dermatitis and eosinophilia, a prompt response to epinephrine and, occasionally, positive skin and patch test reactions, point to allergy.

As an illustration Waldbott[17] reported vasomotor rhinitis, urticaria, severe gastric and intestinal spasms and lower urinary tract disease in a 62-year-old woman, which was precipitated repeatedly by such minute doses as are present in fluoridated water with a fluoride intake of about 1 to 2 mg a day, by fluoride in toothpaste, and by an F- containing tranquilizer. The typical allergic appearance of the nasal mucosa, eosinophilia, and an allergic wheal response to an intradermal injection of as little as 0.1 mg of NaF indicated that this case represented true allergy to F-.

On the other hand, so-called "asthmatic" attacks due to inhalation of airborne F- compounds have been described by Evang[36] as an occupational disease, by Roholm[16] in cryolite workers and by Storm Van Leuwen[37]. Van Leuwen concluded upon investigating the Meuse valley air pollution disaster in 1930 that "asthma" and upper respiratory infections were due mainly to F-, particularly to hydrogen fluoride and silicofluoride. It was not determined whether the respiratory diseases described by the three authors represented true allergic asthma or were merely the result of the traumatic action of the irritating F- compounds—gases, vapors and particulae—upon the mucosa of the respiratory tract, as encountered in experimental animals exposed to inhalation of F-.

Summary

With the expanding use of fluoride compounds in industry, in household articles, in pharmaceuticals and in caries prevention, allergy to the fluoride ion—one of the most reactive ions in existence—must be anticipated.

Hypersensitivity to fluoride has been produced experimentally. Clinical data on urticaria, allergic stomatitis and dermatitis due to fluoride are presented from the records of the writer and from those of other allergists. Three types of dermatitis have been encountered, namely contact dermatitis, atopic dermatitis and fixed drug eruptions. Ingestion, inhalation, application of fluoride to teeth, and contact of fluoride with the skin can account for allergic manifestations.

It may be difficult to establish whether a reaction represents true allergy or is due to the irritating action of fluoride compounds upon mucous membranes. The presence of allergic edema, tissue and blood eosinophilia, prompt response to epinephrine, and positive intradermal and patch test reactions aid in the differentiation.

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WASHINGTON ACTION FOR SAFE WATER

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PETITION FOR RULE MAKING (#5): WATER FLUORIDATION,

This petition relates to the intent of adding fluoride to public water systems, fluoridation. In response to the question of the intent for fluoridation, the Board of Health responded, "This agency, therefore, is not in possession of any records related to the Board's "purpose and intent for supporting the addition of fluoride to public drinking water."[1]

The first step in regulating a substance is a clear and concise understand of the intent of use of the substance.

I. PETITION TO IMPROVE AND PROTECT THE PUBLIC'S HEALTH WITH RULE MAKING ON FLUORIDATION (FLUORIDE ADDED TO PUBLIC DRINKING WATER)

This petition is made in the interest of a safer and healthier Washington.

II. WASHINGTON STATE BOARD OF HEALTH'S AUTHORITY TO REGULATE THE CONCENTRATION OF FLUORIDE ADDED TO PUBLIC WATER

Pursuant to RCW 43.20.50 (1) "The state board of health shall provide a forum for the development of public health policy in Washington state. . . ." RCW 43.20.50 (2) "In order to protect public health, the state board of health shall: (a) Adopt rules for group A public water systems . . . necessary to assure safe and reliable public drinking water and to protect the public health. Such rules shall establish requirements regarding: . . . (ii) Drinking water quality standards . . . (b) Adopt rules as necessary for group B public water systems . . ." And further under RCW 70.142.010 to establish standards for chemical contaminants in public drinking water and "consider the best available scientific information establishing the standards."

III. INTENT OF USE

A. The only intent of fluoridation is to prevent or mitigate dental caries, dental decay.

1. **The FDA**:

"How is a product's intended use established?

Intended use may be established in a number of ways. Among them are:

- **· Claims stated on the product labeling, in advertising, on the Internet, or in other promotional materials.** Certain claims may cause a product to be considered a drug, even if the product is marketed as if it were a cosmetic. Such claims establish the product as a drug because the intended use is to treat or prevent disease or otherwise affect the structure or functions of the human body. Some examples are claims that products will restore hair growth, reduce cellulite, treat varicose veins, or revitalize cells.
- **Consumer perception, which may be established through the product's reputation.** This means asking why the consumer is buying it and what the consumer expects it to do.
- **Ingredients that may cause a product to be considered a drug because they have a well known (to the public and industry) therapeutic use.** An example is fluoride in toothpaste."[2]

2. **The Courts**: The Kaul Court[3] agreed with the trial court's finding

> *"That the addition of fluoride to the Chehalis water supply is intended solely for use in prevention of tooth decay primarily in children up to 14 years of age, and particularly between the ages of 6 and 14 and will prevent some tooth decay in some children." And that "…chlorine is added to water to affect either bacteria or plant life in the water, while fluoride has no effect upon the water or upon the plant life*

in the water but remains free in the water and is artificially added solely for the effect it has on the individual drinking the water." [4]

"Specifically the initiatives would ban certain optional additives, such as fluoride, which has been shown to prevent dental disease.[5]

3. **Federal Level,**

The CDC: ***"****Ingestion of fluoride is not likely to reduce tooth decay."*[6] *"For 65 years, community water fluoridation has been a safe and healthy way to effectively prevent tooth decay."*[7] *". . . fluoride prevents dental caries predominately after eruption of the tooth into the mouth, and its actions primarily are topical for both adults and children…"*[8]

The NIDR: *"An analysis of national survey data collected by the National Institute of Dental Research (NIDR) concludes that children who live in areas of the U.S. where the water supplies are fluoridated have tooth decay rates nearly identical with those who live in nonfluoridated areas"*[9]

The NIH: Evidence for fluoridation preventing disease is incomplete.[10]

4. **State Level**,

Washington State Department of Health *"Community water fluoridation is the process of adjusting the natural fluoride concentration of fluoride-deficient water to a level recommended for prevention of dental caries, approximately 1 ppm (one part per million)."*[11]

The Washington State Dental Association states, *"The ADA and WSDA support water fluoridation to prevent dental disease"*[12]

The Washington Dental Foundation paid about $433,000 for the Port Angeles fluoridation system. There is no indication the Foundation's intent is to poison people or disinfect the water.

5. **Researchers and Publications**

"By 1981, it was therefore possible to propose a paradigm shift concerning the cariostatic mechanisms of fluorides in which it was argued that the predominant, if not the entire, explanation for how fluoride controls caries lesion development lies in its topical effect on de- and remineralization processes taking place at the interface between the tooth surface and the oral fluids. This concept has gained wide acceptance... With today's knowledge about the mechanisms of fluoride action, it is important to appreciate that, as fluoride exerts its predominant effect... at the tooth/oral fluid interface, it is possible for maximum caries protection to be

obtained without the ingestion of fluorides to any significant extent."
SOURCE: Aoba T, Fejerskov O. (2002). *Critical Review of Oral Biology and Medicine* 13: 155-70.

"When it was thought that fluoride had to be present during tooth mineralisation to 'improve' the biological apatite and the 'caries resistance' of the teeth, systemic fluoride administration was necessary for maximum benefit. Caries reduction therefore had to be balanced against increasing dental fluorosis. The 'caries resistance' concept was shown to be erroneous 25 years ago, but the new paradigm is not yet fully adopted in public health dentistry, so we still await real breakthroughs in more effective use of fluorides for caries prevention."
SOURCE: Fejerskov O. (2004). Changing paradigms in concepts on dental caries: consequences for oral health care. *Caries Research* 38: 182-91.

"Our analysis shows no convincing effect of fluoride-intake on caries development. . . A Bayesian analysis of multivariate doubly-interval-censored dental data."[13]

"Since April of 1999, I have publicly decried the addition of fluoride, especially hydrofluosilicic acid, to drinking water for the purpose of preventing tooth decay."
Hardy Limeback, BSc, PhD, DDS, Associate Professor and Head, Preventive Dentistry University of Toronto
http://www.slweb.org/limeback.html

"Fewer fillings had been required in the nonfluoridated part of my district than in the fluoridated part." 1997 John Colquohoun PhD, DDS **http://www.slweb.org/colquhoun.html**

"Decay is not the result of fluoride deficiency." Aoba T, Fejerskov O. (2002). Dental fluorosis: chemistry and biology. Critical Review of Oral Biology and Medicine 13: 155-70.

"A number of recent cessation studies show that stopping fluoridation does literally nothing to increase overall dental decay." Komarek et al, A Bayesian analysis of multivariate doubly-interval-censored dental data, Biostatistics 2005 6 pp 145-155

"it is now accepted that systemic fluoride plays a limited role in caries prevention."
SOURCE: Pizzo G, Piscopo MR, Pizzo I, Giuliana G. (2007). Community water fluoridation and caries prevention: a critical review. Clinical Oral Investigations 11(3):189-93.

"the major anticaries benefit of fluoride is topical and not systemic."
SOURCE: National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 13.

"it is now accepted that systemic fluoride plays a limited role in caries prevention."
SOURCE: Pizzo G, Piscopo MR, Pizzo I, Giuliana G. (2007). Community water fluoridation and caries prevention: a critical review. Clinical Oral Investigations 11(3):189-93.

"the major anticaries benefit of fluoride is topical and not systemic." SOURCE: National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 13.

"Since the current scientific thought is that the cariostatic activity of fluoride is mainly due to its topical effects, the need to provide systemic fluoride

supplementation for caries prevention is questionable."
SOURCE: European Commission. (2005). *The Safety of Fluorine Compounds in Oral Hygiene Products for Children Under the Age of 6 Years*. European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Consumer Products, September 20.

“The results of more recent epidemiological and laboratory studies can be summarized by stating that posteruptive (topical) application of fluoride plays the dominant role in caries prevention."
SOURCE: Hellwig E, Lennon AM. (2004). Systemic versus topical fluoride. *Caries Research* 38: 258-62.

“Current evidence strongly suggests that fluorides work primarily by topical means through direct action on the teeth and dental plaque. Thus ingestion of fluoride is not essential for caries prevention."
SOURCE: Warren JJ, Levy SM. (2003). Current and future role of fluoride in nutrition. *Dental Clinics of North America* 47: 225-43.

"[T]he majority of benefit from fluoride is now believed to be from its topical, rather than systemic, effects."
SOURCE: Brothwell D, Limeback H. (2003). Breastfeeding is protective against dental fluorosis in a nonfluoridated rural area of Ontario, Canada. *Journal of Human Lactation* 19: 386-90.

"For a long time, the systemic effect of fluoride was regarded to be most important, resulting in recommendations to use fluoride supplements such as tablets or drops. However, there is increasing evidence that the local effect of fluoride at the surface of the erupted teeth is by far more important."
SOURCE: Zimmer S, et al. (2003). Recommendations for the Use of Fluoride in Caries Prevention. *Oral Health & Preventive Dentistry* 1: 45-51.

"[F]luoride's predominant effect is posteruptive and topical."
SOURCE*:* Centers for Disease Control and Prevention. (2001). Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States. *Morbidity and Mortality Weekly Report* 50(RR14): 1-42.

"The prevalence of dental caries in a population is not inversely related to the concentration of fluoride in enamel, and a higher concentration of enamel fluoride is not necessarily more efficacious in preventing dental caries."
SOURCE: Centers for Disease Control and Prevention. (2001). Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States. *Morbidity and Mortality Weekly Report* 50(RR14): 1-42.

"Fluoride incorporated during tooth development is insufficient to play a significant role in caries protection."
SOURCE: Featherstone, JDB. (2000). The Science and Practice of Caries Prevention. *Journal of the American Dental Association* 131: 887-899.

"Current evidence suggests that the predominant beneficial effects of fluoride occur locally at the tooth surface, and that systemic (preeruptive) effects are of much less importance."
SOURCE: Formon, SJ; Ekstrand, J; Ziegler, E. (2000). Fluoride Intake and Prevalence of Dental Fluorosis: Trends in Fluoride Intake with Special Attention to Infants. *Journal of Public Health Dentistry* 60: 131-9.

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"Fluoride supplementation regimens suffer from several shortcomings, the first of which may be their derivation from a time when the major effect of fluoride was thought to be systemic. Although evidence that fluoride exerts its effects mainly through topical contact is great, supplementation schemes still focus on the ingestion of fluoride."
SOURCE: Adair SM. (1999). Overview of the history and current status of fluoride supplementation schedules. *Journal of Public Health Dentistry* 1999 59:252-8.

"The case is essentially a risk-benefit issue - fluoride has little preeruptive impact on caries prevention, but presents a clear risk of fluorosis."
SOURCE: Burt BA. (1999). The case for eliminating the use of dietary fluoride supplements for young children. *Journal of Public Health Dentistry* 59: 260-274.

"Until recently the major caries-inhibitory effect of fluoride was thought to be due to its incorporation in tooth mineral during the development of the tooth prior to eruption...There is now overwhelming evidence that the primary caries-preventive mechanisms of action of fluoride are post-eruptive through 'topical' effects for both children and adults."
SOURCE: Featherstone JDB. (1999) Prevention and Reversal of Dental Caries: Role of Low Level Fluoride. *Community Dentistry & Oral Epidemiology* 27: 31-40.

"[L]aboratory and epidemiologic research suggests that fluoride prevents dental caries predominately after eruption of the tooth into the mouth, and its actions primarily are topical for both adults and children."
SOURCE: Centers for Disease Control and Prevention. (1999). Achievements in Public Health, 1900-1999: Fluoridation of Drinking Water to Prevent Dental Caries. *Morbidity and Mortality Weekly Report* 48: 933-940.

"[R]esearchers are discovering that the topical effects of fluoride are likely to mask any benefits that ingesting fluoride might have... This has obvious implications for the use of systemic fluorides to prevent dental caries."
SOURCE: Limeback, H. (1999). A re-examination of the pre-eruptive and post-eruptive mechanism of the anti-caries effects of fluoride: is there any caries benefit from swallowing fluoride? *Community Dentistry and Oral Epidemiology* 27: 62-71.

"Although it was initially thought that the main mode of action of fluoride was through its incorporation into enamel, thereby reducing the solubility of the enamel, this pre-eruptive effect is likely to be minor. The evidence for a post-eruptive effect, particularly its role in inhibiting demineralization and promoting remineralization, is much stronger."
SOURCE: Locker D. (1999). Benefits and Risks of Water Fluoridation. An Update of the 1996 Federal-Provincial Sub-committee Report. Prepared for *Ontario Ministry of Health and Long Term Care.*

"Recent research on the mechanism of action of fluoride in reducing the prevalence of dental caries (tooth decay) in humans shows that fluoride acts topically (at the surface of the teeth) and that there is negligible benefit in ingesting it."
SOURCE: Diesendorf, M. et al. (1997). New Evidence on Fluoridation. *Australian and New Zealand Journal of Public Health* 21 : 187-190.

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"On the basis of the belief that an adequate intake of fluoride in early life is protective against caries in later life, fluoride supplements are recommended for infants and children living in areas in which the fluoride content of the drinking water is low. However, critical reviews of the evidence have led to the conclusion that the effect of fluoride in decreasing the prevalence and severity of dental caries is not primarily systemic but exerted locally within the oral cavity. Because fluoride supplements are quickly cleared from the mouth, the possibility must be considered that they may contribute to enamel fluorosis, which is unquestionably a systemic effect, while providing relatively little protection against dental caries."
SOURCE: Ekstrand J, et al. (1994). Fluoride pharmacokinetics in infancy. *Pediatric Research* 35:157–163.

"It is now well-accepted that the primary anti-caries activity of fluoride is via topical action."
SOURCE: Zero DT, et al. (1992). Fluoride concentrations in plaque, whole saliva, and ductal saliva after application of home-use topical fluorides. *Journal of Dental Research* 71:1768-1775.

"I have argued in this paper that desirable effects of systemically administered fluoride are minimal or perhaps even absent altogether."
SOURCE: Leverett DH. (1991). Appropriate uses of systemic fluoride: considerations for the '90s. *Journal of Public Health Dentistry* 51: 42-7.

"It, therefore, becomes evident that a shift in thinking has taken place in terms of the mode of action of fluorides. Greater emphasis is now placed on topical rather than on systemic mechanisms..."
SOURCE: Wefel JS. (1990). Effects of fluoride on caries development and progression using intra-oral models. *Journal of Dental Research* 69(Spec No):626-33;

"[E]vidence has continued to accumulate to support the hypothesis that the anti-caries mechanism of fluoride is mainly a topical one."
SOURCE: Carlos JP. (1983) Comments on Fluoride. *Journal of Pedodontics* Winter. 135-136.

"Until recently most caries preventive programs using fluoride have aimed at incorporating fluoride into the dental enamel. The relative role of enamel fluoride in caries prevention is now increasingly questioned, and based on rat experiments and reevaluation of human clinical data, it appears to be of minor importance... [A]ny method which places particular emphasis on incorporation of bound fluoride into dental enamel during formation may be of limited importance."
SOURCE: Fejerskov O, Thylstrup A, Larsen MJ. (1981). Rational Use of Fluorides in Caries Prevention: A Concept based on Possible Cariostatic Mechanisms. *Acta Odontologica Scandinavica* 39: 241-249.

"It is estimated that 84% of the caries experience in the 5 to 17 year-old population involves tooth surfaces with pits and fissures. Although fluorides cannot be expected appreciably to reduce our incidence of caries on these surfaces, sealants can."
SOURCE: *Journal of the American Dental Association 1984;* 108:448.

"[E]namel surfaces with pits and fissures receive minimal caries protection from either systemic or topical fluoride agents."

SOURCE: Pinkham JR. (1999). *Pediatric Dentistry: Infancy Through Adolescence.* Third Edition. WB Saunders Co, Philadelphia.

"The type of caries now seen in British Columbia's children of 13 years of age, is mostly the pit and fissure type. Knudsen in 1940, suggested that 70 percent of the caries in children was in pits and fissures. Recent reports indicate that today, 83 percent of all caries in North American children is of this type. Pit and fissure cavities aren't considered to be preventable by fluorides, they are prevented by sealants."
SOURCE: Gray, AS. (1987). Fluoridation: Time for a New Base Line? *Journal of the Canadian Dental Association* 10: 763-765.

"The program focused on four caries-prevention techniques: sealants, a plastic-like coating applied to the chewing surfaces of back teeth and to pits and fissures on the sides of teeth (these surfaces are most prone to decay and ones which fluorides cannot protect adequately)."
SOURCE: Raloff J. (1984). Dental study upsets the accepted wisdom. *Science News*. 125(1): January 7.

It is estimated that 84% of the caries experience in the 5 to 17 year-old population involves tooth surfaces with pits and fissures. Although fluorides cannot be expected appreciably to reduce our incidence of caries on these surfaces, sealants can."
SOURCE: Scholle R. (1984). Editorial: Preserving the perfect tooth. *Journal of the American Dental Association.* 108:448.

Children attending centers showed no significant differences based on fluoride status for the total sample or other variables. Barnes GP, et al. (1992). Ethnicity, location, age, and fluoridation factors in baby bottle tooth decay and caries prevalence of Head Start children. *Public Health Reports* 107: 167-73.

6. Assessment of Efficacy: Testing Water or Testing Patients

The assessment method for evaluating the success of an additive is to test or measure the bacteria in the water. Chlorine treats water.

The assessment method for evaluating the success of a fluoride is to test or measure the disease in the patient. Fluoride treats people.

7. If the intent of fluoride is determined not to be with the intent to prevent disease, then the addition of fluoride is not exempt from poison laws.

Fluoride is known to be highly toxic and the least amount of fluoride necessary is prudent and in the best interest of the safety and health of the public.

The Kaul Court agreed, 1954, with the trial court's finding in that

... fluoride is a deadly poison used commercially for the extermination of rats and other vermin."[14]

The Washington State Legislature has defined poisons.

"RCW 69.38.010 "Poison" defined. As used in this chapter "poison" means: (1) Arsenic and its preparations; (2) Cyanide and its preparations, including hydrocyanic acid; (3) Strychnine; and (4) Any other substance designated by the state board of pharmacy which, when introduced into the human body in quantities of sixty grains or less, causes violent sickness or death."

Sixty grains is 3,889 mg. 15 mg can be lethal for a child. The Washington Board of Pharmacy determined 15 is less than 3,889 and applied RCW 69.38.020 which exempts fluoride as a poison when used as a drug. (Appendix A)

If the Board of Health determines that fluoride is NOT used with the intent to prevent disease and exempt as a drug, then fluoride is defined by RCW 69.38.010 as a poison and poison laws need to be applied to the Board, the Department, and water systems.

Clearly, applying poison laws to the Board, Department and water systems is not a good option. It is in the best interest of the Board, the Department, the water systems and the public to agree with the Board of Pharmacy and others that fluoride is a drug when used with the intent to prevent disease.

In order to develop drinking quality water standards for fluoride, the first critical step for the Board is to determine the intent and purpose of fluoride when added to public water.

IV. PETITION FOR WAC CHANGES: SUGGESTED WORDING

The suggested WAC word changes are as follows in red and italics:

a. "WAC 246-290-460

(2) Where fluoridation is practiced *with the intent to prevent dental caries*, purveyors shall maintain fluoride concentrations . . . .

(3) Where fluoridation is practiced *with the intent to prevent dental caries*, purveyors shall . . . ."

Sincerely Yours,

Bill Osmunson DDS, MPH

WASHINGTON ACTION FOR SAFE WATER

President, Washington Action for Safe Water
1418 – 112th Ave NE 200
Bellevue, WA 98004
425.455.2424

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[1] July 22, 2010 letter to Bill Osmunson regarding public information disclosure request.

[2]http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/ucm074201.htm Acc. 9/26/10

[3] Kaul v. Chehalis, 45 Wn.2d 616, 277 P.2d 352 (1954)

[4] Kaul v. Chehalis, 45 Wn.2d 616, 277 P.2d 352 (1954)

[5] Port Angeles v Our Water-Our Choice 82225-5 Dissenting Justices p 5. http://www.courts.wa.gov/opinions/index.cfm?fa=opinions.showOpinion&filename=822255Di1 Accessed 10/4/10 Footnote #6, "Respondents have conceded that the decision to fluoridate was spurred by local health care professionals who thought fluoridation would produce a measurable benefit for a significant portion of the population."

[6] CDC (1999). Achievements in Public Health, 1900-1999: Fluoridation of Drinking Water to Prevent Dental Caries. MMWR, 48(41); 933-940, October 22

[7] http://www.cdc.gov/fluoridation/ Accessed 9/26/10 CDC does not determine the safety or efficacy of fluoridation.

[8] CDC (1999). Achievements in Public Health, 1900-1999: Fluoridation of Drinking Water to Prevent Dental Caries. MMWR, 48(41); 933-940, October 22.

[9] Chemical and Engineering News, May 8, 1989, Vol 57, Number 19.

[10] 2001 Consensus Development Conference Summary

[11] http://www.doh.wa.gov/SBOH/Meetings/2010/06-09/docs/Tab16n-Fluoridation_Factsheet_DOH.pdf Accessed 9/26/10

[12] http://www.wsda.org/display/Search?searchQuery=fluoridation&moduleId=4293161 Accessed 9/26/10

[13] ARNO˝ST KOMA´ REK∗, EMMANUEL LESAFFRE Biostatistics (2005), 6, 1, pp. 145–155
doi: 10.1093/biostatistics/kxh023

[14] Kaul v. Chehalis, 45 Wn.2d 616, 277 P.2d 352 (1954)

WASHINGTON ACTION FOR SAFE WATER

Washington State Board of Health **December 25, 2010**

Craig McLaughlin, Executive Director

Via e-mail: McLaughlin, Craig D (DOH) <Craig.McLaughlin@DOH.WA.GOV>

PETITION FOR RULE MAKING (#8) WAC 246-290-460

WATER FLUORIDATION,

ETHICS

This petition is for safety and health with rule change under RCW 34.05.330.

I. REVIEW OF PREVIOUS PETITIONS FOR RULE CHANGE

A. Petition #1 FDA CDER New Drug Approval.

The best protection for the public would be to require or advise public water systems to seek FDA CDER approval with a New Drug Application. The FDA CDER has the most competent scientists, policies and procedures to ensure efficacy and safety for drugs. FDA CDER approval is the only method to comply with state statutes and Federal Acts and take this complex situation and put it in the lap of the Federal Agency Congress mandated to regulate drugs such as fluoridation. The Board would simply be requiring public water districts to comply with the Food Drug and Cosmetic Act and Safe Drinking Water Act. If the FDA CDER refused to approve the fluoridated water drug, the municipality could choose to cease fluoridation or continue doing what they are doing. Following this procedure would not only protect the public from harm but would protect the municipality and the state from further liability.

The Board denied WASW's first rule change petition, stating as its reasons that the Board does not regulate additives to tap water and that requiring FDA approval for a drug additive would "effectively rule out" fluoridation. In other words, the Board believes that complying with Federal Law is impossible because fluoridation does not meet standards set up by Congress and the FDA CDER for safe and effective drugs.

If fluoridation were in fact safe and effective, FDA CDER approval would have been achieved 60 years ago.

B. Petition #2 Concentration of Fluoride in Public Water System

With a primary interest in protecting the public, WASW followed the statement in the public meeting by the Board of Health that the Board is responsible for the concentration of fluoride in water. Petition #2 focused on concentration

The Board rejected this second petition to lower the concentration of the fluoride drug stating that the Board is not a "research agency." The Board has not been asked to do any research, simply evaluate the evidence from research. Either health is research based or faith based. Further, the Board stated that it "relies on federal agencies to evaluate best available science"—which, by state and federal law, would be the FDA CDER process which has been circumvented and disregarded by the BOH in Petition #1.

The Legislature vested the Board with responsibility to adopt rules to protect the public health. If scientific research is not used to make rules to protect the public health, then on what basis does the Board of Health make decisions? In this case the Board erroneously chose to rely on the EPA which is prohibited from adding any substances for health purposes (unrelated to disinfection of water) and has no jurisdiction over the approval of drugs. The EPA regulates the removal, not the addition of contaminants.

In actuality, the state and fluoridating municipalities are relying for quality control of fluoridation materials on the National Sanitation Foundation, which promulgates ANSI/NSF Standard 60, known commonly as NSF 60. Washington law, WAC 246-290-220(3), requires that

> any treatment chemicals with the exception of commercially retailed hypochlorite compounds such as Clorox, Purex, etc., added to water intended for potable use must comply with ANSI/NSF Standard 60.

However, NSF is a sham.[1] NSF does not test the efficacy or safety of the chemical contaminant itself.

C. Petition #3 Lead Notice by Fluoride-Class-Action

The Petition on Lead was by Fluoride-Class-Action.[1] WASW fully supports public health education advising the public that fluoridated water will increase the measured blood lead levels in their children. WASW also appreciates and respects the Board's advice to work with an on going rule change committee.

D. Petition #4 Public Health Education Notice for Infants

The intent of this petition was to motivate the Board to pass rules which would result in the education of parents and care givers that the fluoride level in their water would provide their baby with excess fluoride.

The Board denied this health education petition to protect infants based on support for fluoridation by DOH and CDC. However, the CDC has made it clear that it does not determine the safety of fluoridation nor does it have authorization to approve drugs. Neither does DOH. Further, the denial stated "the educational approach of the CDC and ADA"…"is adequate". We emphatically disagree. A statement hidden on the Web is not "adequate education." It has been four full years since the CDC and ADA in November of 2006 began its "educational approach," a web only notification to parents that they should avoid giving fluoridated water to infants. There is no evidence the typical parent, physician

[1] http://washingtonsafewater.com/bd-of-health/rulemaking-lead-9-13-10

or dentist is aware of the risks infants. Our petition would be a simple no cost health education to protect infants.

E. Petition #5 Intent of Use

Although the Board denied this petition, it did indicate agreement with certain points made in this petition. The Board made it clear that it agrees that fluoridation is done to prevent dental disease and agrees with the Board of Pharmacy that fluoride is exempt from poison laws only when fluoride is used as a drug, as in the case of water fluoridation.

F. Petition #6 Public Health Education Notice for Dental Fluorois

In its sixth petition, WASW asked the Board to provide for public health education which would advise parents and caregivers to restrict the intake of fluoridated water for infants and children in order to reduce the damage of dental fluorosis.

The Board denied this sixth petition and gave as its reason that it was relying on EPA standards as set forth in the SDWA which permit contaminants in water, including fluoride up to 4 ppm. However, the SDWA does not authorize adding a contaminant such as fluoride to water; it only requires that it be removed if it exceeds 4 ppm. The Board's bad logic here seems to be that since the EPA permits naturally occurring fluoride at 4 ppm, it is then acceptable to add fluoride (or any other contaminant up to MCLG levels) to water. The Board fails to take note that naturally occurring fluoride is less toxic than artificial fluoridation. The Board makes it clear that it regards toxicology as not being a significant a factor. The Board states,

> *"EPA standards allow fluoride concentrations in water more than a hundred times greater than 0.01 ppm and consider the water to be safe for consumers without such an advisory statement as recommended by the petitioner."*

Apparently the Board believes that all fluoride compounds have the same toxicity. This is far from the truth. Some fluoride compounds, for example, are not readily absorbed in the gut. The EPA 4 ppm MCLG pertains to naturally occurring fluoride, not to artificial fluoridation materials such as sodium fluoride and silicofluorides. Relying on the EPA to determine the safety of any substance for which they are prohibited from evaluating for safety not wise.

For example, an LDL (lethal dose level) of 2 to 8 mg/kg/bw (milligrams per kilogram of body weight) is much more toxic than an LDL of 4,250 LDL. The LDL for Calcium Fluoride, naturally occurring in water, is considered to be 4,250 mg/kg,[2] about the same toxicity as table salt, while the LDL for fluoride compounds put in public water such as sodium fluoride is 2 to 8 mg/kg body weight.[3] "Sodium fluoride readily dissolves in water, but calcium fluoride does not. … Fluoride can bind with serum calcium resulting in hypocalcemia and possibly hyperkalcemia. … Teotia and Teotia (1994) found that deficient calcium intake and elevated fluoride intake (1.1–4.0 ppm) resulted in a significant increase in the occurrence of dental fluorosis (100%) and dental caries (74%)"[4]

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[2] http://msds.chem.ox.ac.uk/CA/calcium_fluoride.html Accessed 12/26/10

[3] http://www.fluoride-journal.com/97-30-2/302-89.htm Accessed 12/26/10

[4] http://www.atsdr.cdc.gov/ToxProfiles/tp11.pdf Accessed 12/26/10, p2 through 162 ATSDR Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine, 2003

Clearly, we should not simply compare the safety exposure (mg/kg/bw) determined by the EPA for calcium fluoride with the safety exposure of fluoride chemicals such as sodium fluoride or silicofluorides which are not regulated by the EPA.

G. Petition #7 Public Health Education Notice to Protect Brains

Petition #7 was presented to urge the Board to enact rules which would protect the human brain (their neurological function, intelligence, and logical thinking, see Xiang 2010) by educating the public not to drink the public water if the water contained excess fluoride.

The Board again denied this petition, citing EPA jurisdiction, the NRC 2006 report and a majority of scientific opinion. The Board is applauded for turning to scientific sources and should carefully read the NRC 2006 report. Indeed, it is the very NRC report cited by the Board whose unanimous opinion finds the EPA standards not protective of human health. The purpose of these petitions is for the Board to carefully review the "majority of scientific opinion" because the majority opinion finds fluoridation is not safe. Unfortunately, the "majority" as picked by the Board excludes the true majority of scientists, the majority of countries,[5] and the majority of published research on the safety of ingesting fluoride. Cherry pick who constitutes the majority and the "majority" changes. Cherry pick the research and the "majority" changes. Whoever gave the Board the idea that the "majority" of scientific opinion supports fluoridation has only reviewed the literature supporting their selected opinion.

On December 17, 2010 the National Institute of Environmental Health Sciences, National Institutes of Health, U.S. Department of Health and Humans Services, Environmental Health Perspectives released a study (attached) by scientists at the Jiangsu Province and Sihong County Centers for Disease Control and Prevention and Fundan University entitled *"Serum Fluoride Level and Children's Intelligence Quotient in Two Villages in China"* by Xiang et al, attached, stated *"there is no cut-off point of serum fluoride which is considered acceptable by WHO or other academic organizations."*[6]

The work by Xiang et al, confirms previous studies of neurological harm from fluoride a few of which were provided to the Board in Petition #7 and more than a hundred studies finding fluoride causes neurological harm are available.

Xiang (2010) reported an 8 point drop in IQ, intelligence, when serum fluoride went from a mean 0.04 mg/L to 0.08 mg/L. Those in Washington on fluoridated water (as well as other fluorides such as fluoride toothpaste) have a mean fluoride serum level of 0.21 mg/L, more than five times higher than found less harmful and more than two and a half times greater than the level causing an 8 IQ point drop. An additional margin of safety is necessary to protect everyone. More studies are available on request.

What will it take to protect everyone and get their serum fluoride down below 0.04 mg/L? To further protect neurological development and function, other steps may also be needed that are beyond the jurisdiction of the Board of Health.

In all its petitions presented to the Board, WASW has not over estimated the risk from current exposure to fluoride. Harm is probably greater than outlined, and this is most likely in the neurological field. Dentists can fix teeth, no one fixes IQ.

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[5] Appendix A Countries and Cities opposing fluoridation
[6] Appendix B Xiang

II. GROUNDS FOR PETITION FOR HUMAN SUBJECT RESEARCH APPROVAL

RCW 43.20.50 (2*) "In order to protect public health, the state board of health shall: (a) Adopt rules for group A public water systems . . . necessary to assure safe and reliable public drinking water and to protect the public health.*

The AGO 1992 No.17,

"2. The Legislature has authorized the Board of Health to establish, and the Department of Health to enforce, a comprehensive regulatory scheme for public water systems."

"The Board does not appear to have authority to adopt rules related to a water district deciding whether to fluoridate. ***The Board's authority is to regulate allowable concentration levels and method of approval of water additives."*** (June 9, 2010 Board Meeting Handout, page 2, emphasis added).

III. METHOD OF APPROVAL: LEGAL GROUNDS FOR IRB

A. Fluoridation is a Drug.

1. Fluoridation fits within the definition of drug approved by Congress: *"21 U.S.C. 321 CHAPTER II—DEFINITIONS (g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia;"*

Sodium Fluoride is listed in the 2007 US Pharmacopoeia pages 3194-3196.[7]

2. And again: *"21 U.S.C. 321 CHAPTER II—DEFINITIONS (g)(1) The term "drug" means . . . (B) articles intended for use in the . . . prevention of disease in man or other animals;"*

The Board agrees in Petition #5 "Intent of Use" fluoride is used with the intent to prevent disease.

3. Under an FOI Request, the FDA Confirmed the Active Ingredients in the Water Fluoridation Drugs are Unapproved Drugs:

"Sodium fluoride used for therapeutic effect would be a drug, not a mineral nutrient."[8]

"A search of the Drugs@FDA database . . . of approved drug products and the Electronic Orange Book . . . does not indicate that sodium fluoride, silicofluoride, or hydrofluorosilicic acid has been approved under a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for ingestion for the prevention or mitigation of dental decay. . . . At the present time, the FDA is deferring any regulatory action on sodium fluoride products. . . ."[9]

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[7] Appendix C 2007 USP NF
[8] Appendix D FDA letter
[9] FOI Email from the FDA (7-22-09) to Bill Osmunson DDS, MPH .

"Fluoride, when used in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animal, is a drug that is subject to Food and Drug Administration (FDA) regulation."[10]

4. The Washington State Board of Pharmacy also Confirmed Fluoride is a Prescription Drug under State and Federal Law.[11]

WSBP stated:
"Fluoride is a legend drug. . .."

The Fluoride supplement manufacturer agrees, fluoride is a drug. If fluoride were a "food," "supplement," or "nutrient" for ingestion, it would not be sold in stores by prescription only.

5. The FDA CDER has Defined Fluoride as a Drug in Toothpaste.

The FDA says:
"For example, fluoride toothpaste, antiperspirants, dandruff shampoos and sunscreens are all considered "drugs."[12]

B. Fluoridation chemicals, regardless of concentration, are Unapproved Drugs, Not Approved by the FDA for Ingestion.

The FDA has stated:

"*Upon review of the Food and Drug Administration's (FDA) drugs@fda site (*http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm *<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>), it identifies one approved NDA fluoride product. Therefore, all other marketed fluoride products without an application are not approved FDA drugs."*[13]

C. One of the First Steps for Drug Approval is Investigational Research Studies, Experiments, Clinical Investigation.

The FDA advises,

"During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

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[10] Appendix E FDA Calvert 2000
[11] Appendix F State of Washington Department of Health Board of Pharmacy June 4, 2009 letter to Bill Osmunson DDS; RCW 69.41.010(12) defines legend drugs; WAC 246-883-020(2) states legend drugs are listed in 2002 *Drug Topics Red Book*.
[12] www.fda.gov/AboutFDA/Transparency/Basics/uxm192696.htm Accessed 11/12/10
[13] FDA email Response to email from Bill Osmunson 2009

"FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system . . .

- *An Investigator IND (Investigational New Drug) is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population."*[14]

D. Title 21 -- Food and Drugs, Chapter 1, Part 50 - - Protection of Human Subjects

"The following regulations apply to the IND application process:[15]

21CFR Part 312	Investigational New Drug Application
21CFR Part 314	INDA and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval)
21CFR Part 316	Orphan Drugs
21CFR Part 58	Good Lab Practice for Nonclinical Laboratory [Animal] Studies
21CFR Part 50	Protection of Human Subjects
21CFR Part 56	Institutional Review Boards
21CFR Part 201	Drug Labeling
21CFR Part 54	Financial Disclosure by Clinical Investigators

"Sec. 50.1 Scope. This part applies to all clinical investigations. . . including foods, including dietary supplements, that bear a nutrient content claim . . . biological products for human use. . . . "

Some important definitions from Sec. 50.3 Until the fluoride article is approved, it is a test article, experiment, or research. Fluoridation is clinical investigation, *en masse.*

"(c) Clinical investigation means any experiment that involves a test article and one or more human subjects. . . "

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[14]http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm Accessed 12/25/10

[15] IBID

"(g) Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. . .

"(h) Institution means any public or private entity or agency (including Federal, State, and other agencies). . . "

"(j) Test article means any drug. . . medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n)."

"(k) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

"(l) Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

"(n) Assent means a child's affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent.

"(r) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation.
Permission must be obtained in compliance with subpart B of this part and must include the elements of informed consent described in Sec. 50.25.

"(s) Guardian means an individual who is authorized under applicable
State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of subpart D of this part, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research."[16]

Subpart B - - Informed Consent of Human Subjects

"§ 50.20 General requirements for informed consent.
Except as provided in §§ 50.23 and 50.24, (life threatening) no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of

[16] http://edocket.access.gpo.gov/cfr_2003/aprqtr/21cfr50.3.htm Accessed 12/25/10

the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."

"Sec. 50.25 Elements of informed consent.

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law."

Sec. 50.27 Documentation of informed consent should be reviewed by the Board and requires written consent documentation.

Sec. 50.50 IRB duties (Investigational Review Board)

Sec. 50.53

"Any clinical investigation within the scope described in Secs. 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in Sec. 50.55."

"Sec. 50.56 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under Sec. 50.53 or Sec. 50.54 only if such clinical investigations are:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.

(1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

(2) One individual may serve as advocate for more than one child.

(3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.

(4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization."

IV. PETITION FOR RULE CHANGE RECOMENDING IRB

A. *"The Washington State Institutional Review Board (WSIRB) is responsible for reviewing and approving human subjects research in the jurisdiction of three*

Washington State Agencies: the Department of Social and Health Services, the Department of Health, and the Department of Labor and Industries (L&I).[17]

If Cities and/or public water systems are not qualified to use WSIRB, most all Universities have Institutional Review Boards and the public water system can use the IRB of their choice.[18] This petition does not mandate an IRB, but rather recommends an IRB which will help the water district rethink their fluoridation policy and understand the importance for educating the public on their fluoridated water drug. This petition does not require approval of an IRB to fluoridate public water.

B. The Use of an Unapproved Drug is Research, but the Prevention of Disease is Not Research.

For example, the recommendation to exercise, wash hands, or brush teeth is not research. The use of an unapproved drug to improve health is research. The use of an approved drug within the label as approved by the FDA CDER is not research.

If the fluoridation drug were an approved drug, the public health activity of fluoridation for prevention of disease would not necessarily be research. In other words, public health preventive disease control measures may not be an experimental or research requiring IRB approval if all aspects of the research process are approved by agencies with jurisdiction.

An unapproved drug is not exempt from IRB simply because it is used to prevent or control disease.

C. Until an FDA CDER Approved Drug is used, the drug is investigational and used in Research.

For example, even in time of war an approved drug used for an unapproved disease is not permitted without consent.

Doe vs Rumsfeld, 2003.

> "The central question before this Court is whether AVA is an "investigational" drug or a drug unapproved for its use against inhalation anthrax. Upon consideration of plaintiffs' motion for a preliminary injunction, the opposition, the reply, and oral arguments, as well as the statutory and case law governing the issues, and for the following reasons, it is, by the Court, hereby **ORDERED** that the Motion for a Preliminary Injunction is **GRANTED**. In the absence of a presidential waiver, defendants are enjoined from inoculating service members without their consent."[19]

Another example is the authorization by the Legislature to build school buildings. Such authorization does not exempt the use of approved building materials. Determining whether the as yet unapproved building materials are structurally sound is research. The

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[17] http://www.dshs.wa.gov/rda/hrrs/ Department of Social and Health Services
Human Research Review Section 1115 Washington Street SE, P.O. Box 45205 Olympia, Washington 98504-5205 **Telephone:** (360) 902-8075 **FAX:** (360) 902-0705 **Email:** wsirb@dshs.wa.gov

[18] for example http://www.irb.wsu.edu/ at WSU, http://www.washington.edu/research/hsd/ at UW

[19] Page 2 2003 U.S. Dist. LEXIS 22990"Commentary: Toward a Taxonomy of Public Health Error", *3

determination of whether a piece of wood has adequate strength to meet building codes does not involve human subject research.

Research is necessary to determine safety and efficacy of unapproved drugs, and until approved by the FDA CDER use is experimental. IRB approval is one component in the research approval process for making the substance legal and ensuring safety and efficacy.

D. "Public Health Errors: Costing Lives, Millions at a Time" by Holtgrave (2010)[20]

Whereas a single medical error may cost one or more lives, a public health error may cost millions of lives and trillions of dollars. Yet public health policy is too often without external scientific evidence based review, open dialogue with stake holders' input, or patient freedom. In the case of fluoridation, the focus is to help the poor, and ironically it is the poor who can least afford the loss of IQ who are most harmed with fluoridation.

Holtgrave divides public health errors into three types of situations, errors of deliberate commission such as contrary to standards, practices, laws or ethical norms (such as fluoridation); willful omission such as not providing action (public health education); and complacency such as paying insufficient attention to a disease. Holtgrave suggests, "A common feature in those three categories of errors is an intent to do harm, or at least the lack of caring about fully discharging one's public health duty to serve the public good." Holtgrave argues, "that policy makers can indeed commit “errors” and should be held accountable for said errors if the policy makers know that the action they are taking is demonstrably harmful (relative to another policy option) and they have the financial, legal, and human resources to avoid implementing the relatively harmful policy."

The Board has the financial (huge cost savings), legal and human resources to take action and educate the public regarding risks of excess fluoride ingestion and lower the concentration and method of fluoridation with rule change as petitioned by WASW. Other less harmful options providing freedom of choice are available.

No doctor could ethically use police powers forcing the ingestion of even an approved drug (let alone an unapproved drug) for a non-contagious non-life threatening disease, without ethical consent from each individual, in an attempt to medicate children ages 1 through 8 while the teeth are developing, with an uncontrolled dosage, based on highly disputed cherry picked low quality scientific evidence, and with the drug readily available off the shelf providing freedom of choice (toothpaste) as an alternative.

Science is not stagnant, is not set in stone, and is constantly being challenged and changing. History has sometimes not been kind to scientists and public health professionals who have used unapproved drugs for treatments on people without their consent (Nuremberg Trials) or with held treatment or even the information, public health education, of potential treatment from cohorts (Tuskegee). The Board must actively **educate** the public towards health rather than **medicate** the public towards "health."

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[20]Appendix G Holtgrave D, Public Health Errors: Costing Lives, Millions at a Time, J Pub Health Man & Prac, May/June 2010 Vol 16 Issue 3 p 211-215 And see Commentary in this Issue by De Ville Novick "Commentary: Toward a Taxonomy of Public Health Error"

Holtgrave reminds us that, "in public health there is not an analogue to the Hippocratic Oath from medicine ("first of all, do no harm")." In public health, the standards of performance are ambiguous and the decision makers less clearly identifiable, more distal and more numerous than in clinical medicine. The attitude and culture of the public health profession is omniscient, omnipresent and *potestas imperium*.

Issues of ethics emerge with value conflicts. Some people value teeth more than brains and have gained enough control to force everyone into submission to their value of mass medication rather than mass education. Even if the masses voted for an illegal act, such as segregation of schools, the vote does not make the act legal. When there are value conflicts, the Board must provide freedom of choice, do no harm, and obey the law.

This petition for IRB and ethical patient consent is a first small step toward legalizing the fluoridation drug.

V. PETITION FOR WAC CHANGE: WAC 246-290-460 TO CHANGE METHOD OF APPROVAL FOR FLUORIDE SUBSTANCES WITH THE FOLLOWING PROPOSED WORDING:

"(5) Where fluoride substances which are unapproved by the FDA CDER are added to water systems, the Washington State Board of Health recommends Public Water Systems make application for IRB (Institutional Review Board) approval."

WASW understands the expectation of an IRB approval is possible, only if the IRB is willing to work with stakeholders to achieve an ethical resolution. Certainly an IRB could provide guidance on health education notification and consent of water consumers. Individual consent is "reasonably" possible. For example, each water customer could be given the option of signing consent, a water filter or bottled water. Continuing to cause the public harm and a massive negative economic impact is unacceptable.

Sincerely yours,

Bill Osmunson DDS, MPH President,
Washington Action for Safe Water
1418 – 112th Ave NE 200,
Bellevue, WA 98004

Washington State Board of Health
Olympia, Washington

June 2, 2022

From::Bill Osmunson DDS MPH
Cosmetic and General Dentist
Board Chair: American Environmental Health Studies Project
1418 112th Ave NE, Bellevue, WA 98004
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A COST BENEFIT-RISK ANALYSIS OF FLUORIDATION
FOR THE
WASHINGTON STATE BOARD OF HEALTH

"The continued increase in fluorosis rates in the U.S. indicates that additional measures need to be implemented to reduce its prevalence."[1] Fluoridation (addition of fluoride to public water), cessation is the most logical source to reduce excess fluoride exposure.

Abstract/summary: The Washington State Department of Health (WSDH) has advised that the Washington State Board of Health (WSBH) has Jurisdiction in Washington State over the addition of fluoride to public water systems. Therefore, it is the ethical responsibility for the Board to be current on the risks and benefit, if any, for all individuals and protect the public with an appropriate label.

As a practicing comprehensive, cosmetic, general dentist, I treat functional and cosmetic damage from dental fluorosis and dental caries contributed by the WSBH's recommendation of fluoride supplementation in water. The estimated cost to treat dental fluorosis damage exceeds the estimated cost of benefit, Thus, fluoridation makes no financial, ethical, or Public Health sense. Excess fluoride exposure financially benefit dentists. When the estimated harm from developmental neurotoxicity is included, public health agencies must no longer support fluoridation. We can fix teeth, not brains.

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[1] Wiener RC, Shen C, Findley P, Tan X, Sambamoorthi U. Dental Fluorosis over Time: A comparison of National Health and Nutrition Examination Survey data from 2001-2002 and 2011-2012. J Dent Hyg. 2018 Feb;92(1):23-29. PMID: 29500282; PMCID: PMC5929463.

Estimated costs Per Person Per Year (PPPY):

Cost to fluoridate water		$3-$10
Averted caries	$6.08	
Dental fluorosis Treatment		$3.24-$153
IQ loss		$2,156 to $2,552

Cost estimates report benefit from fluoridation only if harm is NOT included.

Real world estimates of fluoridation's benefit to teeth including all costs and also including harm from dental fluorosis to teeth, do not report a cost savings. Presumed neurotoxic harm to the developing brain, potential ADHD endocrine, cancer, thyroid, bone, enzymatic harm, and lack of environmental justice add additional costs which must be included in a cost-benefit-risk analysis. The evidence is clear, estimated fluoridation harm far exceeds estimated benefit.

Toxicology's definition of two terms: "hazard" and "risk." Sunshine can be beneficial. A hazard is potential danger, such as sunshine. Risk is the likely hood of danger/harm, or how much of the hazard causes danger/harm, such as a sunburn. How much sunshine becomes a danger depends on several factors and host sensitivity. "The dose makes the poison." (Perecles

Fluoride is similar. Topical fluoride can be beneficial. Ingesting fluoride has risk of danger and actual harm and the FDA approved label includes the warning "Do Not Swallow." Ingesting fluoride has strong evidence of actual harm. We cannot change the hazard of a chemical but we can manage the risk of harm. (See also for a simple review of toxicology)

Bioethics recommends we evaluate the risks from fluoridation based on "potential" risk at total exposures. Sometimes proponents of fluoridation speak only about the source of fluoride which comes from fluoridated water. However, an estimated third to two thirds of fluoride comes from other sources. The dosage fluoridation provides needs to be at least doubled or tripled to achieve total fluoride exposure.

Dental fluorosis is a known risk from excess fluoride exposure, the highest level of confidence.

Developmental neurotoxicity, as evaluated with IQ, is presumed to be a risk and also greater confidence than potential risk. "Potential" risks include ADHD, cancer, thyroid, bone, endocrine,

enzymatic system, mitochondria, GI and kidney harm and the evidence is strong enough for those to stop fluoridation. With 70% of the USA children having dental fluorosis, fluoridation should be stopped just for excess fluoride ingestion. Most developed countries do not fluoridate public water. Public Health's intention to help the poor and those with low intelligence are the very people least able to compensate for the harm and in most need of health education. Fluoridation is not supported by Bioethics, drug regulatory agencies, most developed countries, total exposure, quality of research, environmental justice, toxic substance laws, cost savings and better alternatives are available. Uncontrolled dosage, an uncertainty factor, individual sensitivity and the cumulative harm from all toxic chemical exposures demands action.

Individual dosage is not controlled when dispensed in the public water systems because not everyone drinks the same amount of water and different amounts at different ages. Infants on formula made with fluoridated water receive about 140 times more fluoride than mother's milk. Fluoride at 0.7 mg/l in water to make infant formula does not fit within WSBH guidelines within the first year of life.

OUTLINE

Current scientific evidence supports the USA Environmental Protection Agency (EPA) scientists statement in 2001:

> ***"In summary, we hold that fluoridation is an unreasonable risk. That is, the toxicity of fluoride is so great and the purported benefits associated with it are so small - if there are any at all – that requiring every man, woman and child in America to ingest it borders on criminal behavior on the part of governments."***[2]

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[2]Dr. J. William Hirzy, Senior Vice-President, Headquarters Union, US Environmental Protection Agency, March 26, 2001

I. BIOETHICS: Sound Bioethics Presupposes Sound Science.

I have previously requested the WSBH's cost-benefit-risk analysis and the Board has remained silent.

This report is the most up to date risk-benefit of fluoridation. The addition of fluoride to public water lacks individual consent, randomized controlled trials (quality research), lacks known mechanism of benefit, exceeds "potential" harm with probable and known harm, is without label, adulterated, misbranded and alternatives are available at less expense for those choosing to ingest fluoride.

Note: in contrast, topical fluoride has good scientific evidence of efficacy and the US Food and Drug Administration (FDA) correctly advises on the toothpaste label, "Do Not Swallow."

Since the 1940's bioethical principles have been reasonably constant.[3]

> *"The ethical validity of fluoridation policy does not stand up to scrutiny relative to the Nuremberg Code and other codes of medical ethics, including the Council of Europe's Biomedical Convention of 1999"* [4] *and artificial water fluoridation must be abandoned.*[5]

Dental caries harms the individual, not others. Not to minimize discomfort and harm from dental caries, but dental treatment is sometimes considered elective as a "non-contagious infectious disease"[6] and not highly lethal.

In both clinical practice and research,[7] individual informed consent and autonomy of a competent individual is a self-evident bioethic principle. In contrast, public health interventions may not have individual informed consent and therefore need to be held to an even higher standard of confidence.

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[3]Grady C. Institutional Review Boards: Purpose and Challenges. *Chest*. 2015;148(5):1148-1155. doi:10.1378/chest.15-0706

[4]Douglas W. Cross & Robert J. Carton (2003) Fluoridation: A Violation of Medical Ethics and Human Rights, International Journal of Occupational and Environmental Health, 9:1, 24-29, DOI: 10.1179/107735203800328830

[5]Rajarajan, Giftson; Kumar, R. Pradeep; Priyadorshini, S. Pavithra, A review on the ethics of artificial water fluoridation. Drug Invention Today . Jan2019, Vol. 11 Issue 1, p102-107. 6p. 1 Chart

[6]Vieira, AR, Genetics and Caries- Prospects, Braz Oral Res., (São Paulo) 2012;26(Spec Iss 1):7-9

[7]45 CFR part 46 Subpart D §46.404."**§46.116 General requirements for informed consent.** (2) A description of any reasonably foreseeable risks or discomforts to the subject;"

For example, a clinician making an error may harm that patient. Research error may harm hundreds. WSBH error may harm hundreds of thousands.

The Nuffield Council is consistent with the CDC (Centers for Disease Control and Prevention) ethics, applicable to the WSBH and is more specific to fluoridation, advising:

"public health policy involving the water supply should be considered in relation to:
I. the balance of risks and benefits
II. the potential for alternatives that rank lower on the intervention to achieve the same outcome.
***III. the role of consent where there are potential harms"*[8] (emphasis supplied)**

Bioethics does not include minimizing evidence of risk and maximizing claims of benefit. The public rely on the WSBH's recommendations in their decision making process regarding fluoridation. To avoid very serious harm to hundreds of thousands, the WSBH must have high confidence in their review of empirical evidence as it develops on fluoride ingestion.

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[8] Ethics Consultation Report Ethical Considerations in Community Water Fluoridation, by the Public Health Agency of Canada's Public Health Ethics Consultative Group, December 18, 2018 p.2. https://www.caphd.ca/sites/default/files/Ethical%20Considerations%20for%20Community%20Water%20Fluoridation.pdf

II. Jurisdiction: No Agency Authorized to Approve Fluoride Ingestion with Intent to Prevent Dental Caries has published a Benefit Risk Analysis or Approved Fluoridation

FDA: In the USA, Congress has given the Food and Drug Administration (FDA) jurisdiction over substances used with the intent to prevent disease such as fluoride.[9] The FDA testified to Congress that fluoride is a drug.[10] Fluoride toothpaste is approved and has a label with warning, "Do Not Swallow," referring to a pea size amount, 0.25 mg, the same amount as a glass of fluoridated water. Clearly the public is receiving mixed messages, "Do Not Swallow" the same amount of fluoride administered without choice in each glass of public water. We should not be surprised the public opinion is polarized. Sodium fluoride is listed as a drug in the Pharmacopeias.

The FDA notified 35 fluoride manufacturers of fluoride supplements, "*. . .there is no substantial evidence of drug effectiveness as prescribed, recommended or suggested in its labeling. . . marketing is in violation of the new drug provisions of the Federal Food, Drug, and Cosmetic Act; they have, therefore, requested that marketing of these products be discontinued."* [11] The FDA more recently warned manufacturers of fluoride supplements their product is not approved.

Fluoridated bottled water did not go through the NDA process and has never been approved. The FDA was notified a health claim would be made by manufacturers and the Drug section of the FDA does not regulate bottled water.

WASHINGTON STATE: In Washington State, the Board of Pharmacy (WSBP) has (had) jurisdiction over determining whether fluoride is a drug and the WSBH has jurisdiction over dispensing the fluoride drug. When asked, the WSBP confirmed, fluoride is a drug.[12] In fact, the Washington State laws gave the WSBH little choice.

RCW 69.38.010 "Poison" defined. As used in this chapter "poison" means:
(1) Arsenic and its preparations;
(2) Cyanide and its preparations, including hydrocyanic acid; (3) Strychnine; and (4) Any other substance designated by the state board of pharmacy which, when introduced into the human body in quantities of sixty grains or less, causes violent sickness or death."

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[9] 21 USC 321 (g)(1)(B)

[10] Congressional Investigation 2001

[11] DRUG THERAPY 1975

[12] Letter to the Author Bill Osmunson, June 4, 2009, from the Washington State Board of Health

Sixty grains is 3,887 mg.

Whitford (1996) *"it may be concluded that if a child ingests a fluoride dose in excess of 15 mg F/kg, then death is likely to occur. A dose as low as 5 mg F/kg may be fatal for some children. Therefore, the probably toxic dose (PTD), defined as the threshold dose that could cause serious or life-threatening systemic signs and symptoms and that should trigger immediate emergency treatment and hospitalization, is 5 mg F/kg."* [13]

For a 5 kg child a presumed lethal dose could be 25 mg. The WSBP had a simple calculation to make, is 25 mg less than 3,887 mg? Of course 25 is less than 3,887 and therefore fluoride is a poison. However, fluoride is exempt from poison laws when regulated under either pesticide or drug laws. The WSBP correctly determined fluoride is a drug when used with the intent to prevent disease in humans and not a pesticide. RCW does not exempt poisons when regulated as foods. In fact, the intentional dispensing of poisons into water is prohibited.

Fluoride is not exempt from poison laws when regulated as a food.

The jurisdiction of fluoride is then kicked over to the FDA which has not approved fluoride as a drug and to the WSBH which after 15 years of petitions has remained silent or denied petitions to protect the public.

RCW 57.08.012 Authorizes fluoridation by vote of commissioners or electors. In effect, the complex scientific toxicology, pharmacology, epidemiology, physiology, biochemistry, dentistry and medicine is turned over to 50% of a person's neighbors to medicate everyone with an unapproved drug.

Although the WSBH has remained silent, the Board certainly has the responsibility to protect the public at a minimum with appropriate label and recommendation.

The FDA process for evaluating a new drug should be considered by the WSBH and includes a benefit-dose-risk analysis with randomized controlled trials, label and oversight. The manufacturer before marketing presents the research on efficacy at a specific dosage to the FDA. If the substance is effective at the dosage, the risks are evaluated and a label is made with dose and warnings.[14] The WSBH has a role in fluoridation and must protect the public.

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[13] Whitford G. (1996). Fluoride Toxicology and Health Effects. In: Fejerskov O, Ekstrand J, Burt B, Eds. Fluoride in Dentistry, 2nd Edition. Munksgaard, Denmark. p 171."

[14] FDA Development & Approval Process Drugs, Center for Drug Evaluation and Research, https://www.fda.gov/drugs/development-approval-process-drugs

EPA: The Safe Drinking Water Act[15] includes, *"No national primary drinking water regulation may require the addition of any substance for preventive health care purposes unrelated to contamination of drinking water."* Congress has prohibited the EPA from adding anything to water which has intent to prevent disease.[16]

The Environmental Protection Agency (EPA) advised, *"the FDA, remains responsible for regulating the addition of drugs to the water supply for health care purposes."*[17]

The FDA avoids their responsibility by claiming the FDA does not regulate public water. In effect, no USA Federal Agency accepts jurisdiction over the addition of fluoride to public water, fluoridation, determining the efficacy, dosage and safety of ingested fluoride. The CDC does not evaluate or approve drugs. The WSBH is mistaken to rely on any Federally authorized agency for determining benefit, dosage, risk and label. Private industry promotes fluoridation for their benefit and has persuaded public health agencies to agree.

Proponents reference endorsements of fluoridation by over 100 organizations and claim, *"Not a single credibly recognized scientific group in the world OPPOSES community water fluoridation."* [18] However, their definition of "world" appears to be parochial and limited primarily to English speaking Countries and any organization opposed to fluoridation is therefore not credible.

Austria: "toxic fluorides" NOT added
Belgium: encourages self-determination – those who want fluoride should get it themselves.
Finland: "...do not favor or recommend fluoridation of drinking water. There are better ways of providing the fluoride our teeth need." A recent study found ..."no indication of an increasing trend of caries...."
Germany: stopped fluoridation. A recent study found no evidence of an increasing trend of caries
Denmark: "...toxic fluorides have never been added to the public water supplies in Denmark."
Norway: "...drinking water should not be fluoridated"
Sweden: "not allowed". No safety data available!

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[15] 42 U.S. Code § 300g–1 - National drinking water regulations

[16] FOIA Request HQ-FOI-01418-10

[17] Steve Neugeboren, Ass. General Counsel, Water Law Office EPA 2/14/2013

[18] American Fluoridation Society https://americanfluoridationsociety.org/debunking-anti-claims/myths/supporting-organizations/

Netherlands: Inevitably, whenever there is a court decision against fluoridation, the dental lobby pushes to have the judgment overturned on a technicality or they try to get the laws changed to legalize it. Their tactics didn't work in the vast majority of Europe.
Hungary: stopped for technical reasons in the '60s. However, despite technological advances, Hungary remains unfluoridated.
Japan: "...may cause health problems...." The 0.8 -1.5 mg regulated level is for calcium-fluoride, not the hazardous waste by product which is added with artificial fluoridation.
Israel: suspended mandatory fluoridation until the issue is reexamined from all aspects.: June 21, 2006 "The labor, welfare and health Knesset committee"
China: "not allowed"

Regarding Fluoride Post-harvest fumigant, and applicable to fluoridation, an EPA administrative Judge concluded: "EPA agrees that aggregate exposure to fluoride . . . does not meet the safety standard in FFDCA section 408. The fluoride MCLG (4.0 mg/L) is not protective of the effects of fluoride on teeth and bones; The fluoride MCLG is not protective of other neurotoxic, endocrine, and renal effects of fluoride; EPA has not adequately protected children; EPA cannot determine the safety of sulfuryl fluoride and fluoride in the absence of a developmental neurotoxicity study; EPA has underestimated exposure to fluoride; and EPA has committed procedural errors in violation of the Administrative Procedures Act (APA) (5 U.S.C. 551 *et seq.*)."[19]

Fluoride is not listed in food labels and no approved label for fluoridation or products used with fluoridated water are listed with warnings. Fluoridation is not an approved drug and is without label, misbranded,[20] and adulterated[21] failing to conform to compendium standards of purity.

The absence of fluoride in the diet does not cause dental caries. Fluoride is not an essential nutrient. Dental caries are not caused by inadequate fluoride ingestion.[22] No physiologic process in the body requires fluoride. Fluoride ingestion should not be compared to essential vitamins or minerals required for metabolic functions, the absence of which causes a disease.

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[19] https://www.federalregister.gov/articles/2011/01/19/2011-917/sulfuryl-fluoride-proposed-order-granting-objections-to-tolerances-and-denying-request-for-a-stay
Consolidated Objections at http://www.fluoridealert.org/wp-content/uploads/sf-nov.2006.pdf .

[20] FDA misbranded. https://www.fda.gov/medical-devices/general-device-labeling-requirements/labeling-requirements-misbranding

[21] Section 501(b) of the Food, Drug, and Cosmetic Act
https://www.fda.gov/media/71979/download

[22] Emsley J, Jones DJ, Miller JM, Overill RE, Waddilove RA. An unexpectedly strong hydrogen bond: ab initio calculations and spectroscopic studies of amide-fluoride systems. *Journal of the American Chemical Society.* 1981;103:24–28. [Google Scholar]

III. COSTS TO FLUORIDATE WATER.

Ran[23] reported costs to fluoridate water from $0.11 to $4.92 in 2013 U.S dollars per person per year (PPPY).

Ko[24] corrected for more factors and reported costs to fluoridate water ranged from "about $10 and $3 PPPY." Because Ko's estimate considers real world costs it will be used here.

Costs to purchase the bottled water for those not wanting fluoride should also be added to the costs of fluoridation. Assuming even 1% of the bottled water consumed is to avoid fluoride, 150 million gallons or 568 million liters of bottled water at $1/liter adds an additional $568 million dollars to the cost of fluoridation. An additional $5 per person consuming the fluoridated water costs to fluoridate public water should be added. To keep this complex subject simple, I have stuck with Ko's estimate.

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[23] Ran T, Chattopadhyay SK; Community Preventive Services Task Force. Economic Evaluation of Community Water Fluoridation: A Community Guide Systematic Review. *Am J Prev Med*. 2016;50(6):790-796. doi:10.1016/j.amepre.2015.10.014

[24] Ko L, Thiessen KM, A critique of recent economic evaluations of community water fluoridation, International Journal of Occupational and Environmental Health 2015 VOL. 21 NO. 2 91 DOI 10.1179/2049396714Y.0000000093

IV. BENEFIT of FLUORIDATION.

Ko has the most inclusive and accurate estimation of dental caries mitigation and reports fluoridation savings of $6.08 PPPY ($3-$10 PPPY), which is used here. Serious limitations to the alleged benefit of fluoride ingestion must be noted.

1) No Known Mechanism

Mechanism: Fluoride works by interacting topically after teeth erupt. The evidence for its effectiveness when applied to erupted teeth is well supported. Fluoride incorporation into developing teeth is very minor and does not contribute to caries prevention. Fluoride is not a nutrient nor essential for any bodily function. A very small amount of ingested fluoride makes its way to saliva to provide some topical fluoride after tooth eruption, but this amount is 50 to 100 fold less than what is obtained from fluoride naturally occurring in food and beverages. "The enamel demonstrated significant transport hindrance for the ions, and the effective pore radii of the transport pathways in the enamel were found to be approximately 0.7-0.9 nm."[25]

2) No Randomized Controlled Trials (RCT)

No RCT of fluoridation or fluoride supplements as pills or liquid have been published for infants, children or adults The only published RCT[26] gave 1 mg of fluoride daily to pregnant mothers and followed their child till age 5. No statistical reduction in dental caries was reported. The first RCT has started for fluoridated bottled water.[27]

Without a known mechanism coupled with lack of RCTs, the FDA is correct determining the evidence of benefit from fluoride ingestion is "incomplete."

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[25]Wei Ren, Arif Baig, S Kevin Li, Passive and iontophoretic transport of fluorides across enamel in vitro., Journal of pharmaceutical sciences (2014-04-10) Millipore Sigma

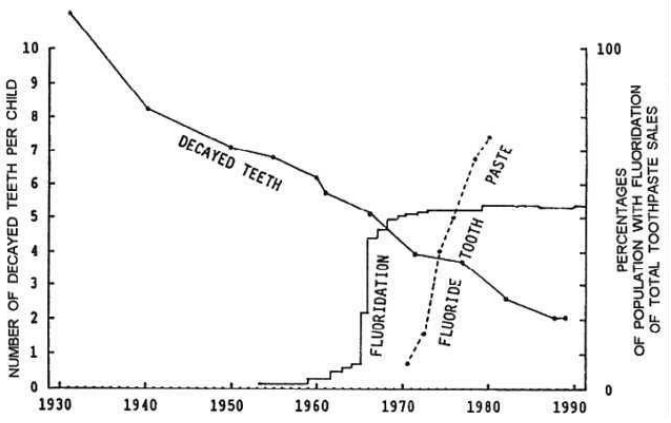
[26]Leverett DH, Adair SM, Vaughan BW, et al, - Caries Research, 1997 - karger.com https://www.karger.com/Article/Abstract/262394#

[27]https://waterbeststudy.com

3) Limited Confidence in Current Fluoridation's Association with Dental Caries:

A. Not one Study corrects for Unknown Confounding Factors such as the highly significant unknown causing caries decline from about 11.5 cavities to about 5.5 cavities before fluoridation.
B. Not one Prospective Randomized Controlled Trial
C. Socioeconomic status not controlled
D. Inadequate size
E. Difficulty in diagnosing decay
F. Delay in tooth eruption not controlled
G. Diet: Vitamin D, calcium, strontium, sugar, fresh and frozen year-round vegetables and fruit consumption not controlled.
H. Total exposure of Fluoride not determined
I. Oral hygiene not determined
J. Not evaluating Life-time benefit
K. Estimating or assuming subject actually drinks the water (about half of water ingested is now bottled water.)[28]
L. Dental treatment expenses not considered
M. Mother's F exposure, Breast fed (almost no fluoride) and infant formula with a high dose of fluoride
N. Fraud, gross errors, and bias not corrected.
O. Genetics not considered

For example, Colquhoun[29] 1997 ISFR Published 1998 published the graph below. No one knows what the unknown(s) were reducing caries prior to fluoridation. Those powerful unknowns have never been controlled for in research. The unknowns are more powerful than the possible effect of fluoridation.



Highly unlikely the unknowns causing the caries decline could have gradually phased out while fluoridation was phased in.

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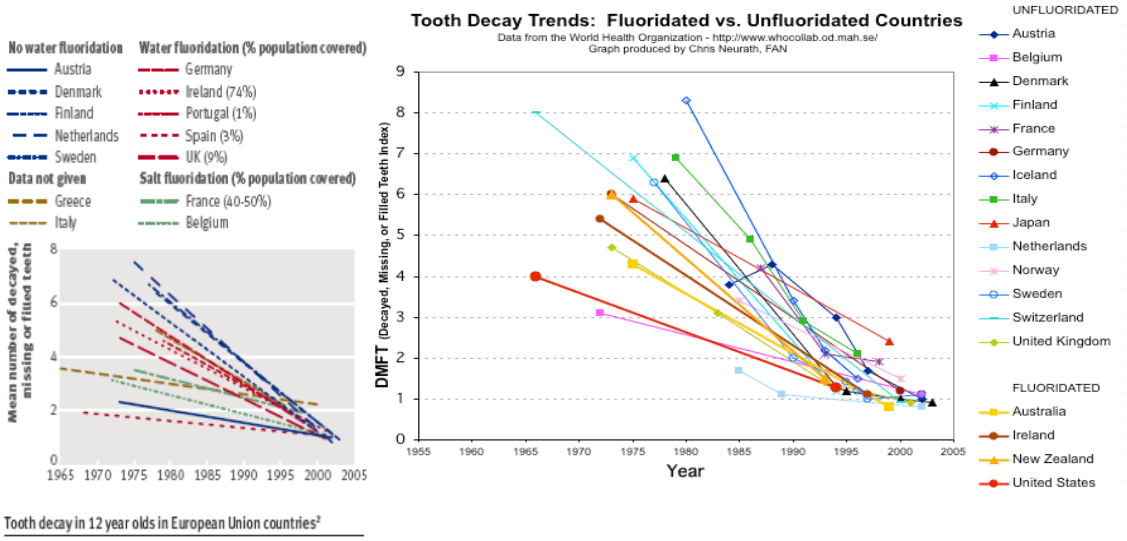
[28] International Bottled Water Association. https://bottledwater.org/bottled-water-consumption-shift/

[29] **Colquhoun 1997 ISFR Published 1998** http://www.fluoride-journal.com/98-31-2/312103-f.htm

Cheng[30] (left graph below) and Neurath[31] using WHO data demonstrate in developed countries, dental caries have declined to similar low levels regardless of fluoridation or fluoridated salt.



4) No Known Effective Dosage

Without RCT published studies or FDA approval, the dosage mg/Kg/day to mitigate dental caries has never been determined. Concentration of fluoride in water is not dosage. Instead of a dosage, an Adequate Intake is used by the National Institute of Health.[32]

Historical research suggested fluoridation was "remarkably effective," however, current research is less confident. A major review in 2000 from the Centre for Reviews and Dissemination at the University of York (York Review) concluded that the best available evidence suggested that fluoridation reduced the prevalence of caries, but found that the reduction was difficult to quantify from the evidence available. The authors also noted, "it is surprising to find that little high quality research has been undertaken."[33]

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[30] Cheng, K. K., Chalmers, I., & Sheldon, T. A. (2007). Adding fluoride to water supplies. *BMJ (Clinical research ed.), 335*(7622), 699–702. https://doi.org/10.1136/bmj.39318.562951.BE

[31] Neurath C, TOOTH DECAY TRENDS FOR 12 YEAR OLDS IN NONFLUORIDATED AND FLUORIDATED COUNTRIES, Research Note Fluoride 38(4)324-325 November 2005.

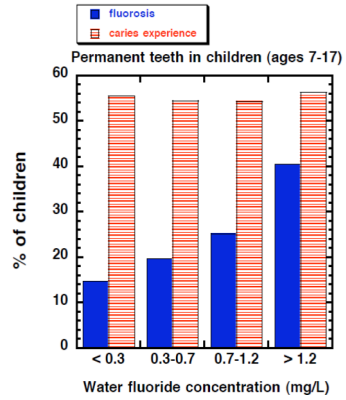
[32] National Institute of Health. AI for Fluoride https://ods.od.nih.gov/factsheets/Fluoride-HealthProfessional/#:~:text=In%201986%2C%20guidelines%20from%20the%20U.S.%20Environmental%20Protection,to%20prevent%20dental%20fluorosis%20%5B%203%2C%2011%20%5D. Accessed May 17, 2022

[33] McDonagh M, Whiting P, Bradley M et al. (2000) A Systematic Review of Public Water Fluoridation (York: NHS Centre for Reviews and Dissemination).

"The results show that the reviewed original studies on economic evaluation of caries prevention do not provide support for the economic value of caries prevention."[34]

Iida et al data from 2009 demonstrates an increase in fluoride concentration increases dental fluorosis, blue lines, but caries experience is minor if any. (Graph of data by Thiessen)

Iida, H., and Kumar, J.V. 2009. The association between enamel fluorosis and dental caries in U.S. schoolchildren. JADA 140:855-862.



Little has changed with fluoridation. According to Dye et al. (2015): "Untreated tooth decay was higher for Hispanic (36%) and non-Hispanic black (42%) adults compared with non-Hispanic white (22%) and non-Hispanic Asian (17%) adults aged 20–64."

Cities fluoridated for over 50 years report a crisis of dental caries and Kentucky was awarded 50 years of 100% fluoridated by the American Dental Association at the same time Kentucky was number one percentage for those without any teeth.

5) Excess exposure. 70% of children are ingesting too much fluoride.

CDC "Dental fluorosis only occurs when younger children consume too much fluoride, . . . when teeth are developing under the gums."[35] Fluoride ingestion prior to 6 years of age causes dental fluorosis.

Water fluoride concentration is not an individual dose, nor a valid indication of total exposure. Fluoridation gives more to everyone regardless of how much they are ingesting from other sources. Although the average intake of water is estimated at 927 ml/day for adults, 90th per-

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[34] Källestål C et al. Economic evaluation of dental caries prevention: a systematic review. Acta Odontol Scand. 2003 Dec;61(6):341-6.

[35] http://www.cdc.gov/fluoridation/safety/dental_fluorosis.htm#a2 Accessed 10 15

centile is just over 2 liters and some drink over 10 liters/day.[36] To protect from potential harm, safety factor of 10 should be used just to protect those drinking the most water such as pregnant women and infants on formula made with fluoridated water.

Rates of dental fluorosis have increased from 10-15% to 70%, moderate/severe from 7% to 28% in the latest NHANES reports.[37] Dong's 2015-16[38] reporting 70% although lower moderate and sever percentage. Espinoza raised concern with the quality of data[39] which has Federal oversight and funding. Photographs were taken and could confirm data quality if released. Data was when fluoridation was at about 1 ppm in water. An estimated 15% decrease in total exposure may reduce the rate of dental fluorosis, but not enough.

In other words, 73% of children are on fluoridated water and 70% of all the children show signs of excess fluoride intake. When fluoridation started, the public was assured only perhaps 15% of the public would get dental fluorosis.

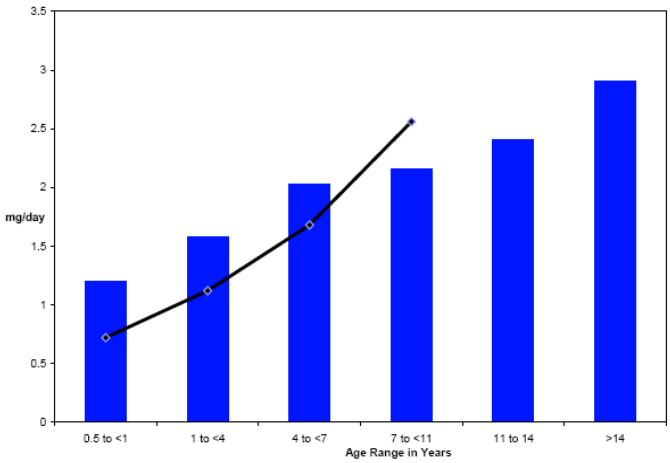

Figure 8-1. Total Daily Fluoride Intake Estimates Relative to the Proposed RfD Using 90th Percentile Drinking Water Intake Data for Consumers Only and the Mean Drinking Water Fluoride Concentration (0.87 mg/L)

There are numerous sources of fluoride, ". . . some children probably get more than the recommended amount of fluoride from toothpaste alone. . . "[40] p 42.

The EPA Dose Response Analysis 2010, Figure 8-1, illustrates the percentage of children exceeding the RfD (EPA safe dose) if the EPA increased the RfD from 0.06 to 0.08 mg/kg/day.

[36] Fluoride in Drinking Water: A Scientific Review of EPA's Standards. 2016. Chapter 2, pp 23-88.

[37] Neurath C, Limeback H, Osmunson B, Connett M, Kanter V, Wells CR. Dental Fluorosis Trends in US Oral Health Surveys: 1986 to 2012. JDR Clin Trans Res. 2019 Oct;4(4):298-308. doi: 10.1177/2380084419830957. Epub 2019 Mar 6. PMID: 30931722.

[38] Dong H, Yang X, Zhang S, Wang X, Guo C, Zhang X, Ma J, Niu P, Chen T. Associations of low level of fluoride exposure with dental fluorosis among U.S. children and adolescents, NHANES 2015-2016. Ecotoxicol Environ Saf. 2021 Sep 15;221:112439. doi: 10.1016/j.ecoenv.2021.112439. Epub 2021 Jun 22. PMID: 34166938.

[39] LorenaEspinozaRachelKaufmann, Corresondence Letter, Ecotoxicology and Environmental Safety, Volume 227, 20 December 2021, 112950https://doi.org/10.1016/j.ecoenv.2021.112950 https://www.sciencedirect.com/science/article/pii/S0147651321010629?via%3Dihub

[40] National Research Council 2006 p. 42.

In other words, EPA is doing the opposite of the NRC 2006 recommendation which reported EPA standards are not protective. EPA is "declaring" fluoride exposure safer and is being less protective. Even with increasing RfD, too many children are still ingest too much fluoride. (Percentage above the black line, previous page.)

Note, in their Figure 8-1 infants are not included, 10% of children and infants ingesting the most fluoride are not included.

The National Institute of Health[41] recommends 0.01 mg/day of fluoride birth to 6 months, compared to mother's milk with mean 0.004 mg/l. Formula fed babies on fluoridated water ingest an estimated average of 140 times more fluoride than breast fed babies.

I was unable to locate WHO's recommendation for fluoride concentration of water used to make infant formula and appears to be 1.5 mg/l.

Fluoride from tap water

-babies fed formula made with fluoridated tap water are overdosed on fluoride

subject	volume fluid intake	fluoride concentration in liquid consumed	fluoride DOSAGE* (µg/ kg per day)
5 kg baby fed breast milk	up to 1 L	≈ 0.005 ppm	1
70 kg adult	1 L	0.7 ppm	10
70 kg adult	4 L	0.7 ppm	40
70 kg adult	2 L	2.0 ppm	57
70 kg adult	1 L	4.0 ppm	57
5 kg baby fed infant formula made with tap water	up to 1 L	0.7 ppm	140

*A **dose** refers to a specified amount of medication taken at one time. By contrast, **dosage** is the prescribed administration of a specific amount, number, and frequency of doses over a specific period of time. AMA Manual of Style

Zohoori[42] "In conclusion, a relatively large proportion of fluoride intake is retained in the body in weaned infants."

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[41] National Institute of Health. AI for Fluoride https://ods.od.nih.gov/factsheets/Fluoride-HealthProfessional/#:~:text=In%201986%2C%20guidelines%20from%20the%20U.S.%20Environmental%20Protection,to%20prevent%20dental%20fluorosis%20%5B%203%2C%2011%20%5D. Accessed May 17, 2022

[42] Zohoori, F., Omid, N., Sanderson, R., Valentine, R., & Maguire, A. (2019). Fluoride retention in infants living in fluoridated and non-fluoridated areas: Effects of weaning. *British Journal of Nutrition, 121*(1), 74-81. doi:10.1017/S0007114518003008

6) Lack of Label.

Drugs and processed foods have labels to tell consumers recommendations and warnings. Without label, consumers don't know how much fluoride is in their foods such as mechanically deboned meat, tea, grapes etc. The only label is on fluoride toothpaste with a warning, "Do Not Swallow."

7) Systematic reviews of benefit

"Five systematic reviews between 2000 and 2015 that fluoridation reduces dental caries in children."[43] However, evidence of efficacy is based mostly on historical studies and lower quality.

The Cochrane systematic review is applicable to public health policy for the precise reasons it is criticized. Critics suggest the review was too restrictive.[44] Cochrane reviews primarily evaluate RCTs "for new drugs and clinical interventions for use with individuals, not public health initiatives targeted at populations."[45] Bioethics of a policy without individual consent should be more protective than one with individual consent and under their doctor's supervision. The FDA appears to be even more restrictive than the Cochrane review, reporting evidence at the same time period prior to the mid 1970's was "incomplete". Without individual consent and a world wide policy, WHO should require the same or greater confidence in the evidence.

The Cochrane review raised concerns for lack of studies to determine; current benefit, lack of benefit for lower socioeconomic status, lack of risk with fluoridation cessation, 97% of studies at high risk of bias, substantial between-study variation, and no studies met their criteria to determine effectiveness for adults.[46] Harm was not considered.

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[43]Lennon, M. The cochrane review of water fluoridation, Editorial, Community Dental Health (2015) **32**, 130–131

[44]Rugg-Gunn, A., Spencer, A., Whelton, H. *et al.* Critique of the review of 'Water fluoridation for the prevention of dental caries' published by the Cochrane Collaboration in 2015. *Br Dent J* **220,** 335–340 (2016). https://doi.org/10.1038/sj.bdj.2016.257

[45]Lennon, M. The cochrane review of water fluoridation, Editorial, Community Dental Health (2015) **32**, 130–131

[46]Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, Alam R, Tugwell P, Welch V, Glenny AM. Water fluoridation for the prevention of dental caries. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD010856. DOI: 10.1002/14651858.CD010856.pub2. Accesse d 17 April 2022.

Current studies fail to report significant benefit. such as Maupome[47] McLaren[48] Slade[49] Meyer[50] Do[51] Chankanka[52],[53] Choo-Wosoba[54]. The CDC also states, "Ingestion of fluoride is not likely to reduce tooth decay."[55] The apparent benefit[56] of fluoride is the precipitation of the less soluble mineral phase of fluorapatite in the tooth structure, a topical action.

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[47]Maupomé G, Clark DC, Levy SM, Berkowitz J. Patterns of dental caries following the cessation of water fluoridation. Community Dent Oral Epidemiol. 2001 Feb;29(1):37-47. PMID: 11153562.

[48]McLaren L, Singhal S. Does cessation of community water fluoridation lead to an increase in tooth decay? A systematic review of published studies. J Epidemiol Community Health. 2016 Sep;70(9):934-40. doi: 10.1136/jech-2015-206502. Epub 2016 May 13. PMID: 27177581; PMCID: PMC5013153.

[49]Slade GD, Grider WB, Maas WR, Sanders AE. Water Fluoridation and Dental Caries in U.S. Children and Adolescents. J Dent Res. 2018 Sep;97(10):1122-1128. doi: 10.1177/0022034518774331. Epub 2018 Jun 14. PMID: 29900806; PMCID: PMC6169031.

[50]Meyer J, Margaritis V, Mendelsohn A. Consequences of community water fluoridation cessation for Medicaid-eligible children and adolescents in Juneau, Alaska. BMC Oral Health. 2018 Dec 13;18(1):215. doi: 10.1186/s12903-018-0684-2. PMID: 30545358; PMCID: PMC6293551.

[51]Do L, Ha D, Peres MA, Skinner J, Byun R, Spencer AJ. Effectiveness of water fluoridation in the prevention of dental caries across adult age groups. Community Dent Oral Epidemiol. 2017 Jun;45(3):225-232. doi: 10.1111/cdoe.12280. Epub 2017 Jan 16. PMID: 28092105.

[52]Chankanka O, Marshall TA, Levy SM, Cavanaugh JE, Warren JJ, Broffitt B, Kolker JL. Mixed dentition cavitated caries incidence and dietary intake frequencies. Pediatr Dent. 2011 May-Jun;33(3):233-40. PMID: 21703076; PMCID: PMC3690298.

[53]Chankanka O, Levy SM, Marshall TA, Cavanaugh JE, Warren JJ, Broffitt B, Kolker JL. The associations between dietary intakes from 36 to 60 months of age and primary dentition non-cavitated caries and cavitated caries. J Public Health Dent. 2015 Fall;75(4):265-73. doi: 10.1111/j.1752-7325.2012.00376.x. Epub

[54]Choo-Wosoba H, Gaskins J, Levy S, Datta S. A Bayesian approach for analyzing zero-inflated clustered count data with dispersion. Stat Med. 2018 Feb 28;37(5):801-812. doi: 10.1002/sim.7541. Epub 2017 Nov 6. PMID: 29108124; PMCID: PMC5799048.

[55]**Achievements in Public Health, 1900-1999: Fluoridation of Drinking Water to Prevent Dental Caries. MMWR, 48(41); 933-940, October 22, 1999**

[56]Limeback H, A re-examination of the pre-eruptive and post-eruptive mechanism of the anti-caries effects of fluoride: is there any anti-caries benefit from swallowing fluoride? Community Dentistry and Oral Epidemiology, First Published 14 February 2007 https://doi.org/10.1111/j.1600-0528.1999.tb01993.x Volume27, Issue1 February 1999 Pages 62-71

V. RISKS: COST OF DENTAL FLUOROSIS (See also Endnote References)

"***estimated costs for restoring function exceeds the cosmetic costs"***

WHO reports,"In acute poisoning, fluoride kills by blocking normal cellular metabolism. Fluoride inhibits enzymes, in particular metalloenzymes involved in essential processes, causing vital functions such as the initiation and transmission of nerve impulses, to cease. Interference with necessary bodily functions controlled by calcium may be even more important."[57] Assuming fluoride has a threshold for everyone which is safe is presumptive.

Researchers have indicated water fluoridation is a crude and rather ineffective policy to prevent dental caries without a detectable threshold for dental damage. (Dong and European Commission, 2011) A detectible threshold of fluoride exposure for dental damage is possible and critical for the policy of fluoridation. Although the odds of developing dental fluorosis increased with increased water fluoride concentration, the potential for harm exists at all water fluoride concentrations and unique for different individuals.

Gu[58] (2020"*"The pathogenesis of dental fluorosis is not totally clear, which may be a complex pathological process involving both genetic and environmental factors. The prevalence of dental fluorosis has an upward trend around the world, thus certain public prevention and treatment strategies need to be taken."*

Jarquín-Yñezá[59] (2018) *"**Conclusions:** An association of rs 412777 polymorphism in the COL1A2 gene with dental fluorosis was found. Therefore, genetic variants represent a relevant risk factor to develop dental fluorosis, as it was proven in this study conducted in Mexican children."*

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[57] Environmental Health Criteria 36, Fluorine and Fluorides, p. 52. 1984

[58] Gu LS, Wei X, Ling JQ. [Etiology, diagnosis, prevention and treatment of dental fluorosis]. Zhonghua Kou Qiang Yi Xue Za Zhi. 2020 May 9;55(5):296-301. Chinese. doi: 10.3760/cma.j.cn112144-20200317-00156. PMID: 32392970

[59] Jarquín-Yñezá L, Alegría-Torres JA, Castillo CG, de Jesús Mejía-Saavedra J. Dental fluorosis and a polymorphism in the COL1A2 gene in Mexican children. Arch Oral Biol. 2018 Dec;96:21-25. doi: 10.1016/j.archoralbio.2018.08.010. Epub 2018 Aug 23. PMID: 30172079.

Suzuki[60] (2015) *We demonstrate that fluoride exposure generates reactive oxygen species (ROS) and the resulting oxidative damage is counteracted by SIRT1/autophagy induction through c-Jun N-terminal kinase (JNK) signaling in ameloblasts. In the mouse-ameloblast-derived cell line LS8, fluoride induced ROS, mitochondrial damage including cytochrome-c release, up-regulation of UCP2, attenuation of ATP synthesis, and H2AX phosphorylation (γH2AX), which is a marker of DNA damage."*

Dental fluorosis is usually considered the singular causation, a biomarker, of excess fluoride ingestion prior to 6-8 years of age; however, other unknowns need to be explored[61] to explain the significant increase in dental fluorosis.

DENTAL FLUOROSIS IS BOTH COSMETIC AND FUNCTIONAL

Collins. [62] (1987) *"A mean cost for all consultants shows that the **estimated costs for restoring function exceeds the cosmetic costs** in all categories except the minimum later costs. This represents a new finding and raises an issue that has been overlooked or ignored by previous investigators and the profession. i.e .. that repair of the cosmetic discoloration was the only cost involved; or that repair of dysfunction was never considered to be a problem."* (Emphasis supplied)

Collins study was funded by the EPA for the EPA and peer reviewed by the EPA to evaluate the cost of fluoride exposure from water at four concentrations. The six consultants do not appear to be blinded, they were chosen from locations with various fluoride concentrations. and do not appear to have been cosmetic dentists. Perhaps the consultants were functional dentists rather than cosmetic dentists and their focus was on functional restorations. Regardless, dental fluorosis is both cosmetic and functional damage.

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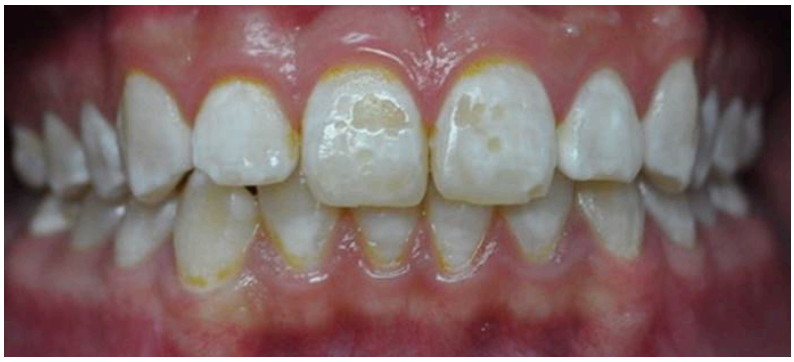
[60] Suzuki M, Bandoski C, Bartlett JD. Fluoride induces oxidative damage and SIRT1/autophagy through ROS-mediated JNK signaling. Free Radic Biol Med. 2015 Dec;89:369-78. doi: 10.1016/j.freeradbiomed.2015.08.015. Epub 2015 Sep 30. PMID: 26431905; PMCID: PMC4684823.

[61] Akpata ES. Occurrence and management of dental fluorosis. Int Dent J. 2001 Oct;51(5):325-33. doi: 10.1002/j.1875-595x.2001.tb00845.x. PMID: 11697585.

[62] Collins, E., V. Segreto, H. Martin, AND H. Dickson. ANALYSIS OF COSTS FOR THE TREATMENT OF DENTAL FLUOROSIS. U.S. Environmental Protection Agency, Washington, D.C., EPA/600/5-87/001 (NTIS PB87170817), 1987.

"Damage is the cost, not the repair." Without patient consent, compensation for damage with quality treatment costs is reasonable. Harm from fluoridation is not self inflicted harm or patient negligence.



The picture of severe fluorosis to the right is of my patient growing up on fluoridated bottled "Nursery Water" (DS Waters of America Inc. <1 ppm) starting at age 4 months. Mom is confident he did not use fluoride toothpaste until about age 4 years old and did not swallow toothpaste. Estimated exposure is less than 1 mg per day when young to about 1 mg at age 4. Dosage estimated at 0.13+ mg/kg/day when 4 months old to 0.05+ mg/kg/day at 4 years. An increase in fluoride exposure when fluoridated toothpaste started would be expected. This severe dental fluorosis damage is known harm from excess fluoride primarily from water below fluoridation concentrations recommended by WHO.

The Nuffield Council suggests the risks for a public health policy should be judged on **"potential harm,"** more protective than "possible, presumed, or known harm."

WHO accepts the known harm calling it an "adverse effect," yet, minimizes the harm. *"However, fluoride can also have an adverse effect on tooth enamel and may give rise to mild dental fluorosis (prevalence: 12–33%) at drinking-water concentrations between 0.9 and 1.2 mg/l, depending on drinking- water intake and exposure to fluoride from other sources."*

WHO falls into the trap of protecting fluoridation by attempting to isolate the exposure of fluoride from total fluoride exposure. Real world life is not lived in isolation and Public Health must NOT ignore total fluoride exposure from all sources and patient sensitivities.

Akpata[63] reports, *In some countries, exposure to apparently low fluoride concentrations in drinking water has resulted in severe dental fluorosis in some children.*

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[63] Akpata ES. Occurrence and management of dental fluorosis. Int Dent J. 2001 Oct;51(5):325-33. doi: 10.1002/j.1875-595x.2001.tb00845.x. PMID: 11697585.

In contrast, the US Centers for Disease Control and Prevention (CDC)[64] and Community Preventive Task Force[65] report no harm from fluoridation except dental fluorosis and only cosmetic, usually only noticed by trained professionals, and other sources of fluoride are not significant.

PERCENTAGE OF THE POPULATION HARMED WITH DENTAL FLUOROSIS

Cosmetic dentistry is subjective and dependent on the dentists opinion, presentation of cosmetic health, their skill, training, materials available, socioeconomics of their patient base and each individual patient's subjective opinion.

In 1993, Riordan[66] reported 17.5% of 7 year olds who do not have all their adult teeth were assessed by members of the public as a notable concern of dental fluorosis. Functional damage was not included. With dental fluorosis about twice as high now as1993, and currently NHANES twice reporting 70% of children with dental fluorosis, a conservative estimation of 17.5% of children have **notable concern and functional damage** is reasonable which would include a percentage of those with mild dental fluorosis and most with moderate and severe fluorosis.

Moderate and severe fluorosis appears to range from 3.6% (Beltran-Aguilar ages 12-15 years in 1999-2004) 6% (Ko) to 28% (NHANES 2012).

An estimated range of 4% to 17.5% of those fluoridated have cosmetic concern and/or functional damage contributed by fluoridation.

DENTAL FLUOROSIS TREATMENT OPTIONS

Treatment options today are potentially different than in the 1980's Collins' study which reported a range between $660 to $12,000 (2019 dollars corrected by 2.2 for inflation). Collins made an assumption a needed treatment would last a lifetime. Because more functional damage was noted in Collins study than cosmetic damage, the possibility the consultants put a higher treatment

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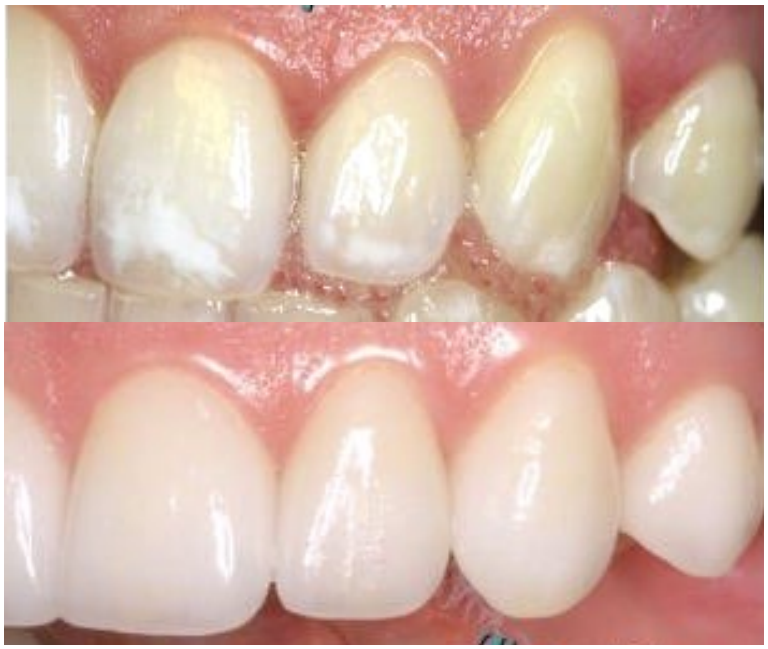
[64] https://www.cdc.gov/fluoridation/faqs/community-water-fluoridation.html accessed May 17, 2022

[65] Community Preventive Services Task Force; https://www.thecommunityguide.org/sites/default/files/assets/Oral-Health-Caries-Community-Water-Fluoridation.pdf 2015 Accessed May 17, 2022

[66] Riordan PJ. Perceptions of Dental Fluorosis. *Journal of Dental Research*. 1993;72(9):1268-1274. doi:10.1177/00220345930720090201

priority on functional harm than cosmetic harm must be considered. Damage is measured here by the cost of quality treatment rather than dental insurance covered procedures.

While practicing in a low socioeconomic community, I almost never treated cosmetic issues. Moving to a high socioeconomic community I frequently treat cosmetic concerns. When people have money, cosmetics becomes a greater concern and dentists tend to diagnose what their patients can afford or is covered by their insurance. There is no wonder why Delta Dental funds fluoridation when they assume benefit and do not cover cosmetic damage.



Micro-abrasion,[67] grinding away the outer layer of enamel, can improve superficial defects of dental fluorosis. Treatment estimated $500 to $2,500 per patient life time and may need additional vital bleaching. Some patients consider micro-abrasion additional damage, but certainly less than a typical crown or veneer.

Bleaching is more acceptable to some but tends to whiten all areas and a contrast in shade is, for some, not fully restored. Bleaching needs to be retreated and an estimate is $100 to $600 every 2 years. We use an estimated $100 PPPY (per person per year) for 60 years, $6,000 life time

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[67] Azzahim L, Chala S, Abdallaoui F. La micro-abrasion amélaire associée à l'éclaircissement externe: intérêt dans la prise en charge de la fluorose [Role of enamel microabrasion associated with external bleaching in the management of patients with dental fluorosis]. Pan Afr Med J. 2019 Oct 4;34:72. French. doi: 10.11604/pamj.2019.34.72.20401. PMID: 31819788; PMCID: PMC6884726.

treatment costs. Statista survey[68] reports 37 million in the USA had bleaching in 2020, about 14% of the age range of dental fluorosis.

Placing a value on the damage for patient perceived damage, assumed to be mostly in moderate to severe fluorosis found objectionable with high quality cosmetic and functional treatment is estimated at $1,000 to $2,500 per tooth, $1,200 is used here. The diagnosis of dental fluorosis is based on the two worst teeth, although 1 to 28 teeth can be damaged. If costs are not the controlling factor, a cosmetic patient will want several or all upper and lower teeth treated. An estimate of an average of 10 teeth at $1,200 per tooth damage both functional and cosmetic is at the high end of Collins EPA study and in keeping with high quality cosmetic restorative treatment. For a lifetime cost, the work is estimated to be replaced an average of every 12 years, or $1,000 PPPY, 60 year lifetime of $60,000 damage. Damage is determined by cost of damage.

Assuming 4% to 17.5%% of the population have fluorosis of noticeable and functional harm which they would choose to be compensated for ($2,400-$10,500), and 1.46% at each year of life, an average per capita harm to teeth from excess fluoride exposure is $35 to $153 PPPY harm to teeth compared to $6 PPPY benefit to teeth.

From just an evaluation of dental benefit cost analysis, fluoridation does not make sense.

An example of high quality dental fluorosis treatment (not my patient):

[68] https://www.statista.com/statistics/287384/usage-of-tooth-whiteners-in-the-us-trend/

VI. COST OF FLUOROSIS DAMAGE (See also Endnote References)

"The principle hazard at issue from exposure to fluoridation chemicals is IQ loss.[69]"

Several streams of evidence should be kept in mind. Fluoride concentrations in water are not individual total exposure because not everyone drinks the same amount of water, some drink 10 times more than the mean, and some ingest more from other sources such as swallowing toothpaste. Genetic factors need inclusion. An uncertainty factor should be included and a range of total exposure of at least 10 should be used. Pregnant moms are of particular concern because the placenta does not significantly protect the developing fetus from fluoride.

Whereas the mechanism for potential benefit from swallowing fluoride is not well understood, the mechanism of fluoride's developmental neurotoxicity has been reported. *"NaF induces developmental neurotoxicity by decreasing lysosomal V-ATPase expression, increasing lysosomal pH, disrupting lysosomal degradation capacity, and blocking autophagic flux, induced neurotoxicity*."[70]

Over 70 human IQ studies have reported developmental neurotoxicity from fluoride. Most studies prior to 2015 were ecological in design as opposed to individual level exposure and most not reasonably applicable to fluoridation concentrations. Since 2015, high-quality USA government funded studies included measurements at the individual level, at fluoridation concentrations 0.7 mg/L fluoride or less and report harm.

Twenty seven of the IQ studies published between 1988-2012 were used in a meta-analysis by a Harvard University team including Philippe Grandjean (Choi et al 2012). The consistent results from several countries found lower IQ in the "high-fluoride" villages compared with the low-fluoride villages, averaging 7 IQ points lower. Most were at levels above 0.7 mg/l.

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[69] Bruce Lamphear MD MPH Professor of Health Sciences at Simon Fraser University. Authored the seminal research on the neurotoxicity of lead.

[70] Han X, Tang Y, Zhang Y, Zhang J, Hu Z, Xu W, Xu S, Niu Q, Impaired V-ATPase leads to increased lysosomal pH, results in disrupted lysosomal degradation and autophagic flux blockage, contributes to fluoride-induced developmental neurotoxicity, Ecotoxicology and Environmental Safety, Accepted 6 April 2022 www.elsevier.com/locate/ecoenv https://doi.org/10.1016/j.ecoenv.2022.113500

Some may suggest the findings are irrelevant to fluoridation programs at 0.7 mg/L; however, potential harm to some or many should consider: (a.) the individual amount of water ingested, (b) total fluoride exposure, (c) patient sensitivity, (d) nutritional status (e) other toxicants such as arsenic, (f) and lack of uncertainty factor.

The NTP's systematic review of fluoride's neurotoxicity (2016-2022).

The US National Toxicology Program (NTP) Draft Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects[71] concludes fluoride is presumed to have a developmental neurotoxic effect on the developing brain, resulting in lower IQ. "Presumed" determination is stronger confidence than Nuffield's "potential harm." *"Fluoride is presumed to be a cognitive neurodevelopmental hazard to humans is based on consistent evidence from 26 lower risk-of-bias studies that evaluated fluoride exposure and effects on children's IQ and other cognitive effects."*[72]

The National Academy of Science (NAS) did a peer review of the NTP draft but *"did not conduct its own independent evaluation of the evidence, and it did not conduct a data audit,"* nor was the review blinded. The NAS did not refute the conclusion, in part because the NTP did not conduct a formal dose-response assessment. NTP did not evaluate benefit, only developmental neurotoxicity.

The NAS draft concluded, *"the committee does not find that NTP has adequately supported its conclusion. That finding does not mean that the conclusion is incorrect; rather, further analysis or reanalysis as noted in the present report is needed to support conclusions in the monograph."*

The NTP has published two drafts of its review of fluoride's neurotoxicity, (NTP,2019, NTP,2020).

The draft versions have indicated that of 29 High Quality (i.e. low risk of bias), 27 found a lowering of IQ and only 2 found no effect. Of these 27, 10 were conducted at 0.7 ppm or lower; another 8 conducted between 0.7 and 1.5 ppm and 9 at 1.5 ppm or higher (ISEE-2020 poster).

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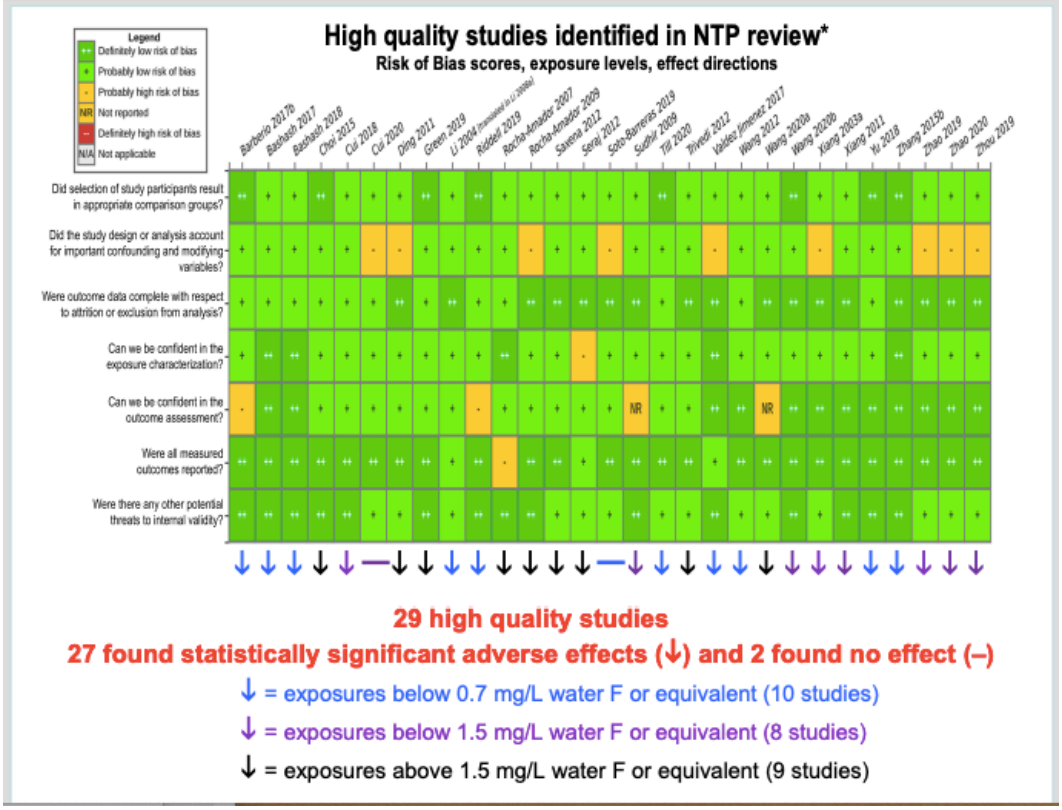
[71] https://www.asdwa.org/wp-content/uploads/2019/10/draft_fluoride_monograph_20190906_5081.pdf

[72] DRAFT NTP MONOGRAPH ON THE SYSTEMATIC REVIEW OF FLUORIDE EXPOSURE AND NEURODEVELOPMENTAL AND COGNITIVE HEALTH EFFECTS p. 72. https://fluoridealert.org/wp-content/uploads/ntp.revised-monograph.9-16-2020.pdf



]The top of the half of this figure is the NTP's summary of the quality (risk of bias) ratings given by the NTP for 29 studies. The color code ranges from green to red, where green represents low risk of bias (i.e. high-quality) and red means high risk of bias (i.e. low-quality). The lower part of the figure has been added by Chris Neurath, FAN's research director, who has identified the water fluoridation measured in each study (see ISEE-2020 poster).

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The finding of lowering IQ at 1.5 ppm offers no adequate margin of safety when you are exposing a large population of children to 0.7 ppm of fluoride in their drinking water. There are two reasons for this a) children drink different amounts of water and b) there is a wide range of sensitivity to any toxic substance among a large population. Typically, regulatory agencies like the EPA would like a margin of safety of 10, in this case 1.5 ppm only offers a margin of safety of 2.

Three benchmark dose analysis have been done for fluoride's developmental neurotoxicity, with consistent results.

Hirzy (2016) reported 1 IQ loss at 0.22 mg/L fluoride in water.

Grandjean (2021)[73] 1 IQ loss at 0.2 mg/L fluoride in urine or water. *"Thus, the joint data show a BMCL in terms of the adjusted U-F (urine fluoride) concentrations in the pregnant women of approximately 0.2 mg/L. These results can be used to guide decisions on preventing excess fluoride exposure in pregnant women."*

The third by Thiessen[74] for the TSCA ongoing trial against the EPA.

Table 6 of the NTP 2020 draft report lists only three studies from the year 2020, Wang, Cui, and Till, no studies from 2021 or 2022. The potential that additional studies will contradict the combined strength of current studies reporting harm is highly unlikely.

Three studies to consider based on individual measurements of fluoride exposure (Bashash et al., 2017) published in *Environmental Health Perspectives,* then Green et al., 2019 published in JAMA Pediatrics and Till et al., 2020) in *Environment International*. They controlled for confounding variables and were conducted either in fluoridated communities at 0.7 ppm (Green, 2019 and Till, 2020) or in communities with exposures (from other sources) in the same range as fluoridated communities (Bashash, 2017 and 2018).

Bashash, et al. 2017, a 12-year, prospective mother-child cohort study reported a 4 to 5 point loss of IQ in offspring, associated with maternal fluoride intake, typical of a fluoridated community. The mother's fluoride exposure was measured directly via urinary fluoride level and the paired offspring's IQ was measured (again individually) at 4 and 6-12 years of age. Measured urinary fluoride concentration evaluates total fluoride exposure regardless of the source.
Graphing the Bashash 2017 data below.

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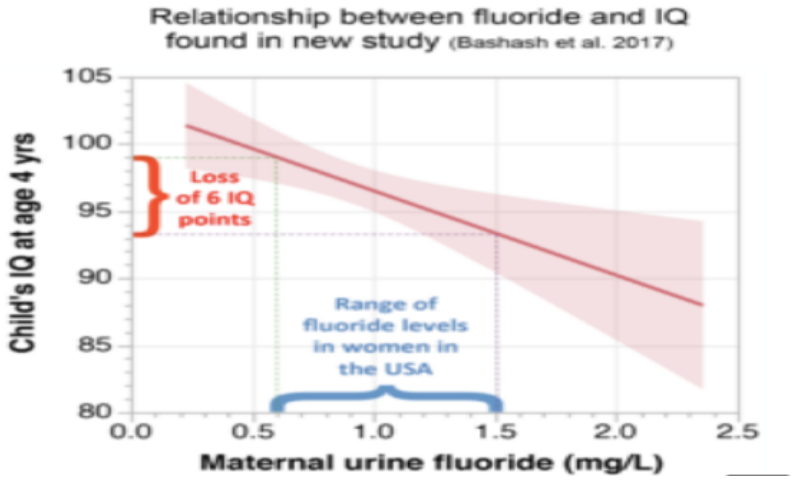
[73]Grandjean P, Hu H, Till C, Green R, Bashash M, Flora D, Tellez-Rojo MM, Song PXK, Lanphear B, Budtz-Jørgensen E. A Benchmark Dose Analysis for Maternal Pregnancy Urine-Fluoride and IQ in Children. Risk Anal. 2021 Jun 8. doi: 10.1111/risa.13767. Epub ahead of print. PMID: 34101876.

[74]Kathleen Thiessen Ph.D Director and senior scientist at Oak Ridge Center for Risk Analysis. Served on the 2006 National Research Council panel that reviewed the toxicologic literature on fluoride.



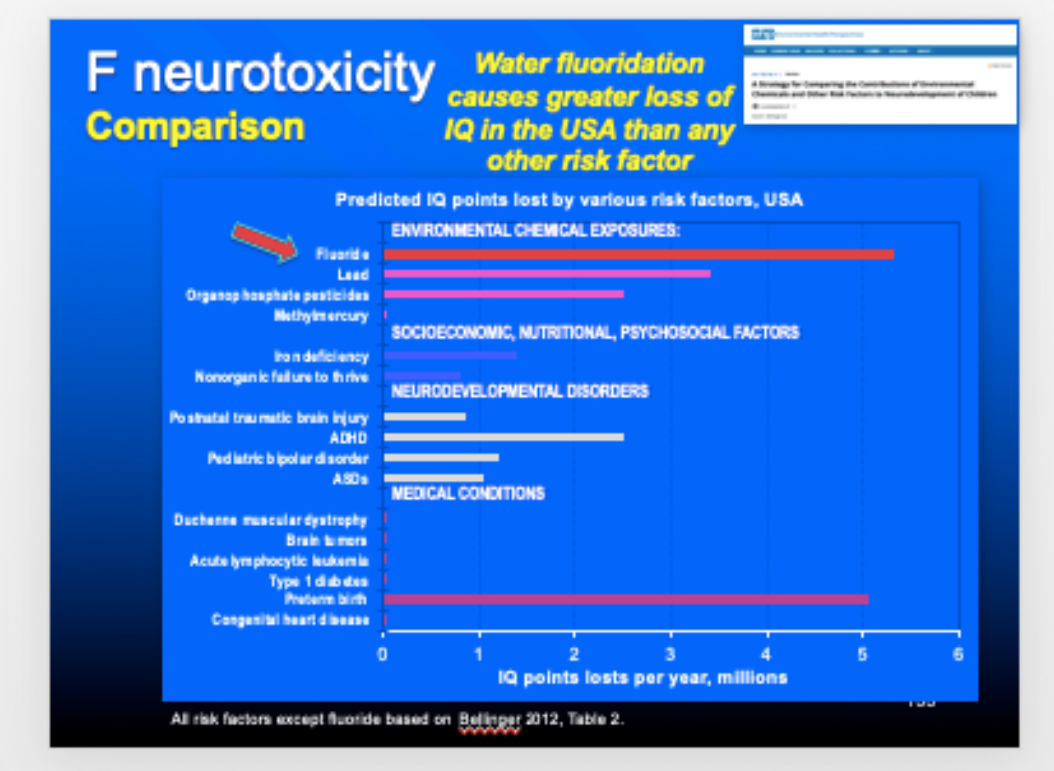
(Graph by Connett and Neurath)

Till et al, 2018. again measured the urine fluoride levels in pregnant women across Canada and reported the urine fluoride levels were twice as high in fluoridated communities as in non-fluoridated communities. Till et al reported the average levels in the fluoridated communities were similar to the levels found by Bashash, i.e. 0.91 versus 0.87 ppm.

Green et al., 2019 published in *JAMA Pediatrics* essentially replicated the Bashash, 2017 findings IQ lower in boys associated with maternal fluoride exposure but not in girls. Using two other ways of assessing maternal fluoride exposure they reported IQ low for boys and girls.

A podcast (LINK) by two of the *JAMA Pediatrics* editors is short and well worth watching. The editors also published in the same issue of the journal an editorial explaining this and an article from Dr. David Bellinger.

Till et al., 2020. showed that early infancy is another vulnerable period from fluoride for the developing brain. Till found a large significant lowering of IQ (i.e. up to 9 IQ points) for children who were bottle-fed in *fluoridated communities* in Canada (F level = 0.7 ppm or less) compared to those who were bottle-fed in *non-fluoridated communities.*



This figure is based on data collected by David Bellinger (Bellinger, 2012, Table 2) only the fluoride data line has been added. Figure by Chris Neurath (ISEE-2020 poster)

Gram for gram, based on our current understanding, fluoride is not more neurotoxic than lead. Lead levels and IQ loss is measured in parts per *billion* fluoride and IQ loss is measured in parts per *million*. However, millions of people every day in the USA is leading to a greater overall loss of IQ points at the population level.

Studies reporting no IQ concerns.

Broadbent et al. (2015) The draft versions of the systematic review by the NTP gave this study a low-quality rating (a high risk of bias). Osmunson[75] reported the study had little power to find a difference in IQ between the children who drank fluoridated water and those who didn't. There were nearly 1000 children who grew up in a fluoridated area but less than 100 who did not. Only fluoride via water was measured and not via tea, toothpaste or via supplements which are seldom prescribed to those on fluoridated water; therefore, most supplements would have been pre-

[75]Osmunson, B., Limeback, H., & Neurath, C. (2016). Study Incapable Of Detecting IQ Loss From Fluoride. *American journal of public health*, *106*(2), 212–213. https://doi.org/10.2105/AJPH.2015.302918

scribed in the non fluoridated 100 children. Exposure during fetal and infant development were not measured.

Aggeborn and Öhman (2016). The Effects of Fluoride In The Drinking Water. looked at populations by region in Sweden and used the average naturally occurring fluoride level because Sweden is not artificially fluoridated. The authors considered population measurements for cognitive ability and achievement. Individual measurements of fluoride exposure were not made. Dr. Vyvyan Howard, an infant and fetal pathologist, "Anybody who accepts that this paper trumps Bashash and/or Green can't have read any of the studies very thoroughly - or has an agenda."

Guth et al. 2020 and 2021 incorrectly give more weight to the Broadbent study than to the Green study with individual measured fluoride concentrations.

Miranda et al., 2021 only considered studies of children aged 8- 12. (See https://www.qeios.-com/read/X3MKH8).

Ibarluzea et al., 2022. This prospective cohort study from Spain is an outlier. They did *not* find a loss of IQ in the fluoridated community compared to the non-fluoridated community, rather they found a *15 IQ point benefit* for boys. Ibarluzea et al appears to have failed to adequately control for other toxins such as for lead and arsenic in the industrial non-fluoridated community.

TOXIC SUBSTANCE CONTROL ACT LEGAL ACTION

In 2017, the EPA was taken to Federal court (Region 9, San Francisco). Experts for the plaintiffs were Howard Hu (director of the ELEMENT cohort in Mexico City which was used in the Bashash, 2017 and 2018 studies); Bruce Lanphear, a world-renowned expert on lead's neurotoxicity and co-author of the Green, 2019 and Till, 2021 studies and Philippe Grandjean, a world-renowned expert on mercury's neurotoxicity and author of a risk assessment (BMD analysis) on fluoride's neurotoxicity.

EPA used Exponent, Inc. experts. The EPA lawyers chose not to use scientists from within the agency, but instead used experts from the firm *Exponent, Inc.* This firm is well known for being highly industry-friendly defending the safety of such chemicals as dioxins, PCBs, PFOS and Monsanto's glyphosate. The Exponent's experts agreed the four US government-funded studies (Bashash, 2017, 2018; Green, 2019 and Till, 2020) are the highest quality human studies on fluoride conducted to date.

Hu, "Fluoride is a developmental neurotoxicant at levels of exposure seen in the general population in water-fluoridated communities."

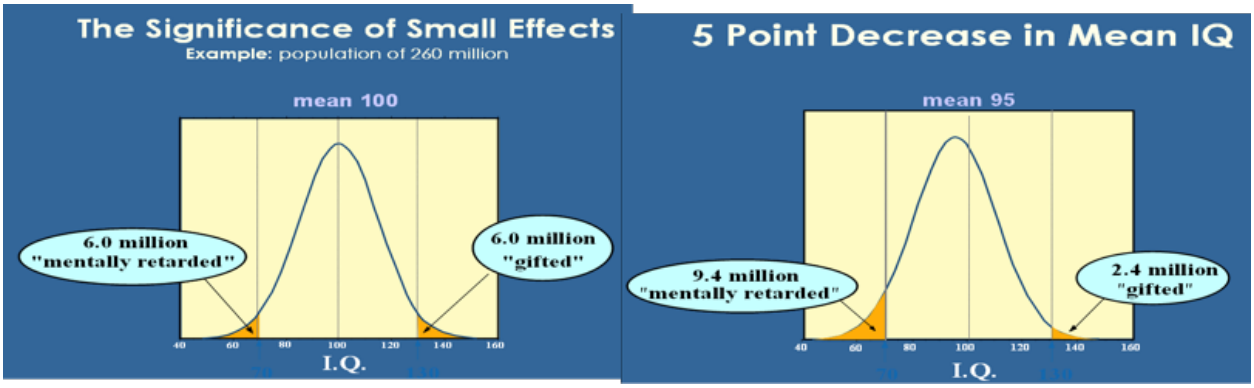
Grandjean[76] "IQ losses associated with community water fluoridation are substantial and of significant public health concern."

Lamphear[77] "Fluoride exposure during early brain development diminishes the intellectual abilities in young children."

Estimating the cost of lower IQ depends in part on what is included in lower IQ. Research indicates we can expect more than 50% increase in special education students, half as many gifted, increase in incarceration, increase in divorce, increase in job loss and less job retention. Higher IQ is also associated with increased happiness.

For more human studies reporting fluoride's developmental neurotoxicity, see https://fluoridealert.org/studies/brain01/ where a review of studies which do not report an association between fluoride and IQ can be found.

Graphing the effect of 5 IQ loss on the population below raises serious concern.



(Illustration used by Physicians for Social Responsibility and effects of lead)

[76]Phillipe Grandjean MD DMSc Chair of Environmental Medicine at the University of Southern Denmark. Nearly 500 papers published, specialized in developmental exposures to environmental chemicals like mercury, fluoride, and lead.

[77]Bruce Lamphear MD MPH Professor of Health Sciences at Simon Fraser University.

In addition, blood lead levels in fluoridated communities are twice as high for whites and six times higher for African Americans.[78],[79],[80]

There is an incredible correlation between IQ and income. Various reports find homeless mean IQ of 80, average American welfare recipient IQ 92, millionaires IQ 118 and billionaires 130.[81] However there is not a direct correlation between dollars and IQ. For example, some professions such as University Professors, Judges, and Humanitarian agency employees often have very high IQ but chose the betterment of society rather their own financial benefit.

We are just beginning to determine what dimension of IQ is harmed the most with fluoride ingestion. *"*According to professor Howard Gardner of Harvard University, intelligence can be measured along seven different dimensions: Visual-spatial, bodily-kinesthetic, musical, social, emotional, linguistic, and logical-mathematical. At most, an IQ test tries to measure three of these: Visual-spatial, linguistic, and logical-mathematical. Some people see even more dimensions — creativity, memory and retention, reaction time, etc."

As scientists test fluoride's neurotoxic effects in more specific ages, races, genders, nutrients, diseases, medications, and various intelligence dimensions, we will have a more clear and elevated confidence on precisely how much and what aspects of the human brain and nervous system is being harmed.

There will always be some who in effect require RCTs of harm to prove damage. However, an ethical approach only requires our confidence to be at a potential of harm.

78Coplan MJ, Patch SC, Masters RD, Bachman MS. Confirmation of and explanations for elevated blood lead and other disorders in children exposed to water disinfection and fluoridation chemicals. Neurotoxicology. 2007 Sep;28(5):1032-42. doi: 10.1016/j.neuro.2007.02.012. Epub 2007 Mar 1. PMID: 17420053.

79Maas RP, Patch SC, Christian AM, Coplan MJ. Effects of fluoridation and disinfection agent combinations on lead leaching from leaded-brass parts. Neurotoxicology. 2007 Sep;28(5):1023-31. doi: 10.1016/j.neuro.2007.06.006. Epub 2007 Jun 30. PMID: 17697714.

80Masters RD, Coplan MJ, Hone BT, Dykes JE. Association of silicofluoride treated water with elevated blood lead. Neurotoxicology. 2000 Dec;21(6):1091-100. PMID: 11233755.

81https://pumpkinperson.com/2016/02/11/the-incredible-correlation-between-iq-income/

Muir[82] (2001) estimated 5 IQ loss in the USA of $275 and $326 Billion per year or $980 to $1,160 PPPY in 2001 and correcting 2.2 for 2010 dollars is $2,156 to $2,552PPPY

The highest estimate of fluoridation's benefit is lost when including cosmetic and functional harm and presumed developmental neurotoxic effects are more confident than a judgment of potential harm.

Attempting to measure harm to the brain with money, fails to include the emotional harm and grief for the patient, their families and friends.

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[82]Muir T, Zegarac M., Societal Costs of Exposure to Toxic Substances: Economic and Health Costs of Four Case Studies That Are Candidates for Environmental Causation. Environmental Health Perspectives Volume 109 Supplement 6. December 2001.

VII. RISK: POTENTIAL ADHD INCREASE.

Attention Deficit Hyperactivity Disorder (ADHD) has become one of the most commonly diagnosed childhood behavioral disorders. Its basic characteristics are inattention, hyperactivity and impulsivity. "ADHD often continues into adolescence and adulthood, which can lead to medication dependency and a lifetime of treatment (Maddox et al.YEAR) "

Malin and Till examined the relationship between exposure to fluoridated water and ADHD prevalence among children and adolescents, ages 4-17, in the United States. The authors found that, the percentage of each state fluoridated as assessed in 1992, "significantly positively predicted state prevalence of ADHD in 2003, 2007 and 2011, even after controlling for socioeconomic status."

A multivariate regression analysis showed that after socioeconomic status was controlled each 1% increase in artificial fluoridation prevalence in 1992 was associated with approximately 67,000 to 131,000 additional ADHD diagnoses from 2003 to 2011. Overall state water fluoridation prevalence (not distinguishing between fluoridation types) was also significantly positively correlated with state prevalence of ADHD for all but one year examined." (Malin & Till, 2015). See figure below

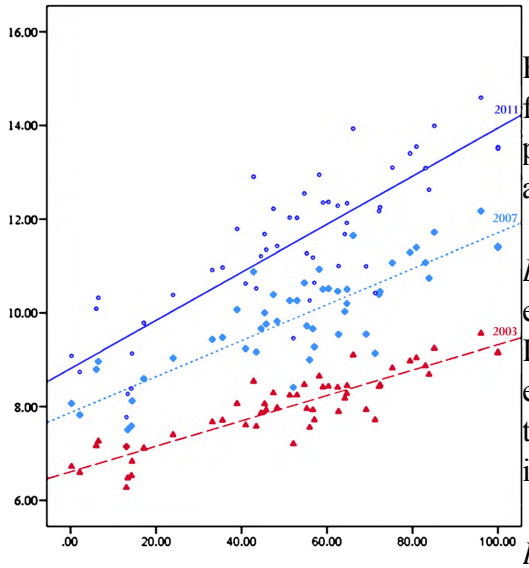

Figure 12: Percent of children with ADHD (by state) for 2003, 2007 and 2011 plotted against the % of the population in each state fluoridated in 1992 (Mallin and Till, 2015)

Bashash et al., 2018 using the same ELEMENT mother-child cohort in Mexico City that they used in their IQ study (Bashash et al, 2017) found that as the mothers' exposure to fluoride increased (as measured in their urine) so did the number of symptoms of ADHD increase in their offspring

Riddell, et al. 2019. Reported 284% increase in the prevalence of ADHD among adolescents in fluoridated communities in Canada compared to non-fluoridated communities.

ADHD appears to have different phases and life long effect.[83]

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[83]Brod, M., Schmitt, E., Goodwin, M. et al. ADHD burden of illness in older adults: a life course perspective. Qual Life Res **21,** 795–799 (2012). https://doi.org/10.1007/s11136-011-9981-9

CDC[84] 2016 reported National Prevalence of ADHD at 6.1% children 2-17. That reduces 4.5% of the total population are on fluoridated water. We estimate half or 2.25% of the ADHD is from fluoridation.

Miller[85] estimated excess ADHD costs from $143 to $266 Billion per year, we use 2.25% of 180 Billion resulting in $4 Billion per year, 60 year lifespan, for $240 Billion ADHD lifetime harm from fluoridation. For every dollar saved with fluoridation, ADHD costs increase by $1,700. However, some of these costs would overlap with costs for lower IQ.

84Danielson M, Bitsko R, Ghandour RM, Holbrook J, Kogan,M, Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment among U.S. Children and Adolescents, 2016.. Journal of Clinical Child and Adolescent Psychology. Published online before print January 24, 2018

85Miller C, Study Finds Substantial Economic Impact of ADHD in the United States. American Psychiatric Association Foundation, November 2016.

VIII. RISK: ENDOCRINE AND HORMONE DISRUPTION (See also endnotes)

"Endocrine systems, also referred to as hormone systems, are found in all mammals, birds, fish, and many other types of living organisms. They are made up of:

-Glands located throughout the body;

-Hormones that are made by the glands and released into the bloodstream or the fluid surrounding cells; and

-Receptors in various organs and tissues that recognize and respond to the hormones."[86], [87]

Hormones regulate many biological processes and regulate blood sugar, growth, , reproductive organs, metabolism, sex hormones, development of the brain, and nervous system, testes, ovaries, pituitary, thyroid and adrenal glands.

The National Research Council (NRC, 2006) panel devoted a whole chapter to a discussion of fluoride and the endocrine system.

The panel concluded that fluoride was an endocrine disruptor. The authors state:

> *"The chief endocrine effects of fluoride exposures in experimental animals and in humans include decreased thyroid function, increased calcitonin activity, increased parathyroid hormone activity, secondary hyperparathyroidism, impaired glucose intolerance, and possible effects on the timing of sexual maturity. Some of these effects are associated with fluoride intake that is achievable at fluoride concentrations in drinking water of 4 mg/L or less, especially for young children or for individuals with high water intake. (p. 8, NRC 2006)*
>
> *"In summary, evidence of several types indicates that fluoride affects normal endocrine function or response; the effects of the fluoride-induced changes vary in degree and kind in different individuals. Fluoride is therefore an endocrine disruptor in the broad sense of altering normal endocrine function or response, although probably not in the sense of mimicking a normal hormone." (p. 266, NRC 2006)*

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[86] https://www.epa.gov/endocrine-disruption/what-endocrine-system#hormones

[87] United States Environmental Protection Agency, What is the Endocrine System? https://www.epa.gov/endocrine-disruption/what-endocrine-system#hormones

Endocrine damage is a serious concern. Endocrine disruption can cause developmental malformations, reproductive harm, increased cancer risk, disturbances in the immune and nervous system function.

Cost of Endocrine disruption from fluoride. Attina[88] (2016) estimated the economic burden due to the health effects of endocrine-disrupting chemicals at $340 Billion which maybe low. Estimating how much damage is caused by each specific endocrine disrupting chemical has not been published. The amount of damage from fluoride exposure is not know and probably overlap with lower IQ and ADHD.

Liang[89] *"These results revealed that fluoride could induce mitochondrial impairment and excessive PINK1/Parkin-mediated mitophagy in testicular cells, especially in Leydig cells, which could contribute to the elucidation of the mechanisms of F-induced male reproductive toxicity.*"

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88 Attina TM Hauser R Sathyanarayana S et al. Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. Lancet Diabetes Endocrinol. 2016; 4: 996-1003

89 Liang C, Gao Y, He Y, Han Y, Manthari RK, Tikka C, Chen C, Wang J, Zhang J. Fluoride induced mitochondrial impairment and PINK1-mediated mitophagy in Leydig cells of mice: In vivo and in vitro studies. Environ Pollut. 2020 Jan;256:113438. doi: 10.1016/j.envpol.2019.113438. Epub 2019 Oct 21. PMID: 31672359.

IX. RISK: POTENTIAL FOR THYROID HARM (See also endnotes)

In 2006, the NRC panel reported: "Fluoride exposure in humans is associated with elevated TSH concentrations, increased goiter prevalence, and altered T4 and T3 concentrations; similar effects in T4 and T3 are reported in experimental animals, but TSH has not been measured in most studies." (p. 262) An elevated TSH level is an indicator of low thyroid function.

The NRC panel also indicated that effects on the thyroid have been observed at very low levels. They state that, "In humans, effects on thyroid function were associated with fluoride exposures of 0.05-0.13 mg/kg/day when iodine intake was adequate and 0.01-0.03 mg/kg/day when iodine intake was inadequate (Table 8-2)." (p. 263, NRC 2006).

Hypothyroid and fluoride study from UK. These concerns were further reinforced by new research conducted in the UK and published in 2015 by Peckham et al.[90]

Peckham et al. used the records of over 98% of the General practices in England on the numbers of patients treated for hypothyroidism and examined the prevalence of this condition as a function of the fluoride levels in the local drinking water supplies. The authors noted that:

"Approximately, six million people (10%) in England live in areas where drinking water contains natural fluoride or which has been artificially fluoridated at a target concentration of 1 ppm (1 mg/L). Using prevalence data from the UK QOF, an analysis was undertaken to determine whether prevalence was affected by practice populations being situated in fluoridated areas at >0.7 mg/L and areas with lower levels of fluoride. While there are other sources of fluoride in people's diet (eg, tea), drinking water is the most significant source of ingested fluorides in the UK." (Peckham et al, 2015)

The UK research team found that higher levels of fluoride in drinking water was a useful predictor of the prevalence of hypothyroidism. They found that general medical practices located in the West Midlands (a wholly fluoridated area) are nearly twice as likely to report high hypothyroidism prevalence in comparison to Greater Manchester (non-fluoridated area). (Peckham et al, 2015)

Peckham et al, concluded:

"In many areas of the world, hypothyroidism is a major health concern and in addition to other factors—such as iodine deficiency— fluoride exposure should be considered as a contributing factor. The findings of the study raise particular concerns about the validity of community fluoridation as a safe public health measure." (Peckham et al, 2015)

90Peckham S, Lowery D, Spencer S. 2015. Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water. J Epidemiol Community Health 69(7):619-24. https://www.ncbi.nlm.nih.gov/pubmed/25714098

A. Peckham's findings are not totally unexpected, because of the experience of doctors using fluoride to lower thyroid function in patients with hyperthyroidism. Hypothyroidism is a very common disorder in the US. In fact, one of the most prescribed drugs in the USA is synthroid, which is used to treat hypothyroidism. It can have serious adverse health effects.

B. Race may be a factor in sensitivity to certain thyroid diseases, which may make minorities more vulnerable to fluoride's impacts on thyroid function

C. Reduced thyroid function in pregnant women is linked to reduced IQ in their children and there is accumulating evidence that fluoride, at levels within the range to which fluoridated populations are exposed, is associated with lowered IQ (see section 14 above). Fluoride's effect on thyroid function might be one mechanism by which it lowers IQ.

Malin et al, 2018. In a large study of the Canadian population did not find an association between fluoride exposure and TSH levels (a biomarker for HYPOthyroidism) in the general population but she did find that *the subset of the population which had outright or borderline iodine deficiency had their TSH levels raised further by fluoride exposure.*

In other words, those who were already pre-disposed to low thyroid function (because of low iodine intake) had their condition made worse by fluoride exposure.

X. RISK: CANCER

The Nuffield Committee recommended evaluating fluoridation on the "potential" of harm.

Thiessen[91] (2010) "The EPA should be aware that three U.S. courts have found fluoridated water to be carcinogenic to humans (described in detail by Graham and Morin 1999).The NRC's committee on fluoride toxicology unanimously concluded that 'Fluoride appears to have the potential to initiate or promote cancers,' even though the overall evidence is 'mixed' (NRC 2006a). . . The question becomes one of how strongly carcinogenic fluoride is, and under what circumstances."

Bassin (2006)"We observed that for males diagnosed before the age of 20 years, fluoride level in drinking water during growth was associated with an increased risk of osteosarcoma, demonstrating a peak in the odds ratios from 6 to 8 years of age. All of our models were remarkably robust in showing this effect, which coincides with the mid-childhood growth spurt." (Bassin, et al., Cancer, Causes & Control, 2006)

Osteosarcoma is a rare, but deadly, form of cancer that strikes primarily during the teenage years. A national case control study published in 2006 by Harvard scientists found that boys exposed to fluoridated water during their 6th, 7th, and 8th years of life (the mid-childhood growth spurt) had a significantly elevated risk of developing osteosarcoma during adolescence. (Bassin 2006). The sex-specific link between fluoride and osteosarcoma in young males is consistent with the government's animal study, (NTP 1990), which found osteosarcomas in the fluoride-treated male rats, but not the female ones. It is also consistent with previous studies by the National Cancer Institute and New Jersey Department of Health, which both found associations between fluoridation and osteosarcoma in young males, but not females. (Cohn 1992; NCI 1990)

The plausibility of a fluoride/osteosarcoma connection is grounded in the three considerations:

1. Bone is the principal site of fluoride accumulation, particularly during the growth spurts of childhood;
2. Fluoride is a mutagen when present at sufficient concentrations; and
3. Fluoride stimulates the proliferation of bone-forming cells (osteoblasts), which may "increase the risk for some of the dividing cells to become malignant." (NRC 2006).

A number of studies did not find an association between fluoride and osteosarcoma. However, they were not "age-specific" and not as carefully controlled. Douglass compared bone tumors with osteosarcoma and did not repot a significant increase in bone fluoride concentrations. However, he did not compare fluoride concentrations with age controlled healthy bone fluoride

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[91] KM Thiessen, Senes Oak Ridge, Inc. Center for Risk Analysis. Comments on the Need for Revision of the NPDWR for Fluoride May 27, 2010 p. 8. https://fluoridealert.org/wp-content/uploads/connett-2010.pdf

concentrations. Similar age normal bone has about 200 ppm, the tumors double and osteosarcoma triple the fluoride concentration. Comparing the osteosarcoma bone with normal bone does show a significance.

Takahashi[92] (2001) reported, "cancers of the oral cavity and pharynx, colon and rectum, hepatobiliary and urinary organs were positively associated with FD. This was also the case for bone cancers in male, in line with results of rat experiments. Brain tumors and T-cell system Hodgkin's disease, Non-Hodgkin lymphoma, multiple myeloma, melanoma of the skin and monocytic leukaemia were also correlated with FD. Of the 36 sites, 23 were positively significant (63.9%), 9 not significant (25.0%) and 4 negatively significant (11.1%). This may indicate a complexity of mechanisms of action of fluoride in the body, especially in view of the coexising positive and negative correlations with the fluoridation index. The likelihood of fluoride acting as a genetic cause of cancer requires consideration."

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[92] Kosei Takahashi, Kenji Akiniwa, Kenichi Narita. Regression Analysis of Cancer Incidence Rates and Water Fluoride in the U.S.A. based on IACR/IARC (WHO) Data (1978-1992). Journal of Epidemiology. https://www.jstage.jst.go.jp/article/jea1991/11/4/11_4_170/_article/-char/ja/

XI. RISK: ENVIRONMENTAL JUSTICE

Other Potential Harm. (See also endnotes)

Fluoride ingested appears to go to all tissues. There are no tissues which appear safe from ingested fluoride. Only time will confirm whether fluoride harms all tissues. Some scientists have the greatest concern for the harm to the mitochondria.

A major prospective cohort study from Sweden demonstrates a higher risk of hip fractures in post-menopausal women associated with long term exposure to natural fluoride *at levels in water in the same range as America fluoridates its water* [Helte et al., 2021].

Recent epidemiological studies conducted in the United States, using individual biomarker measures of fluoride exposure, reported an association between low to moderate fluoride intake and impaired renal and hepatic function [Malin et al., 2019], increased risk of hyperuricemia [Wei et al., 2021], as well as adverse effects on reproductive endocrinology in U.S adolescents [Bai et al., 2020].

African Americans and Hispanics have been shown to be at an increased risk of developing dental fluorosis, and have a higher risk of suffering from the more severe forms of this condition (Russell, 1962; Butler et al., 1985; Williams and Zwemer, 1990; Beltrán-Aguilar et al., 2005; Martinez-Mier and Soto-Rojas, 2010).

Fluoride is more toxic when exposure is accompanied by poor nutrition, especially low iodine and calcium intake. Poor nutrition is more likely to occur in low-income families than those with higher incomes.

Lactose intolerance is more frequent among Blacks and other ethnic groups than whites. Central and East Asians are 80-100% lactose intolerant (de Vrese, 2001); Native Americans are 80-100% lactose intolerant (National Institute of Child Health and Human Development, 2006); African Americans are 75% lactose intolerant, and Southern Indians are 70% lactose intolerant (de Vrese, 2001). Less consumption of dairy products typically means lower exposure to calcium. Calcium in the diet helps to a certain extent to protect against absorption of fluoride from the gut.

African Americans consume significantly more total fluids and plain water, and thus receive more fluoride from drinking water, than white children (Sohn et al., 2009).

Minority families are less likely to breast-feed their children. As human milk contains very low levels of fluoride (Ekstrand et al., 1981, 1984; Sener et al., 2007), when baby formula is made up with fluoridated water it leads to over 100 times more exposure to fluoride than breast-feeding (see 6.5 above). African Americans are less likely to breastfeed than most other racial groups: “non-Hispanic blacks had a lower prevalence of breastfeeding initiation than non-Hispanic whites in all but two states…”-(CDC, 2010).. If the parent reduces the amount of formula to save

money as many poor parents do (Stein 2008; Egemen et al., 2002; Parraga et al., 1988), and adds more water than recommended, these children will receive even higher levels of fluoride.

Minority communities have a greater incidence of kidney disease. Poor kidney function increases fluoride's uptake into the bone, which is likely to increase the rates of arthritis and hip fractures (over a lifetime).

Minority communities have a greater incidence of diabetes, some forms of which lead to an increased consumption of water, which in turn leads to a greater consumption of fluoride.

(Sohn et al., 2009). Sener et al., 2007), African Americans are less likely to breastfeed than most other racial groups: "non-Hispanic blacks had a lower prevalence of breastfeeding initiation than non-Hispanic whites in all but two states…" (CDC, 2010).. If the parent reduces the amount of formula to save money as many poor parents do (Stein 2008; Egemen et al., 2002; Parraga et al., 1988),

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XII. ALTERNATIVES TO FLUORIDATION

If a person seriously wants to ingest fluoride, alternatives are available. The FDA has not approved fluoridation nor swallowing fluoride toothpaste. Swallowing a pea size of fluoridated toothpaste is an alternative, provides individual choice, is less expensive but still not ethically ideal. Prescriptions for supplements and topical fluoride application in schools and oral hygiene has been suggested.[93]

However, the best alternative is oral hygiene and diet instruction along with raising the socioeconomic status of a community.

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[93]Ethics Consultation Report Ethical Considerations in Community Water Fluoridation, by the Public Health Agency of Canada's Public Health Ethics Consultative Group, December 18, 2018 p.1. https://www.caphd.ca/sites/default/files/Ethical%20Considerations%20for%20Community%20Water%20Fluoridation.pdf

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PDF **WAC 246-290-220**

Drinking water materials and additives.

(1) All materials shall conform to the ANSI/NSF Standard 61 if in substantial contact with potable water supplies. For the purposes of this section, "substantial contact" means the elevated degree that a material in contact with water may release leachable contaminants into the water such that levels of these contaminants may be unacceptable with respect to either public health or aesthetic concerns. It should take into consideration the total material/water interface area of exposure, volume of water exposed, length of time water is in contact with the material, and level of public health risk. Examples of water system components that would be considered to be in "substantial contact" with drinking water are filter media, storage tank interiors or liners, distribution piping, membranes, exchange or adsorption media, or other similar components that would have high potential for contacting the water. Materials associated with components such as valves, pipe fittings, debris screens, gaskets, or similar appurtenances would not be considered to be in substantial contact.

(2) Materials or additives in use prior to the effective date of these regulations that have not been listed under ANSI/NSF Standard 60 or 61 may be used for their current applications until the materials are scheduled for replacement, or that stocks of existing additives are depleted and scheduled for reorder.

(3) Any treatment chemicals, with the exception of commercially retailed hypochlorite compounds such as unscented Clorox, Purex, etc., added to water intended for potable use must comply with ANSI/NSF Standard 60. The maximum application dosage recommendation for the product certified by the ANSI/NSF Standard 60 shall not be exceeded in practice.

(4) Any products used to coat, line, seal, patch water contact surfaces or that have substantial water contact within the collection, treatment, or distribution systems must comply with the appropriate ANSI/NSF Standard 60 or 61. Application of these products must comply with recommendations contained in the product certification.

(5) The department may accept continued use of, and proposals involving, certain noncertified chemicals or materials on a case-by-case basis, if all of the following criteria are met:

(a) The chemical or material has an acknowledged and demonstrable history of use in the state for drinking water applications;

(b) There exists no substantial evidence that the use of the chemical or material has caused consumers to register complaints about aesthetic issues, or health related concerns, that could be associated with leachable residues from the material; and

(c) The chemical or material has undergone testing through a protocol acceptable to the department and has been found to not contribute leachable compounds into drinking water at levels that would be of public health concern.

(6) Any pipe, pipe fittings, plumbing fittings, fixtures, solder, or flux used in the installation or repair of a public water system shall be lead-free:

(a) This prohibition shall not apply to leaded joints necessary for the repair of cast iron pipes; and

(b) Within the context of this section, lead-free shall mean:

(i) No more than a weighted average of twenty-five one-hundredths of one percent lead, calculated in accordance with 42 U.S.C. 300g-6 654(d)(2); and

(ii) No more than two-tenths of one percent lead in solder and flux.

(7) Exceptions to the lead-free requirements of subsection (6) of this section include:

(a) Pipes, pipe fittings, plumbing fittings, or fixtures, including backflow preventers, that are used exclusively for nonpotable services such as manufacturing, industrial processing, irrigation, outdoor watering, or any other uses where the water is not anticipated to be used for human consumption; or

(b) Toilets, bidets, urinals, fill valves, flushometer valves, tub fillers, fire hydrants, shower valves, service saddles, or water distribution main gate valves that are two inches in diameter or larger.

[Statutory Authority: RCW **43.20.050** and **70.119A.080**. WSR 17-01-062, § 246-290-220, filed 12/14/16, effective 1/14/17. Statutory Authority: RCW **43.20.050** (2) and (3) and **70.119A.080**. WSR 03-08-037, § 246-290-220, filed 3/27/03, effective 4/27/03. Statutory Authority: RCW **43.02.050** [43.20.050]. WSR 99-07-021, § 246-290-220, filed 3/9/99, effective 4/9/99. Statutory Authority: RCW **43.20.050**. WSR 91-02-051 (Order 124B), recodified as § 246-290-220, filed 12/27/90, effective 1/31/91. Statutory Authority: RCW **34.04.045**. WSR 88-05-057 (Order 307), § 248-54-131, filed 2/17/88.]

Petition for Rulemaking

WAC 246-290-220, Drinking Water Materials and Additives

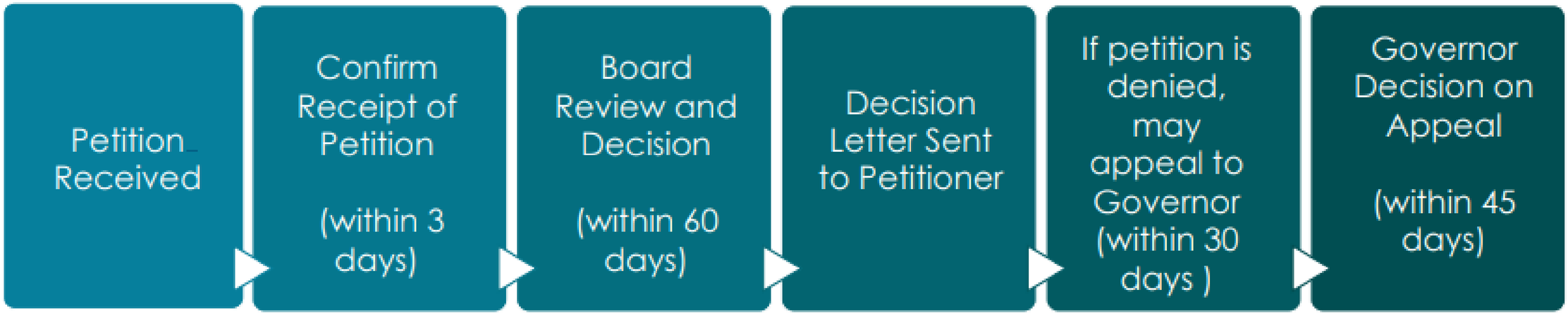
Shay Bauman, Policy Advisor – November 13, 2024

WASHINGTON STATE BOARD OF HEALTH

Background

Under the Administrative Procedures Act, RCW 34.05.330, any person may petition a state agency to adopt, repeal, or amend any rule within its authority.

Overview of the Board's Petition Process



RCW 43.20.050 grants the Board authority to adopt rules for Group A Public Water Systems necessary to assure safe and reliable drinking water and protect the public health. These rules are within Chapter 246-290 WAC.

Petition

The petition requests the Board add a new subsection to WAC 246-290-220 stating either of the following:

The Board of Health does not recommend adding fluoridation chemicals to water with the intent to treat humans or animals;

OR (alternate wording)

In keeping with the Federal Safe Drinking Water Standards, the Board of Health does not recommend chemicals, including fluoride compounds, be added to the water with the intent to treat or prevent disease in humans or animals.

WAC 246-290-220 – Drinking Water Materials and Additives

WAC 246-290-220 requires Group A public water systems to test and certify for conformance with NSF/ANSI Standards 60 and 61 for:

- treatment chemicals added to public drinking water supplies; and

- public water system components in substantial contact with potable water such as water pipes, tank coatings or liners, and treatment system media.

Additional Complaint

WAC 246-290-220(5)

(5) The department may accept continued use of, and proposals involving, certain noncertified chemicals or materials on a case-by-case basis, if all of the following criteria are met:

(a) The chemical or material has an acknowledged and demonstrable history of use in the state for drinking water applications;

(**b) There exists no substantial evidence that the use of the chemical or material has caused consumers to register complaints about aesthetic issues, or health related concerns, that could be associated with leachable residues from the material;** and

(c) The chemical or material has undergone testing through a protocol acceptable to the department and has been found to not contribute leachable compounds into drinking water at levels that would be of public health concern.

This subsection is not relevant to fluoride, as fluoride additives are required to be certified under NSF/ANSI 60

NTP Monograph

- Systematic review of the published scientific literature.
- **Higher levels of fluoride exposure, such as drinking water containing more than 1.5 milligrams of fluoride per liter, are associated with lower IQ in children (moderate confidence level).**
- Evaluates total fluoride exposure, not the health effects of fluoridated drinking water alone.
- Based primarily on epidemiology studies in non-U.S. countries.
- It notes many substances are healthy and beneficial when taken in small doses but may cause harm at high doses and that more research is needed to better understand if there are health risks associated with low fluoride exposures.

District Court Ruling

Food & Water Watch, Inc., et al, v. United States Environmental Protection Agency

- Food & Water Watch and other groups challenged the EPA in court after their petition to ban water fluoridation was denied by the EPA in 2017.
- A federal district court ordered the agency take action, heavily citing the NTP Monograph.
- Does not require the EPA to ban water fluoridation, nor specify what action they must take.
- The EPA may issue a new rule or appeal the decision.
- **In addition to reviewing the Monograph, staff is monitoring what action the EPA will take.**

Recommendation

The Board declines the petition for rulemaking to amend WAC 246-290-220 for the reasons articulated by Board Members. The Board directs staff to notify the petitioner of the Board's decision.

Petition Request: add a new subsection to WAC 246-290-220 stating either of the following:

The Board of Health does not recommend adding fluoridation chemicals to water with the intent to treat humans or animals;

OR (alternate wording)

In keeping with the Federal Safe Drinking Water Standards, the Board of Health does not recommend chemicals, including fluoride compounds, be added to the water with the intent to treat or prevent disease in humans or animals.

WASHINGTON STATE BOARD OF HEALTH

THANK YOU

To request this document in an alternate format, please contact the Washington State Board of Health at 360-236-4110, or by email at **wsboh@sboh.wa.gov** | TTY users can dial 711

ACCESSIBILITY AND THE AMERICANS WITH DISABILITIES ACT (ADA)

- The Washington State Board of Health (Board) is committed to providing information and services that are accessible to people with disabilities. We provide reasonable accommodations, and strive to make all our meetings, programs, and activities accessible to all persons, regardless of ability, in accordance with all relevant state and federal laws.
- Our agency, website, and online services follow the Americans with Disabilities (ADA) standards, Section 508 of the Rehabilitation Act of 1973, Washington State Policy 188, and Web Content Accessibility Guidelines (WCAG) 2.0, level AA. We regularly monitor for compliance and invite our users to submit a request if they need additional assistance or would like to notify us of issues to improve accessibility.
- We are committed to providing access to all individuals visiting our agency website, including persons with disabilities. If you cannot access content on our website because of a disability, have questions about content accessibility or would like to report problems accessing information on our website, please call (360) 236-4110 or email wsboh@sboh.wa.gov and describe the following details in your message:
    - The nature of the accessibility needs
    - The URL (web address) of the content you would like to access
    - Your contact information

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