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Washington Action for Safe Water
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EPA Dose-Response Analysis and Exposure and Relative Source Contribution Analysis Comment FluorideScience@epa.gov
HHS (Health and Human Services) Kathleen Sebelius
CDC (US Centers for Disease Control) CWFcomments@cdc.gov

PREFACE

COMMENT AND ADVISORY: EPA (US Environmental Protection Agency)

(DRA) Fluoride: Dose-Response Analysis For Non-cancer Effects; Fluoride-Related Skeletal Effects: Evaluations of Key Studies; Dental Fluorosis: Evaluations of Key Studies; Comment-response Summary Report for the Peer Review of Fluoride: Dose-Response Analysis for Non-cancer Effects;

(RSC) Fluoride Exposure and Relative Source Contribution Analysis; Comment-Response Summary Report for the Peer Review of the Fluoride: Exposure and Relative Source Contribution Analysis. For risk assessment, the EPA must include total exposure of fluoride and not just a relative dose of fluoride from water. One of our concerns is an EPA risk assessment will avoid total exposure.

EPA: To protect those infants predominantly ingesting public water, those infants on 100% or close to 100% total nutritional intake from public water, relative source contribution is 100% public water, the EPA should set MCLG of fluoride at ZERO ppm. "Mother's Milk is definitive evidence the Absence of Fluoride is the Normal Reference Dose for Infants. The EPA has failed to utilize current dose-response measurements for infants or include risks. The EPA has also violated the SDWA by determining the safety of fluoride concentration in water based on a flawed overriding assumption of benefit.

The authors, contributors and reviewers of the DRA and RSC must certainly be well meaning; however, due to policy or process, the end result has failed miserably, credibility is lost, millions are being harmed and the estimated negative economic impact is greater than $1.5 trillion/year.

The latest documents we have are from EPA Region 10 who responded 4/7/11 to our request for clairification on the roll of the EPA in regards to fluoride in public water.

> *"Under SDWA, EPA's role in drinking water regulation is to set standards that define the maximum allowable concentrations of contaminants in order to prevent adverse health effects."*[1]

These comments will repeatedly provide good scientific evidence that the EPA

[1] Appendix 122 EPA Region 10 4/7/11

has violated the SDWA and has set a standard of fluoride contaminant NOT to "prevent adverse health effects" but rather the standard is set high in order to prevent dental caries, for health care purposes, unrelated to the disinfection of water.

Nothing in the SDWA authorizes the EPA to permit public water systems to contaminat public water. Intentional contamination of water is not the intent of the SDWA. The Washington State Board of Health suggests the EPA/SDWA allow contaminating public water, *"The . . . EPA sets national safety standards for drinking water, which allow fluoride concentrations. . . ."*[2] The EPA should clarify to state Health Agencies that the SDWA does not allow the intentional addition of contaminants for health related purposes other than disinfecting of water. The EPA should regulate contaminants rather than protecting contaminants.

The Washington State Board of Health continues, *"this Board relies on existing federal standards and guidelines. . . . The Board will consider rule revisions as quickly as possible if federal standards or guidelines change."* The EPA and HHS/CDC should fully understand that state agencies are not evaluating the scientific evidence. Unless the EPA and HHS clearly state otherwise, the weight of safety and efficacy is fully on the shoulders of the EPA and HHS. EPA and CDC lack Congressional authorization to determine or balance the safety and efficacy of any substances used with the intent to prevent disease.

Nothing in the SDWA authorizes the EPA to provide grants or funding to public water systems which intentionally contaminate public water. The EPA should stop funding public water systems which violate the intent of the SDWA.

The EPA Region 10 response continues, the *"SDWA . . . requires EPA to determine the level of contaminants that may be found in drinking water at which no adverse health effects are likely to occur. These non-enforceable health goals, based solely on possible health risks and exposure over a lifetime with an adequate margin of safety, are called maximum contaminant level goals (MCLGs)."*[3]

The EPA has vigerously protected the fluoride contaminant rather than protecting the public. Members of the NRC (2006) fluoride report were instructed by the EPA to determine risks at a confidence level they would "stake the farm" on. In other words, confidence needed to be virtually 100% before determining the adverse effect was indeed a risk. The committee was not instructed to determine risks at the level of confidence of "likely or possible health risks" as instructed by the SDWA but at a far higher level of confidence.

The EPA Region 10 response continues regarding the updated recommendation of 0.7 mg/L, is to *"balance the benefits of preventing tooth decay while limiting any unwanted health effects."*[4] Weighing the "balance" of benefits and risks of substances used with the intent to prevent disease is clearly and specifically delegated by Congress and the President to the FDA CDER and weighing the balance is outside the jurisdiction of both the CDC, EPA and specifically denied by the SDWA to the EPA.

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[2] Appendix 123 WBOH 4/14/11
[3] Appendix 122 EPA Region 10 4/7/11
[4] Appendix 122 EPA Region 10 4/7/11

The current DRA and RSC further compound the flawed charge to the NRC (2006) NOT including current scientific literature over the last 5 or 8 years, providing NO margin of safety, NOT including infants under 6 months of age, NOT including prenatal fetuses, NOT including subpopulations drinking more than the 90th percentile of water, NOT using current exposure assessment methods of serum, urine or tissue fluoride concentration, NOT including cancer or other risks which are likely or possible health risks, using a relative contribution of fluoride from water rather than total fluoride exposure from all sources, relying primarily on flawed research more than half a century old, and not including subpopulations or races at higher risk.

COMMENT AND ADVISORY: HHS/CDC (US Health and Human Services Centers for Disease Control) Advisory to Limit Fluoride Concentration in public water.

HHS: To protect health, HHS/CDC has recommended lowering the concentration of fluoride added to public water. However, the addition of 0.7 ppm fluoride to public water still does not protect infants, youth or adults and those highly sensitive or with kidney disfunction AND does not make the drug legal. HHS/CDC should recommend a cessation of adding fluoride to water until manufacturers gain FDA CDER NDA approval. To protect the health of all, HHS/CDC must cease all promoting, marketing and advertising of the illicit fluoridated water drug until FDA CDER NDA approval.

HHS/CDC evidence[5] is cherry picked excluding evidence contrary to the desired HHS conclusion. The HHS Federal Panel on Community Water Fluoridation failed to include stakeholder inclusion, failed to include FDA CDER senior Pharmacologists, failed to follow Congress's specific mandate in the FFDCA and SDWA, and failed to include confounding factors, or ethics of patient right of informed consent.

THE FUNDAMENTAL OVERRIDING PRINCIPLES ARE
FIRST THE LAW FOR JURISDICTION
AND
THEN SCIENCE TO DETERMINE EFFICACY AND SAFETY.

The President, Congress and the Courts over many decades in both the FFDCA and SDWA and Amendments have mandated the FDA CDER to have oversight regulation of substances used with the intent to prevent disease. Harm to the public of unimaginable proportions has resulted from Federal, state, local governments and corporations failing to make a New Drug Application (NDA) for fluoridation and absence of FDA CDER regulatory oversight. Failure by manufacturers, HHS, EPA, CDC, FDA CDER, state and local governments is one of the top ten public health crimes against humanity of the 20th Century.

Without FDA CDER NDA approval, adjusting the concentration of a substance in water, up or down, with the intent to prevent disease is unapproved and illegal and renders the drug misbranded, adulterated, and contaminated. HHS/CDC recommending a lower concentration of an illegal drug does not make the drug legal.

The current EPA DRA protection of the unapproved fluoride drug is outside the

[5] http://www.hhs.gov/news/press/2011pres/01/pre_pub_frn_fluoride.html

jurisdiction of the EPA and prohibited by the SDWA. The SDWA mandates the EPA to write a DRA with an overriding principle of public safety for all, rather than protecting the pollutant with an assumption of efficacy. And those of us scientists and clinicians who blindly promoted, with the force of police powers, the unapproved illegal fluoride drug share the blame. The EPA is mandated to regulate the safety of fluoride existing in water, but is not authorized to defer to anyone but the FDA CDER to evaluate effectiveness of fluoride with the intent to prevent disease. The CDC is authorized to promote health and control disease, but not push illegal drugs.

With the division of efficacy and safety between two Agencies rather than with the FDA CDER, scientific and ethical risk/benefit judgment is lacking. This comment regarding fluoridation, the addition of a substance used with health care intent (not disinfection of water) includes both EPA and CDC because to do a risk/benefit analysis, both EPA and CDC share the problem and neither has jurisdiction.

We do not dispute that fluoride existing in water as a pollutant is regulated by the EPA. However, fluoride concentration in water adjusted up or down with the overriding intent to prevent disease is an unapproved illegal drug. The EPA must regulate fluoride with the same strict single focus on safety as it does lead and arsenic and not assume efficacy. Plenty of other sources of fluoride are available if a person chooses to ingest more fluoride. The CDC must insist those who fluoridate seek FDA CDER NDA.

EMERGENCY AND IMMEDIATE ACTION BY HHS/CDC TO PROTECT THE PUBLIC

RECOMMENDATIONS

A. The EPA AND HHS/CDC shall direct public water systems to seek FDA CDER approval for adjusting the concentration of fluoride in public water when the intent is to prevent dental caries. Unless FDA CDER approval is made, the EPA and HHS/CDC shall not promote fluoridation.

B. The EPA shall lower concentration of fluoride in public water until acute fluride serum levels drop below 0.02 ppm (as recommended by the CDC) and chronic serum fluoride levels are below 0.01 ppm for adults and 0.005 ppm for infants. Part of CDC currently recommends serum fluoride <0.02 ppm and part of CDC recommends fluoridation which frequently causes higher fluoride serum concentrations. The CDC is not consistent with itself. The EPA protects the pollutant in water rather than protecting people from excess pollutant.

C. Unless approved by the FDA CDER, HHS/CDC not set a minimum fluoridation concentration.

D. Unless approved by the FDA CDER, EPA set MCLG for fluoride at zero ppm, the same as arsenic and lead.

Note: The term “fluoride” in these comments and recommendations is used as understood by the public (fluoride ion) and not in a strict sense. The term “fluoridation” refers to the addition of various chemicals to water to increase or decrease the fluoride ion content of water and buffer the resulting acid. The term “fluoridated water drug” and “artificial fluoridation” are used the same as “fluoridation,” as the final manufactured drug, the mixture of water with fluoride at, for example, 0.7 ppm.

OUTLINE

[6] The CRS Report RL 30022 "Summaries of Environmental Laws Administered by the EPA reference by the FDA Denial was not available at http://www.nceonline.org/NLE/CRSreports/BriefingBooks/Laws/g.cfm. Perhaps it has been removed or is not available to the public. A search of RCS documents located the January 7, 2008 CRS Report for Congress: Summaries of Major Statutes Administered by the EPA. At http://assets.opencrs.com/rpts/RL30798_20080107.pdf

[7] Appendix 1 EPA/FDA MOU

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[8] *21 U.S.C. 321 CHAPTER II—DEFINITIONS (g)(1)(A) AND (B)*

[9] www.ada.org
[10] www.cdc.gov

[11] DRA (2010) p i.

I. CONGRESS HAS DEFINED FLUORIDE AS A DRUG, NOT A FOOD.

A. Regardless of Concentration or Whether the Manufacturer Increases or Decreases the Concentration of Fluoride in Water, the Intent to Prevent Disease Defines Fluoridation as a Drug. Fluoride is a Poison and Exempt from Poison Laws when Regulated as a Drug.[12] Contaminating Public Water is Not an Exemption from Poison Laws.

1. *"21 U.S.C. 321 CHAPTER II—DEFINITIONS (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;"*

Sodium Fluoride is listed in the 2007 US Pharmacopoeia pages 3194-3196.[13] Congress and the President have clearly defined drugs, and fluoride is listed as one of the drugs.

Fluoride is exempt from Federal and state "poison" and "highly toxic" laws as a drug[14] and not exempt as a food.

21 U.S.C. 321 CHAPTER II—DEFINITIONS (g)(1)(A), is sufficient grounds and cause for HHS/CDC to immediately insist FDA CDER take enforcement action and require NDA approval (US Food and Drug Administration Center for Drug Evaluation and Research New Drug Application). The following pages are additional and added evidence for immediate emergency action.

Congress has not exempted fluoride from drug laws as a food nor exempted public water systems, cities, or state legislatures from the FFDCA as drug manufacturers. Congress has not authorized HHS, CDC or EPA to make drug safety and efficacy determinations, to weigh on balance efficacy and safety.

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;"*

HHS suggests, *"Community water fluoridation is a major factor responsible for the decline of the prevalence and severity of dental caries (tooth decay) during the second half of the 20th century."*[15]

At #12, the DRA report asks Reviewers:

"Do you support the OW's conclusion that an RfD of 0.07 mg/kg/day will be

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[12] **The Grim Truth about Fluoridation**, Robert M. Buck, G.P. Putnam & Son, New York, 1964. **Blakiston's Medical Dictionary,** 1960, 3rd edition. **The Merck Index,** 9th edition, Merck and Co., Inc., Rahway, New Jersey, 1976. **Clinical Toxicology of Commercial Products**, Gleason, M., ed. Williams and Wilkins, Baltimore, 3rd edition, 1969.

[13] Appendix 2 2007 USP NF

[14] TITLE 15 > CHAPTER 30 > § 1261 Definitions http://www.law.cornell.edu/uscode/uscode15/usc_sec_15_00001261----000-.html

[15] http://www.hhs.gov/news/press/2011pres/01/pre_pub_frn_fluoride.html Accessed 4/6/11

protective for severe dental fluorosis in children and skeletal effects in adults while still providing for the beneficial effects of fluoride?"

And DRA (2010) report starts out (page xiv):

"At low intake levels, fluoride has been shown to have a therapeutic value in the prevention of dental caries."

Regulatory Oversight by the EPA or CDC of the Therapeutic Value of Fluoride, Attempting to Adjust (up or down) the Daily Dosage of Fluoride, Weighing on Balance, for Efficacy and Safety is "ultra vires," Outside the Jurisdiction of the SDWA and Under the Jurisdiction of the FFDCA FDA CDER.

How is a product's intended use established? The EPA DRA (2010) states: "At low intake levels, fluoride has been shown to have therapeutic value in the prevention of dental caries."[16] The EPA has no authority to protect the fluoride unapproved drug because they mistakenly assume efficacy.

Even if the EPA and CDC removed reference to the therapeutic value of fluoride, based on public perception, fluoridation would still need FDA CDER approval as a drug. The FDA states:

- ***"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."*[17]

Fluoride added to water is a well known assumption of the public and industry to be added or some left in with the intent to "prevent dental caries", a disease. "21 U.S.C. 321 CHAPTER II—DEFINITIONS (g)(1)(B) is again, in and of itself, sufficient grounds and cause for immediate enforcement action by the FDA CDER. Before fluoridation of public water is started, the drug manufacturers must make FDA CDER NDA. HHS/CDC and EPA shall notify existing public water system manufacturers adding or leaving fluoride in public water with the intent to prevent disease to make FDA CDER NDA application.

B. According to Repeated Statements by the FDA and Under a

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[16] DRA (2010) p xiv

[17] http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/ucm074201.htm 9/26/10

Freedom of Information Request, the FDA Confirmed the Active Ingredients in the Water Fluoridation Drugs are Unapproved Drugs,

The FDA responded, *"Sodium fluoride used for therapeutic effect would be a drug, not a mineral nutrient."*[18]

The FDA responded again,

"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. . . ."[19]

C. The FDA responded to Representative Ken Calvert that Fluoride is a Drug.

"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."[20]

D. The Washington State Board of Pharmacy also Confirmed Fluoride is a Prescription Drug under State and Federal Law.

Under state and Federal law it is unlawful to manufacture, market, formulate, prescribe, dispense, possess or administer a legend (prescription) drug without a license and without compliance with relevant drug laws.[21] There is consensus that fluoride (hydroflurosilicic acid, silicofluoride, sodium fluoride) is added solely to water with the intent to prevent or mitigate dental caries. This intent alone is enough to define artificially fluoridated water as a drug.[22] The EPA (Environmental Protection Agency) does not regulate drugs and has no business pretending to approve or protect the fluoride drug without FDA CDER approval.[23] The FDA (Food and Drug Administration) regulates drugs in interstate commerce.[24] The State Board of Pharmacy (BOP) regulates drugs in intrastate commerce.[25] WBOH (Washington State Board of Health) should promulgate proper rules and regulations pertaining to fluoridation and should enforce such rules and regulations.[26] However, the WBOH relies on the EPA and CDC for

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[18] Appendix 3 FDA letter
[19] FOI Email from the FDA (7-22-09) to Bill Osmunson DDS, MPH .
[20] Appendix 4 FDA Calvert 2000
[21] Chapter 69.41 RCW; U.S.C. 21, Chapter 9 ("Federal Food, Drug, and Cosmetic Act" abbreviated herein as "FD&C Act").
[22] Federal and Washington laws define a drug as a substance or article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease." 21 U.S.C. sec. 321(g)(1)(B) RCW 69.41.010(9)(b)
[23] Under the Safe Drinking Water Act, the EPA regulates clean-up of contaminants and regulates additives to treat water to clean-up contaminants.
[24] 21 U.S.C. sec. 355(a).
[25] RCW 18.64.005.
[26] AG Opinion IBID

fluoridation approval and the CDC and EPA must advise states not to rely on the CDC and EPA for drug approval.[27] Public water systems obtain the bulk fluoridation drug[28] in interstate commerce and do the final manufacturing, formulating, compounding, buffering and dispensing of the fluoridated water drug in intrastate commerce.[29] Thus both Federal and state drug laws apply.

The Washington State Board of Pharmacy (BOP) has issued its interpretive opinion that fluoride, when used to prevent, mitigate or treat disease is a legend drug:

> *"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."*[30,31]

Washington State Law and Federal Law require correct, truthful and FDA CDER approved labeling for drugs. The unapproved artificial fluoridated water and EPA protected fluoride polutant does not have an approved label. No caution or warning is provided for the fluoridated water drug for high risk individuals. The artificially fluoridated water drug should have a label which warns care givers of infants that fluoridated water has a much higher fluoride content than mother's milk, that children should only drink one glass of the water a day, that adults should limit their water intake to a specific amount, or the risks to brain, thyroid, bones, teeth, heart, digestive system and other physiological systems may cause serious side effects.

> *"To every box, bottle, jar, tube or other container of a legend drug, which is dispensed by a practitioner authorized to prescribe legend drugs, there shall be affixed a label bearing the name of the prescriber, complete directions for use, the name of the drug either by the brand or generic name and strength per unit dose, name of patient and date. . . ." RCW 69.41.050(1).*

The fetus, infants and children are at a higher risk from environmental toxins than adults[32] and should have additional protection, not less.

E. The Idaho Board of Pharmacy Confirmed fluoride is a Drug.[33]

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[27] Appendixes 12, Response and 6 WA BOP
[28] A bulk drug is a substance that becomes an active ingredient of a drug. 21 C.F.R. sec. 207.3(a)(4).
[29] RCW 69.04.004.
[30] Appendix 6, 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*.
[31] The above-referenced Board letter continues, "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." However, RCW 69.41.010 does not exempt Federal Oversight or FDA CDER NDA.
[32] Appendix 121 Barton (2005)
[33] Appendix 7, Idaho Board of Pharmacy

There is no reason to doubt that all state Board's of Pharmacy would agree with the FFDCA and FDA CDER that fluoride for ingestion with the intent to prevent disease is a drug.

F. Pharmacists Require a Doctor's Prescription to Purchase Fluoride for Ingestion. Pharmacists will also Confirm that Fluoride for Ingestion is Not an FDA approved Drug.

If fluoride were a "food," "supplement," or "nutrient" for ingestion, or required for optimal health, fluoride for ingestion would not be sold in stores by prescription only. In the event the EPA employs Pharmacists, they should be consulted for the definition and approval process for drugs.

The CDC has no authority to recommend unapproved drugs either diluted in fluoridated water or supplements.[34] The EPA has no authority to protect a pollutant based on assumptions of dental therapeutic value.

G. Professional and Public Opinion, Proponents and Opponents, and All Federal and State Health Agencies Including the DRA Agree: the Intent of the Addition of Fluoridation Chemicals is Done to Prevent Disease, Dental Caries.[35]

The DRA protects fluoride in water under the flawed assumption that fluoride has benefit in reducing dental caries. However, the DRA does not rely on the FDA CDER to determine the effectiveness of the fluoride. Until fluoride is approved, the EPA is experimenting on the public with an illegal drug without the patient's consent.

H. The U.S. Supreme Court has Confirmed that it is Congress and the Language of Its Statutes that Controls the Jurisdiction of the Food and Drug Administration. (FDA v. Brown & Williamson, 529 U.S. 120 (2000))

I. The FDA CDER has Defined Fluoride as a Drug in Toothpaste.

1. *"For example, fluoride toothpaste, antiperspirants, dandruff shampoos and sunscreens are all considered "drugs."*[86]

"*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*

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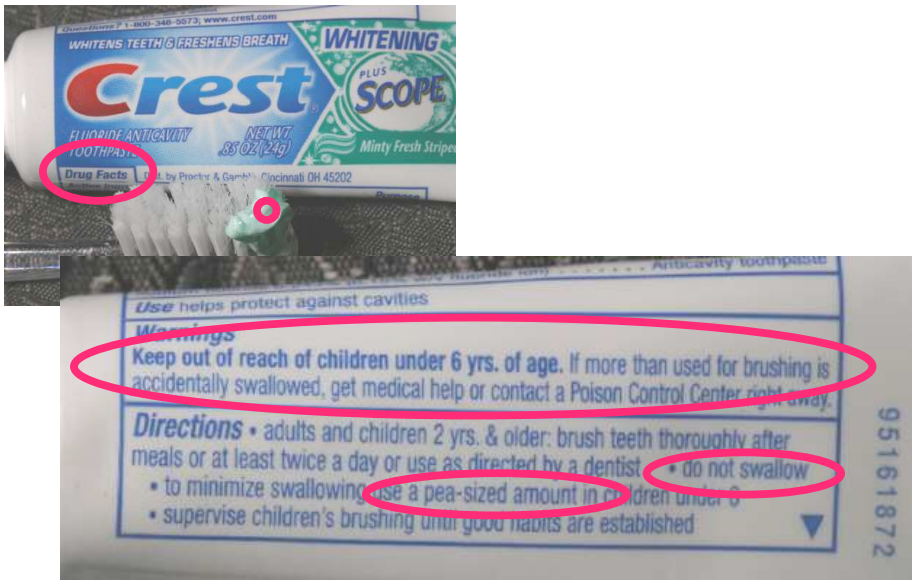
[34] CDC web page www.cdc.gov/fluoridationfact_sheets/engineering/wfadditives.htm

[35] See the American Dental Association, Fluoride Action Network, International Academy of Oral Medicine and Toxicology, Centers for Disease Control, Oregon Department of Human Services, Surgeon General, US Public Health, California AB733 and online searches of the web.

[36] www.fda.gov/AboutFDA/Transparency/Basics/uxm192696.htm Accessed 11/12/10

drugs."[37]



The toothpaste label (above photo of Crest Toothpaste) is appropriately labeled and states, "Drug Facts" "Do Not Swallow" (0.25 mg F, in a "pea" size amount).[38] For the FDA CDER to require a statement on fluoride toothpaste that fluoride is a drug when used topically and yet the HHS/CDC and EPA suggest the systemic use of fluoride at the same amount of 0.25 mg/glass of water (at 1 ppm) miraculously becomes a safe contaminant or food, is scientifically irrational and a gross material contradiction of fact, science, law and ethics. **There is no scientific or legal evidence to suggest that ingesting 0.25 mg of fluoride in fluoridated water is safer, less toxic, or exempt from FDA CDER jurisdiction than 0.25 mg of fluoride in toothpaste. If toothpaste has a warning not to ingest more than a pea size amount, fluoridated water should have the same warning on a little more than a glass of water.** The public loses confidence when HHS/CDC and EPA statements and actions conflict and don't make sense.

Fluoridation concentration if FDA CDER NDA risk/benefit analysis is done and approved would be less than 0.1 ppm fluoride concentration in public water.

For safety, the EPA MCLG has no reason to be greater than 0 ppm. For safety, the goal for fluoride in water should be zero, the same as arsenic and lead. If someone wants fluoride they can disregard the FDA CDER warnings and swallow toothpaste.

Because **topical use** of fluoride is defined by the FDA CDER as a drug, then for the safety of the public and credibility of the FDA CDER, CDC, EPA, HHS, the **systemic**

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[37] FDA email Response to email from Bill Osmunson 2009

[38] http://www.cdc.gov/mmwr/PDF/rr/rr5014.pdf top of page 28 use 0.25g of toothpaste. Crest is 0.16% fluoride w/v.

use with the same intent, the same amount and higher risk, must also be defined and regulated by the FDA CDER as a drug. Argument to the contrary is made without consideration of total current individual exposure, individual sensitivity, Federal or state poison or drug laws, ethics and human subject research consent.[39] The public loses confidence when Agency statements conflict and don't make sense.

In brief, the regulatory jurisdiction for toxic substances involves different criteria by different agencies. For example,

EPA "takes out" and FDA "puts in".

The **EPA** leaves a contaminant in water until the level of confidence in the science available creates enough confidence of **risk to take the substance out of water**. EPA regulates the contaminant existing in the water, not the manufacturing, formulating, labeling or distribution of drugs made with public water.

In contrast:

The **FDA CDER** "keeps" the substance out of the market until the science required of manufacturers gives confidence the substance is effective and **safe to put into market".**

Neither Agency makes a change until confidence is adequate . . . except for fluoridation. Because the CDC and EPA are attempting to regulate the "putting into market" fluoride and FDA CDER has deferred regulatory action, the burden of proof of harm and lack of efficacy is shifted from the manufacturer to the patient. And unlike a legend drug which is under the authority of a licensed drug manufacturer and licensed health care provider, fluoridation has no "doctor" or legal intermediary and CDC/EPA are without liability concerns or constraints. The worst that happens to the CDC/EPA for public health harm from pushing the illicit drug is, "oops."

Neither CDC nor EPA has appropriate regulatory procedures and approval processes for drug approval. The public is harmed when Agencies violate law.

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[39]The Belmont Report (1979), FDA and HHS human subject research recommendations; Code of Nuremberg (1949); Declaration of Helsinki (1974); and almost all journals which publish research of human research. Also see http://heinonline.org/HOL/LandingPage?collection=journals&handle=hein.journals/washlr78&div=12&id=&page=

II. CONGRESS HAS MANDATED THE FDA TO REGULATE DRUGS.

A. For the Safety of the Public, FDA Drug Approval Regulatory Enforcement Action Must be Implemented IMMEDIATELY

- - EMERGENCY ACTION - -

The FD&C Act became effective in 1938 and required new drug applications demonstrating safety. Fluoridation was started about 10 years later. In 1962 the FD&C Act was amended requiring demonstration of effectiveness in addition to safety.[40]

FDA Guidance Includes: (Items in italics quoted from FDA)[41]

"American consumers benefit from having access to the safest and most advanced pharmaceutical system in the world."

WASW Response: Other countries are more advanced in providing consumers with freedom and safety against the unapproved and misbranded fluoridated water drug. See Appendix I for a list of countries who have banned, discontinued, or rejected the addition of fluoride to water based on both freedom of choice and scientific safety issues.

The main consumer watchdog in this system is the U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER). The center's best-known job is to evaluate new drugs before they can be sold. The center's evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both brand-name and generic, work correctly and that their health benefits outweigh their known risks.

WASW Response: The public loses confidence in HHS FDA CDER as a "consumer watch dog" when it defers regulatory action on an illegal drug forcibly administered without label directly in public water to about 200 million of the public[42] and the other 100 million indirectly. The HHS and FDA CDER have not prevented the quackery of fluoridation, nor provided doctors and patients with information needed to use fluoride wisely, nor whether fluoridation works and health benefits outweigh their known risks.[43]

"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

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[40] FDA letter to Assemblyman John Kelly, 1993. Appendix 9

[41] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm Accessed 10/26/10

[42] About 74% of the USA has fluoride at about 1 ppm. Some areas have natural occurring fluoride. Canada, Australia, New Zealand, and Ireland look to the USA for evidence of fluoridation's safety and efficacy.

[43] See Some Research Below on Selected Risks.

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 conduct limited research in the areas of drug quality, safety, and effectiveness standards."

WASW Response: The fluoridated water drug has NOT been appropriately reviewed by competent scientists, pharmacologists, chemists, statisticians, and physicians inclusive of all valid research and laws. Scientific evidence and participants in reviews to date have generally been cherry picked to support a predetermined conclusion.[44] The CDC is not qualified nor charged by Congress to determine the safety or efficacy of drugs. The EPA is prohibited from adding substances to water for the prevention of disease. The FFDCA does not give HHS the jurisdiction to approve or regulate the dosage of drugs.

"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."[45]

WASW Response: Not one randomized controlled human trial is available either for benefits, risks/harm, or safety. No tests have been done to determine current and safe serum, urine, or other body tissue fluoride levels in the public. The intended target tissue for fluoride is the tooth and no optimal enamel or dentin fluoride concentration has been suggested. The primary DRA research is over a half century old. Using half a century old estimates of fluoride exposure rather than measurements of fluoride existing in tissues is unacceptable and the public is being harmed. Any competent scientist will consider measurements better than estimates.

An absence of quality evidence has been irresponsibly used as proof of safety, and low quality studies evading known and unknown factors are quoted because they appear to support fluoridation, while current studies refuting or raising concerns of risk are ignored. However, the FDA CDER is the most competent organization to determine scientifically whether the benefits outweigh the risks.

B. Congress' Mandate to the FDA CDER to Ensure the Safety of Drugs is Not Upheld by Delegating Drug Regulatory Authority to the EPA, an Agency that has No Empirical Evidence of the Safety or Benefits of Water Fluoridation[46] and No Mission or Intent to Seek or Require Evidence of Safety or Benefit, and which is Forbidden by the SDWA from the Addition of Drugs to Water.

Since 1938, every new drug should have been the subject of an approved NDA before U.S. commercialization. Fluoridation started about 1950 and is not and has never

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[44] Robert Thurau, Chief, Treatment Technology Evaluation Branch, Water Supply and Water Resources Division EPA Office of Research and Development 11/16/2000 letter to Roger Masters http://www.dartmouth.edu/~rmasters/AHABS

[45] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm Accessed 10/26/10

[46] Robert Thurau, Chief, Treatment Technology Evaluation Branch, Water Supply and Water Resources Division EPA Office of Research and Development 11/16/2000 letter to Roger Masters http://www.dartmouth.edu/~rmasters/AHABS

been grandfathered. The NDA is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. Neither the fluoridated water drug, fluoride bottled water, fluoride chewing gum, nor any fluoride supplement has ever been approved by the FDA CDER for ingestion with the intent to prevent caries.[47] Lack of approval and lack of regulatory action has resulted in serious harm to the public, for example with tooth damage,[48] thyroid damage,[49] cancer and brain damage.[50]

C. The Fluoridated Water Drug Manufacturers are in Violation of Title 21: Food and Drugs§ 314.50 and Title 15 Chapter 30 §1261 [51]

Fluoridated water **raw product** drug manufacturers have not provided a full description of the drug raw products including physical and chemical characteristics, stability, method of synthesis or isolation. Records of purification are behind locked doors at the NSF, a private corporation without any duty to divulge evidence to the public on purity of the raw toxic compounds. The fluoridated water drug raw product manufacturers provide no information on process controls, quality, purity, bioavailability, analytical procedures, stability, sterility, or particle size. Perhaps these are provided to NSF under agreement that they not be released to the public. The fluoridated water drug raw product manufacturers do not meet the current edition of the U.S. Pharmacopeia and the National Formulary,[52] and are not licensed as drug manufacturers with the FDA CDER nor are they manufacturing with good drug manufacturing practices.

The **final** fluoridated water drug manufacturers—water districts, cities, and health departments—do not manufacture the final product under good drug manufacturing practices nor are they licensed with state boards of pharmacy or the FDA CDER. The final fluoridated water drug is misbranded and contaminated. The fluoridated water drug manufacturers provide no label, dispense without license, administer without license or supervision, and without patient consent. Without FDA CDER approval, fluoridation is simply a poorly run experiment of an illegal drug on the public without cohort consent.

When questioned about lack of appropriate regulatory action on fluoridation, both federal and state authorities often give the brush off, "Fluoridation is a local decision," "on the local level," or it's out of our hands because the voters approved it." However, those arguments do not exempt voters, cities, public utilities or boards of health from following the FFDCA intent to protect the public with a NDA. Voting in fluoridation does not exempt the drug from FDA CDER NDA.

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[47] The claim of health benefit on fluoridated bottled water does not appear to have been CDER approved and the FDA Food section was notified rather than a drug application made.
[48] See Section IX p 48 below & Section XII
[49] See Section IX & Section XII
[50] See Secdtion IX & XII
[51] TITLE 15 > CHAPTER 30 > § 1261 Definitions http://www.law.cornell.edu/uscode/uscode15/usc_sec_15_00001261----000-.html
[52] http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=2a88f275a8609a20ed3f25adbeb7205f&rgn=div5&view=text&node=21:5.0.1.1.4&idno=21#21:5.0.1.1.4.1.1.1 accessed 10/30/10

D. The IOM (Institute of Medicine): the Role of Drug Approval is with the FDA.

When cautioning about identifying and preventing medical errors, the IOM stated:

"As used in this study, the phrase "drug safety and quality" did not include known risks associated with the medication itself, product purity, or integrity, that are the subject of extensive FDA oversight and regulation through the drug approval process and good manufacturing practice (GMP) regulations and guidance."[53]

IOM support for a drug does not exempt the drug from FDA CDER NDA (new drug application and approval) nor is the IOM authorized to define fluoride as a food.

E. The Surgeon General's Office also Relies on the FDA for Drug Approval.

"The level of evidence, for example, to justify the entry of a new drug into the marketplace has to be substantial enough to meet with approval by the U.S. Food and Drug Administration (FDA)."[54]

A Surgeon General's support for a drug does not exempt the drug from FDA CDER NDA nor define the drug as a food.

F. The FDA has No Records of Congressional Approval for FDA to Relinquish Drug Regulatory Approval for Fluoride in Drinking Water or Congressional Approval for EPA to Assume Jurisdiction as Related to Public Water Systems.[55]

G. FDA's Effort to Remove Unapproved Drugs From the Market

1. Quoting the **FDA:**

"Pharmacists are often not aware of the unapproved status of some drugs and have continued to unknowingly dispense unapproved drugs because the labeling does not disclose that they lack FDA approval. FDA estimates that there are several thousand unapproved drugs illegally marketed in the United States. FDA is stepping up its efforts to remove unapproved drugs from the market. . . .

"FDA has serious concerns that drugs marketed without FDA approval may not meet modern standards for safety, effectiveness, manufacturing quality, labeling, and post-market surveillance. For example, FDA-approved drugs must demonstrate that their manufacturing processes can reliably produce drug products of expected identity, strength, quality, and purity. . . ." Enforcement Priorities

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[53] http://iom.edu/Activities/Quality/MedicationErrors.aspx Accessed 10/16/10
[54] http://www.surgeongeneral.gov/library/mentalhealth/chapter1/sec2.html Accessed 12/3/10
[55] Appendix 8 FDA Response to FOI

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.

Most recently, in June 2006, FDA issued a guidance entitled "Marketed Unapproved Drugs – Compliance Policy Guide" (CPG) outlining its enforcement policies aimed at bringing all such drugs into the approval process. (www.fda.gov/cder/guidance/6911fnl.pdf)"[57] (emphasis added)

The EPA DRA (2010) continues to treat fluoride as a protected pollutant and include assumed and alleged flawed theories of efficacy. The EPA permits contaminants until science proves harm. The FDA is required to prevent the marketing of contaminants until science proves safety. The EPA lacks "post-market" surveillance of fluoridation and the drug does not meet modern standards for safety nor current assessment measurement standards.

And every day the public is harmed because the FDA CDER continues to defer regulatory action.

2. State Assemblyman John Kelly of New Jersey wrote to Senator Smith, August 14, 2000,

"It is my understanding that in 1975, the FDA issued a regulatory letter asking manufacturers to remove fluoride supplements from the market. To date, the FDA has not responded to my inquiry asking for clarification of their actions in 1975. Also, in 1993 I petitioned the FDA to enforce the law and remove children's fluoride supplements from the market. The FDA has ignored my repeated requests."[58]

[57] http://www.doh.wa.gov/hsqa/professions/Pharmacy/documents/July2008.pdf
[58] Appendix 9 Kelly

III. CONGRESS HAS PROHIBITED THE EPA FROM REGULATING FLUORIDE FOR HEALTH RELATED PURPOSES.

A. The SDWA with Cause, Prohibits the EPA from Regulating the Addition of Fluoride to Water for Health Care Purposes.

42 USC 300g-1(b)(11) states:

> *"**No** national primary drinking water regulation may require the addition of any substance for preventive health care purposes unrelated to contamination of drinking water."* (emphasis added)

For greater clarification, the **EPA** was contacted and responded:

> *"**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. Decisions on whether or not to fluoridate drinking water are made at a state or local level.*[59] (emphasis added)

However, by assuming efficacy of fluoride, the EPA violates the intent of the SDWA and protects the fluoride contaminant based on health care purposes which in practice forces the public to ingest, with harm, excess fluoride. The EPA DRA has NO jurisdiction to adjust fluoride concentration in water based on health–related purposes or determine the safety of the pollutant with a primary over riding medicinal intent.

B. The EPA Could Not Enter Into an MOU[61] With the FDA Which Requires the EPA to Violate the SDWA. If the EPA Did, Then the MOU is Invalid. The MOU Relates to Food and NOT the Addition of Fluoride to Water With the Intent to Prevent Disease, Drugs. (See p 31 Section V these comments)

C. Decisions by States and Municipalities to Fluoridate Drinking Water do Not Exempt Those Governments From Other General Laws Such as Gaining FDA CDER Approval and Licensing the Marketing of Drugs. State Governments Mistakenly rely on the EPA to Determine the Safety of Fluoridation.[62]

D. The EPA Correctly Understands the SDWA's Charge to Regulate Fluoride Existing in Drinking Water as a Contaminant.

The FDA CDER has jurisdiction, authority and mandate by Congress under 21 U.S.C. 321 CHAPTER II—DEFINITIONS (g)(1) both (a) and (b) to regulate any substance used with the intent to prevent disease, including the fluoride concentration in water. Other drugs are sometimes detected in public water systems. Adjusting the concentration of lithium, penicillin or any other drug with heath-related intent is not within the jurisdiction of the EPA.

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[59] Appendix 10 FOI response from EPA
[61] Appendix 1 MOU between FDA and EPA
[62] See Appendix 11 and 12. See also XIII G page 203 this paper.

Local governments trust HHS and Divisions of HHS and the EPA.[63] HHS, EPA, and the DRA must clear up that mistaken trust. The lack of FDA CDER regulatory action of determining fluoridate concentration in water based on health-related purposes and fluoride supplement manufacturers is the bailiwick of the FDA CDER. The CDC and EPA shall refer manufacturers of the fluoridation drug to the FDA CDER for approval.

E. The SDWA is the Federal Law Intended to Protect Public Water Systems From Harmful Contaminants.

> *"The Safe Drinking Water Act (SDWA) is the main federal law that ensures the quality of Americans' drinking water. Under SDWA, EPA sets standards for drinking water quality and oversees the states, localities, and water suppliers who implement those standards."*[64]

The states, localities and water suppliers in turn rely on the EPA for guidance on water contaminants and on the FDA CDER and Boards of Pharmacy for oversight of the manufacturing of drugs. EPA for contaminants, poisons such as fluoride, existing in water. **FDA CDER** for concentration of drugs made with water. The DRA's sole focus must be on safety and not altered by assumptions of efficacy. The EPA does not have jurisdiction to weigh the balance between efficacy and safety and pretend to be a sham FDA CDER with drug regulatory judgment.

The CDC has no authority to approve drugs nor recommend the use of unapproved drugs or formulation of unapproved drugs.

F. EPA Was Not Able to Identify Any Empirical Scientific Data Because the SDWA Does Not Authorize the EPA with Drug Regulatory Approval.

The EPA presented to Congress:

> *"To answer your first question of whether we have in our possession any empirical scientific data on the effects of fluosilicic acid or sodium silicofluoride on health and behavior, the answer is no."*[66]

G. The EPA Scientists NFFE Amicus Curiae, Appendix DD, is Essential for the HHS, FDA CDER, CDC OFFICE OF WATER AND ORAL HEALTH, and EPA to Carefully Review at This Time. The EPA Scientists have taken the Legal, Moral, and Scientific High Ground. [67]

The EPA professionals have been brutally concise, clear and ethical:

1. *"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*

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[63] Appendixes 11 and 12
[64] http://water.epa.gov/lawsregs/rulesregs/sdwa/index.cfm Accessed 11/8/10
[66] Robert C. Thurnau, Chief, Treatment Technology Evaluation Branch, Water Supply and Water Resources Division, U.S. EPA National Risk Management Research Laboratory, November 16, 2000,
[67] http://www.cdc.gov/fluoridation/pdf/natures_way.pdf

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."[68]

These EPA scientists appear to be at serious odds with the DRA. It is not too late for Joyce Morrissey, Tina Duke, Dennis Opresko, Annetta Watson, Bruce Tomkins, Brenda Foos, Denis Borum, Lisa Melnyk, Linda Abbott, Mary Fox, E. Angeles Martinez Mier, and/or David Ozsvath to carefully review DRA report in light of laws, science, and ethics, and remove your names, demand the report be corrected, or at least write a minority report.

2. Perhaps the most striking example of the severe polarization between proponents and opponents of the unapproved fluoridated water drug is between the CDC/ADA and the EPA scientists. The CDC/ADA claim fluoridation is safe, effective and necessary for everyone and the EPA scientists claim fluoridation borders on criminal behavior.

3. The EPA scientists (NFFE) testified to the Court regarding the scientific basis for the authorized Recommended Maximum Contaminant Level (RMCL) for fluoride in drinking water.

". . . NFFE believes that serious errors were made by the Agency in setting the fluoride RMCL . . . the Agency deliberately chose not to base its decision on relevant expertise. . . . The process by which EPA arrived at the RMCL for fluoride is scientifically irrational and displays an unprofessional review of relevant scientific data."[69]

And the EPA scientists advised the Court:

"Fluoride as a Protected Pollutant The classic example of EPA's protective treatment of this substance, recognized the world over and in the U.S. before the linguistic de-toxification campaign of the 1940's and 1950's as a major environmental pollutant, is the 1983 statement by EPA's then Deputy Assistant Administrator for Water, Rebecca Hanmer (15), that EPA views the use of hydrofluosilicic acid recovered from the waste stream of phosphate fertilizer manufacture as, "...an ideal solution to a long standing problem. By recovering by-product fluosilicic acid (sic) from fertilizer manufacturing, water and air pollution are minimized, and water authorities have a low-cost source of fluoride..."

In other words, the solution to pollution is dilution, as long as the pollutant is dumped straight into drinking water systems and not into rivers or the atmosphere."[70] In the 1950's Harold C. Hodge erroneously suggested it would take a daily dose of 20-80 mg to get skeletal fluorosis. The EPA relies predominantly on biased research from that historical era to set the RfD.

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[68] Dr. J. William Hirzy, Senior Vice-President, Headquarters Union, US Environmental Protection Agency, March 26, 2001. This letter describes some of the harms of water fluoridation as seen by water fluoridation opponents.
[69] Appendix 13, Amicus to the US Court of Appeals, DC Circuit, Natural Resources Defense Council, Inc., v EPA Civ. No. 85-1839 http://www.fluoridealert.org/health/epa/nrdc/union-brief1986.pdf
[70] Appendix 14 NTEU 280 page 3

4. **FDA** is negligent in not providing a senior toxicologist to help the EPA scientists. Under the MOU, the FDA is responsible for providing the EPA with a senior toxicologist. However, the FDA needs to provide a senior Pharmacologist to explain to the EPA the difference between drugs and contaminants and the laws relating jurisdiction, poisons, drugs, and human subject research.

5. Some EPA scientists have taken the moral high ground in attempting to protect the public. It is time FDA scientists, HHS and FDA CDER administration cease deferral of regulatory action on fluoridation drugs, and join the many civilized nations which no longer allow public water systems to be used to conduct a forced medication experiment on the public.[71]

6. January 2011 the EPA withdrew approval of SF post-harvest fumigants. The current EPA management should be applauded for starting to reduce the excess fluoride exposure in foods. However, fluoridation of public water is far worse and provides no benefit for the preservation of food products or improvement of water. At least SF had a food preservation benefit. Fluoridation of water does not improve the water.

H. The FDA Refusal to Enforce Regulatory Action in Denial (FDA 2007-P-0346) is in Error and the FDA's Legal Reference[72] Relates to Contaminants Found in or Added to Public Water Systems, not to the Addition of Drugs, the Manufacturing of Drugs or the Marketing of Drugs by Public Water Systems. The SDWA does Not give States Primacy of Oversight and Enforcement for Drug Manufacturing, Marketing or Approval.

> *CRS -44, "The Safe Drinking Water Act (SDWA), Title XIV of the Public Health Service Act, is the key federal law for protecting public water supplies from harmful contaminants."*

1. Naturally occurring fluoride is considered a "contaminant." There is no provision in the SDWA or the CRS documents which permits or authorizes the opposite of "protecting public water supplies from harmful contaminants."
2. There is no provision in the SDWA or the CRS documents which permits or authorizes federal or state to "contaminate," public drinking water.
3. The SDWA does not authorize the EPA to regulate the addition of contaminants, additives, or any other term used for substances with the intent to prevent disease, a drug to treat people.
4. The states may have primacy over contaminants in water, but not the manufacturing and marketing of drugs just because the drug is compounded with public water.

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[71] To our knowledge, no national drug regulatory agency world wide has approved water fluoridation. Most European Dental Associations no longer recommend fluoride supplements. Zimmer 2003
Austria Belgium Finland Germany Denmark Norway Sweden Netherlands Hungary Japan China Cuba have rejected or banned fluoridation of public water. The Canadian Dental Association says No to fluoride supplements. **http://www.cda-adc.ca/_files/position_statements/fluorides.pdf** See also Appendix 15

[72] The CRS Report RL 30022 "Summaries of Environmental Laws Administered by the EPA reference by the FDA Denial was not available at http://www.nceonline.org/NLE/CRSreports/BriefingBooks/Laws/g.cfm. Perhaps it has been removed or is not available to the public. A search of RCS documents located the January 7, 2008 CRS Report for Congress: Summaries of Major Statutes Administered by the EPA. At http://assets.opencrs.com/rpts/RL30798_20080107.pdf

5. Neither does the FFDCA exempt the FDA CDER from oversight regulation when a public agency or private company mixes public water with raw products marketed with the intent to prevent disease.

6. However, the FDA reference includes "The Lead Contamination Control Act of 1988 (P.L. 100-572)" and fluoridation is in violation of the LCC Act because fluoridation increases the blood lead level of children.

7. Most states have agreed to abide by the SDWA which prohibits the addition of substances intended for the prevention of disease. Like the FDA CDER, the EPA has failed to enforce the SDWA and prevent states and public water systems from intentionally violating the SDWA with fluoridation.

8. Federal Law does not permit the addition of highly toxic poisons[73] to public water. Chlorine does not fit within the highly toxic poison laws.

H. The fluoride Substance Added to Public Water is Highly Toxic and Defined by Law as a Poison and Exempt as a Drug.

If the addition of fluoride is found not to be a drug, then poison laws apply. Attempting to throw Health Department and Water System boards into jail for criminal acts of poisoning public water is not the best method of drug regulatory oversight.

J. The DRA should include a Review of the Toxicity of Fluoride and like Lead, which is Less Toxic, set the MCLG of Fluoride at Zero ppm.

[73] http://www.law.cornell.edu/uscode/uscode15/usc_sec_15_00001261----000-.html

IV. CURRENT OPTIONS FOR QUANTIFYING DOSE-RESPONSE INCLUDE MEASURED CONCENTRATIONS IN SUBJECT TISSUES

A. Tooth Fluoride Concentration

The intent of ingesting fluoride is to increase the fluoride content of tooth structure with the intent to prevent dental caries. No other intent for ingesting fluoride has been suggested. Fluoride is not used with the intent to treat water.

Fundamental questions have not been answered by promoters of fluoridation and fluoride supplements. What concentration of fluoride do we want in the enamel and dentin?

1. LOW END: At what lower concentration of fluoride in enamel and dentin do dental caries increase? The CDC appropriately has no lower serum fluoride limit for the **safety** of fluoride exposure.[74] And **NO** lower concentration of enamel and dentin fluoride concentration has been determined for the prevention of dental caries.

2. MIDDLE: What range of enamel and dentin fluoride concentration is "optimal" or "normal" showing reduced dental caries? NO "optimal" enamel or dentin fluoride concentration has been determined. The overlap between benefit and risk makes an "optimal" enamel and dentin fluoride concentration problematic.

3. HIGH END: Above what enamel and dentin fluoride concentration is safe without risk of adverse health effects for enamel and dentin fluorosis or tooth fracture?

Until HHS/CDC and scientific literature have answered those questions, discussion of the concentration of fluoride in serum and water are premature. It is simply impossible to determine optimal serum, urine, or water fluoride concentration or protect an RfD if we don't know what the tooth concentration should be. Intent is to treat teeth, not water.

Fluoride concentration in the outer layer of enamel appears to increase with topical fluoride use. The relationship between fluoride concentration in enamel and dentin and fluoride concentration in water is mixed. Waszkiel (2004) reported both decreased fluoride and magnesium concentrations in teeth with erosions than controls.[75] However, we don't know whether the erosions started out with a similar concentration of fluoride and the etiology for the erosions removed the fluoride or the lack of fluoride resulted in the erosions. Other confounding factors such as magnesium, calcium, iron, and B-12, C and D in the diet are seldom considered.

> Vieira (2004*) "Our results showed correlation between dentin F concentration and* (dental fluorosis) *DF (r_S = 0.316, p = 0.001), but no correlation between enamel F concentration and DF (r_S = 0.154, p = 0.133). No correlation was*

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[74] http://www.bt.cdc.gov/agent/sulfurylfluoride/casedef.asp Accessed 2/9/11
[75] Appendix 109 Waszkiel http://www.fluorideresearch.org/374/files/374271-277.pdf

observed between dentin and enamel F concentrations in the same tooth (r_S = 0.064, p = 0.536)."[76]

Featherston (1990) *"The clinical implications are (i) that simply increasing fluoride concentration may not necessarily give increased cariostatic benefit, and (ii) that improving the means of delivery of relatively low fluoride concentrations for longer times should be more appropriate for enhancing clinical efficacy."*[77]

Vieira (2005) reported*, "Teeth were analyzed for DF* (dental fluorosis) *severity, dentin [F], enamel [F], dentin microhardness, and dentin mineralization. Dentin [F] correlated with DF severity; enamel [F] correlated with dentin microhardness and dentin mineralization; DF severity correlated with dentin microhardness. Genetic factors (e.g., DF severity) and environmental factors (e.g., tooth [F]) influenced the mechanical properties (microhardness) of the teeth, while only the environmental factors influenced their material properties (e.g., mineralization). Fortaleza teeth* (0.7 ppm water F) *were harder and less mineralized and presented higher dentin [F] values. Montreal teeth* (0.2 ppm water F) *presented lower levels of DF when compared with both Toronto* (1.0 ppm water F) *and Fortaleza teeth. . . Differences seen in tooth microhardness and mineralization in the 3 cities studied. . . may be due to differences in ethnic background and/or geographical location."*[78]

HHS/CDC and the literature have not determined whether a concentration of fluoride in dentin with increased microhardness increases tooth fractures. A harder tooth appears to fracture more often.

Proponents of fluoride ingestion, including HHS/CDC and EPA have failed to determine the desired concentration of fluoride in the target tissues, enamel and dentin. Until an "optimal" safe concentration of fluoride in tooth structure is determined and FDA CDER approval is achieved, the experimentation of the concentration of the unapproved drug in water dispensed to patients without their consent is human research without consent.

B. Serum Fluoride Concentration.

1. With skeletal fluorosis, the Office of Water did not identify any studies that were good candidates for dose- or concentration-response modeling, in part because current assessment methods no longer limit assessment to the inaccurate, crude and historic method of estimating exposure by measuring fluoride concentrations in water. Too many sources of fluoride exist to reasonably estimate exposure for specific individuals. Compounding the problem is the highly variable excretion of fluoride. And further compounding the problem is the genetic differences for dental

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[76] Appendix 110 Vieira (2004) http://jdr.sagepub.com/content/83/1/76.full.pdf+html

[77] Feathersone JD et al , Dependence of in vitro demineralization of apatite and remineralization of dental enamel on fluoride concentration, J Dent Res. 1990 Feb;69

[78] Appendix 111Vieira et al. How Does Fluoride Affect Dentin Microharness and Mineralization?

fluorosis. The scientific gold standard for measuring fluoride exposure is to include measured fluoride concentrations in subjects of serum/plasma, urine, enamel, dentin and other tissues. Determining individual fluoride exposure from water is crude, inaccurate, guessing and problematic.

2. The CDC reports, "Normal serum fluoride levels are <20 mcg/L but varies substantially on the basis of dietary intake and environmental levels."[79] Less than 0.02 ppm for adults is high, but should be protective for most and the EPA RfD of 0.08 mg/kg/day is estimated to usually exceed serum fluoride levels of 0.02 ppm. In other words, the proposed RfD for fluorosis is not protective based on CDC recommendations.

3. As shown below, the no adverse effect for **serum fluoride concentration** with a margin of safety should be considered less than **0.013 ppm for most adults.** Taves[80] considered normal at 0.7 micromolar (0.013 ppm). Torra[81] (1998) reported 1-47 microg/L (17.5 microg/L mean or 0.0175 ppm). The CDC recommendation of less than 0.02 ppm is higher than current concentrations contributing to disease.

4. Sandhu used controls with mean fluoride serum at 0.0421 ppm, and reported bone-forming tumors at 0.072 ppm and osteosarcoma at 0.143 ppm. Rathee[82] (below) reported serum fluoride for controls without stones at a mean 0.025 ppm and subjects at a mean 0.12 ppm. Historically, Singer[83] reported as "normal" average serum fluoride value of 8 micromolar (0.15 p.p.m.) a serum fluoride level which is now found excessive. A margin of safety for high risk subpopulations is not provided.

5. The DRA report must include the serum fluoride levels for adults, children, infants and fetus, resulting from a 0.08 mg F/kg/day RfD especially for pregnant mothers since the placenta does not appear to prevent fluoride from reaching the infant.

6. Hossney (2003)[84] reported, "the fluoride levels in mothers' milk reflected the serum levels of their own infants." More than half of mother's milk tested in a Canadian study[85] had no detectible fluoride, mean 0.004 ppm. HHS/CDC is advised to protect infants with a warning not to use water containing more than 0.005 ppm fluoride for drinking and making infant formula.

7. The human fetus and infants should be more protected, not less protected. Executive Order 13045 does not authorize the EPA to ignore and abandon

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[79] http://www.bt.cdc.gov/agent/sulfurylfluoride/casedef.asp Accessed 2/9/11
[80] Taves D, Normal Human Serum Fluoride Concentrations, Nature 211, 192-193 (09 July 1966; doi:10.1038/211192b0
[81] Torra M et al Serum and urine ionic fluoride: normal range in a nonexposed population. Biol Trace Elem Res. 1998 Jul;63(1):67-71.
[82] http://medind.nic.in/iaf/t04/i2/iaft04i2p100.pdf Accessed 2/3/2011
[83] As reported by Taves, either in Singer, L and Armstrong, W.D. J. App. Physiol., 15,508 (1960) or the same authors in Anal. Biochem., 10,495 (1965).
[84] Hossney E, Reda S, Marzouk S, Diab D, Fahmy H. Serum fluoride levels in a group of Egyptian infants and children from Cairo city. Arch Environ Health. 2003 May;58(5):306-15.
[85] NRC (2006)

the fetus, infants and children when determining health risks. EPA Guidelines (1-1)[86] state: *The overall characterization of risk is conducted within the context of broader policies and guidance such as Executive Order 13045, "Protection of Children From Environmental Health Risks and Safety Risks"(Executive Order 13045, 1997) which is the primary directive to federal agencies and departments to identify and assess environmental health risks and safety risks that may disproportionately affect children".* Fluoridation disproportionately affects the fetus, infants and children.

8. Xiang (2003 and 2005)[87] reported lower IQ comparing serum fluorides of 0.08 ppm (4.2 µmol/L) with 0.04 ppm (2.1 µmol/L). The EPA references Sowers (2005)[88] when evaluating skeletal fluorosis. Sowers (2005) reported the 4th quartile (25%) of the control community had mean serum fluoride concentrations of 0.05 ppm (2.54 µmol/L to 2.60 µmol/L) and high-fluoride community 4th quartile at 0.08 ppm (3.97 +/- 0.18 µmol/L) which is similar to the 0.08 ppm (4.2 µmol/L) Xiang reported as having 8 IQ point loss. The EPA is not protective.

Once again:	Controls	Subjects
Skeletal Fluorosis	0.05 ppm F	0.08 ppm F
Loss of 8 IQ	0.04 ppm F	0.08 ppm F
Skeletal Fluorosis		0.06 ppm F

And just because harm was found at higher levels, does not mean the controls were at a level without harm. And further, mean concentrations do not protect subpopulations and a margin of safety must be included.

9. Itai (2010) found "Mean SIF (serum ionic fluoride) concentrations were 0.495mumol/l in men and 0.457mumol/l in women." (0.495 mumol/l X 0.019mg/mumol= 0.009 ppm) And he concluded SIF "concentrations in middle-aged healthy subjects were increased with an age-related degeneration in renal function. SIF concentrations in post-menopausal women arise from the increased fluoride release from bone after menopause. Age is not related to SIF concentrations."[89]

10. A safe non-pregnant healthy adult serum fluoride level around 0.01 ppm, certainly less than 0.02 ppm is consistent with most research and the CDC. Our goal for serum fluoride levels in infants should be zero, similar to most samples of mother's milk.

11. The question begs, what serum fluoride level exists with 4 ppm, 1ppm or 0.7 ppm in water? The answer in large part depends on the quantity of water consumed, kidney function, Iodine, calcium, diet, age, elevation, genetics and other sources of fluoride exposure. Adjusting the concentration of fluoride in water to achieve

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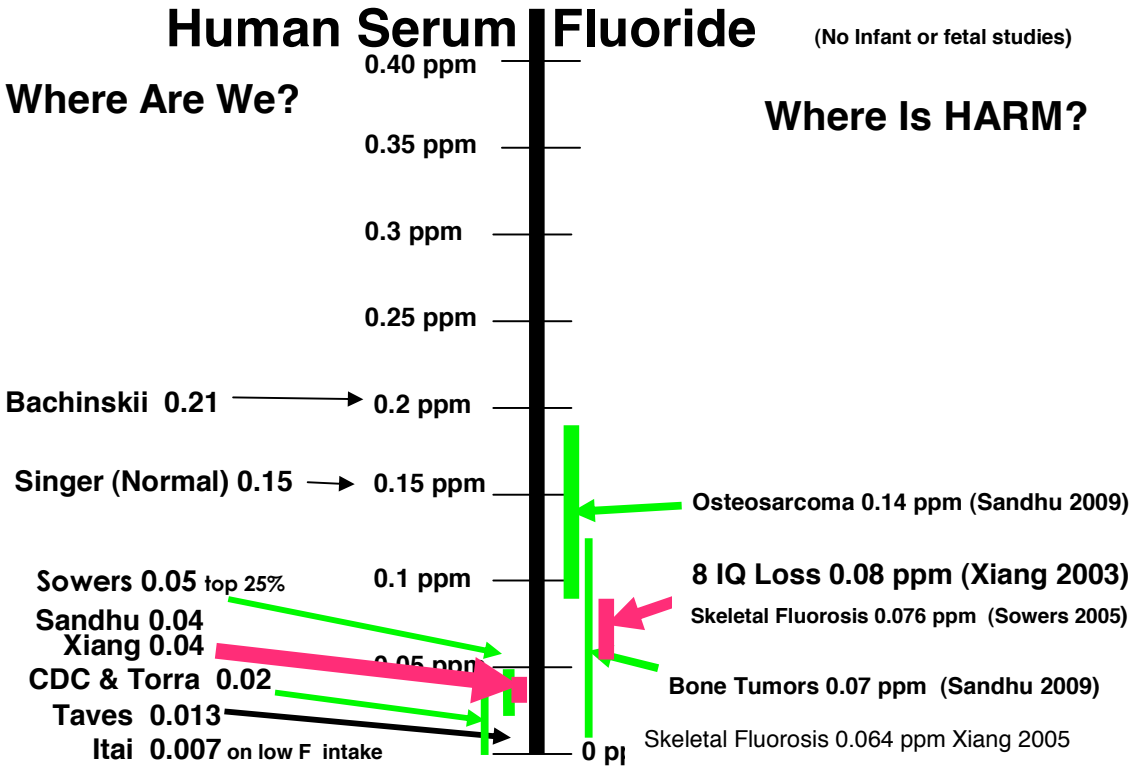
[86] Appendix 120 p 1-1.
[87] Appendix 16 & 70 See also Appendix 118, Lead was not a confounding factor.
[88] http://water.epa.gov/action/advisories/drinking/upload/skeletal_effects.pdf accessed 1/21/11 Fluoride: Dose-Response Analysis for Non-cancer Effects, Fluoride-Related Skeletal Effects Evaluations of Key Studies, Table 2 p 52.
[89] Appendix 17: Itai K et al, Serum ionic floride concentrations are related to renal function and menopause status but not to age in a Japanese general population. Clin Chim Acta. 2010 Feb;411 (3-4):263-6.

a safe fluoride serum level for everyone is problematic, especially for the fetus, infants and children.

The table below illustrates some of the literature.



12. Connett M (2004) compiled data on fluoride concentration in water and bone damage with water fluoride concentrations.[90] Table 1 lists several studies reporting damage at current fluoridation levels and one as low as 0.6 ppm. Because water is only one source of fluoride, fluoride exposure from water represents perhaps half the total exposure for many people. Serum and urine fluoride concentrations are necessary to evaluate exposure and retention of fluoride. Table 3a from Connett M (2004) lists ten studies with measured serum fluoride levels. Of particular note should be the repeated reporting of higher serum fluoride levels in people with kidney disease on water at 1 ppm and as fluoride concentration in water increases often serum fluoride levels increase. Water is only one source of fluoride.

The CDC recommends <0.02 ppm serum fluoride levels and as of 2004 at least 8 human studies of people on fluoride water with 1 ppm had reported serum fluoride ranges averaging 5 to 14 times (0.1 – 0.28 ppm) higher than maximum CDC recommendations. Those with kidney disease had significantly higher serum fluoride levels.

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[90] Appendix 107

TABLE 3a: Average Serum Fluoride Levels Reported in Human Skeletal Fluorosis

Study	Serum F (umol/L)	Serum F (ppb)
Susheela 1981	25.3	480
Bo 2003	17.2	326
Barot 1998	14.6	278
Susheela 1996	12.6	240
Jin 2003*	10.5-12.1*	200-230*
Singla 1976	8.8	166
Li 1986	6.6	125
Li 1990	6.2	118
Yildiz 2003	5.8	110
Savas 2001	5.3	100

RELEVANCE TO CURRENT DRINKING WATER STANDARDS:

Red indicates serum F levels detected in people without kidney disease in 1 ppm areas (see Table 3c).

Blue indicates serum F levels detected in people with kidney disease in 1 ppm areas (see Table 3c).

Black indicates serum F levels detected in people with kidney disease in $\leq$1.9 ppm areas (see Table 3c).

NOTE: In 1979, Johnson & Jowsey of the Mayo Clinic, recommended that people with serum fluoride levels in excess of 5 umol/L reduce their fluoride exposure in order to prevent skeletal fluorosis. To quote:

> "It would seem prudent to monitor the fluoride intake of patients with renal failure living in high fluoride areas. The serum concentration may indicate whether the patient should be advised to drink low fluoride water and will provide a check regarding compliance. Tentatively, **a shift to low fluoride water should be made before the serum fluoride concentration reaches 5 umol/L**, since evidence of (skeletal) fluorosis has been reported when the average serum concentrations of fluoride are 8 umol/L."

As can be seen in Table 3c, even people without kidney disease have been found to have in excess of 5 umol/L in their blood in fluoridated (1 ppm) areas.

* Children with severe dental fluorosis in a severe endemic fluorosis area. The skeletal status was not investigated.

Torra (1998)[91] *"Mean (±S.D.) serum fluoride concentration was 17.5±9.5 µg/l, ranging from 1 to 47 µg/l, in the control group and 58±31 µg/l, ranging from 28 to 185 µg/l, in renal patients. Urine fluoride concentration in the healthy group was 671±373 µg/24 h, ranging from 156 to 1900 µg/24 h. Fluoride status in the patient group was significantly greater than the control group*." RfD should have a a margin of safety to protect renal patients.

C. Urine Fluoride Concentration

1. Xiang (2003) compared urine fluoride concentrations, as fluoride concentration in drinking water goes up, a greater percentage appears to be retained Table 9:

Table 9. Fluoride in drinking water and in urine (Mean±SD)

No. samples	Drinking water F (mg/L)	Urinary fluoride (mg/L)	Urinary fluoride mg/mmol Cre
142	0.39±0.15	1.14±0.49	0.25±0.22
32	1.15±0.29	2.59±1.70	0.61±0.47
80	2.44±0.30	3.67±1.97	0.85±0.67
32	3.22±0.18	3.77±1.86	0.86±0.81
4	4.05±0.01	4.65±2.39	2.17±1.73

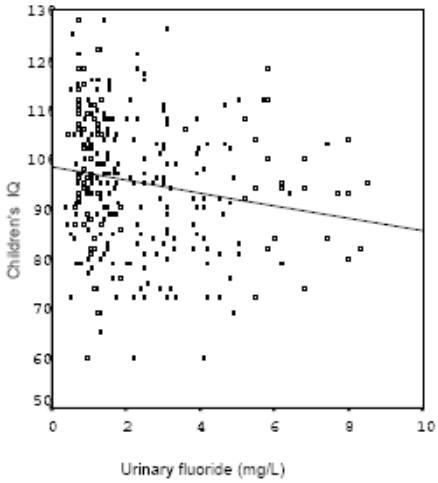

Figure 2. Correlation between urinary fluoride (directly measured) and IQ

Xiang (2003 & 5)[92] provided Figure 2. Children's IQ decreases with increased urinary fluoride concentration.

2. Fanco Hector (2009) at the Colgate-Palmolive Tech Center reported intake of fluoride ranged from 0.04 to 0.12 mg/kg/day for children 15 to 72 months of age. The EPA DRA (2010) proposed RfD of 0.08 mg/kg/day would still not be protective of the full range of fluoride intake children are actually receiving. And no margin of safety is added. Some children will be ingesting too much fluoride. HHS, EPA, CDC, FDA CDER must also protect these children from excess fluoride ingestion.

3. Singh (2007) reported ranges of fluoride in urine between 1.6 ppm to 3.4 ppm with water fluoride concentrations between 1.68 to 3.22 ppm. Urine and water concentrations appear similar at high concentrations, although not all researchers have found the same consistency.[93] When water and urine concentrations are similar,

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[91] Torra M, et al. (1998). Serum and urine fluoride concentration: relationships to age, sex and renal function in a non-fluoridated population. Science of the Total Environment 220: 81-5.
[92] Appendix 16 & 19
[93] Franco Hector (2009)

the concern is the additional fluoride from other sources must be taken up by the bones, teeth and other tissues and homeostasis of fluoride is not achieved.

4. Li[94] (2009) reported urine fluoride concentrations from 3 towns which also use brick tea. These levels had lower urine fluoride concentrations than Xiang above and higher urine fluoride than just the concentration of fluoride in water.

0.32 mgF/L of water had mean 0.59 mgF/L urine;
0.7 mgF/L of water had mean 1.45 mgF/L urine;
2.68 mgF/L of water had mean 3.06 mgF/L urine

At lower concentrations with good kidney function, the kidneys are often able to achieve a reasonable homeostasis between intake and excretion. However, blood serum levels are elevated. Potential damage is with higher blood serum and urine fluoride levels and "mean" levels do not properly reflect the 1 in 4 who are unable to adequately excrete fluoride.

5. Oporowska-Moszyk (1997) reported mean fluoride urine between 0.3 and 0.9 ppm and hair at 2.2 mg F/g and 3.3 mg F/g (higher due to Fertilizer Chemical Works)[95] at a level of concern for harm.

6. CDC's[96] suggestion of 0.2 to 3.2 mg/L normal range for fluoride urine appears too high at the upper limit. Providing these people with additional fluoride in water should be contraindicated and the patients warned not to drink public water. The CDC's "normal" urine fluoride level is where people are being harmed and is not consistent with CDC recommended serum fluoride levels. From Xiang's work above and assuming a linear effect, for every 1 mg/L F in urine, a decrease of about 1.5 to 2 IQ can be expected.

7. Measuring urine fluoride concentration is a more accurate estimate of fluoride exposure than estimating a dose response from fluoride concentration in water. However, inadequate kidney function and loss of water in sweat are two significant variables which make serum fluoride concentration a better measure of exposure. The EPA RfD should include measured serum fluoride levels rather than exclusively rely on relative estimates of exposure from water and some food.

8. Connett M (2004)[97] Table 5a lists research reporting bone effects associated with urine fluoride concentration. Table 5b is from Mansfield (1999) of people on 1 ppm fluoride in water listing the percentage of people with urinary fluoride concentrations over 2.0 ppm, fluoride levels of some skeletal fluorosis cases.

Li (number 5 above) measured mean fluoride in urine at 1.45 ppm for those on 0.7 ppm fluoride in water. However, Connett M (2004) Table 5b finds a significant

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[94] Appendix 20: Li HR et al, Fluoride in drinking water, brick tea infusion and human urine in two counties in Inner Mongolia, China, J Hazard Mater, 2009 Aug 15:167(1-3):892-5.
[95] Appendix 18: Oporowska-Moszyk K [Exposure of Poznan inhabitants to florides. II. Fluorides in urine and hair of school children], Rocz Panstw Zakl Hig. 1997;48(1):53-8.
[96] http://www.cdc.gov/niosh/docs/2003-154/pdfs/8308.pdf Accessed 2/9/11
[97] Appendix 107

number of people are not at “mean” urinary fluoride levels. 0.7 ppm fluoride in water will result in high fluoride urine concentrations for many people. Further, urine fluoride concentrations may not reflect the inability of the kidneys to excrete the fluoride.

Table 5b: Urine Fluoride Levels in Fluoridated (1 ppm) Areas*

Urine F (ppm)	West Midlands, UK No. (percent)	East Midlands, UK No. (percent)
< 0.3	4 (1.5)	4 (4.5)
0.3 < 0.7	30 (11.5)	20 (22.7)
0.7 < 1.0	60 (23.0)	11 (12.5)
1.0 < 1.3	49 (18.8)	22 (25.0)
1.3 < 1.7	31 (11.9)	10 (11.4)
1.7 < 2.0	28 (10.7)	5 (5.7)
2.0 < 2.3	25 (9.6)	5 (5.7)
2.3 < 2.7	8 (3.1)	4 (4.5)
2.7 < 3.0	9 (3.4)	2 (2.3)
3.0 < 3.3	4 (1.5)	1 (1.1)
3.3 < 3.7	4 (1.5)	1 (1.1)
3.7 < 4.0	4 (1.5)	2 (2.3)
≥ 4.0	5 (1.9)	1 (1.1)
Total No.	261 (99.9)	88 (99.9)
Mean F	1.46	1.28
Median F	1.2	1.1

RELEVANCE TO CURRENT DRINKING WATER STANDARDS:
Red indicates urine fluoride levels found in some people with skeletal fluorosis (see Table 5a).

* Table reproduced from Mansfield (1999) .

D. Fluoride Concentration in Other Body Tissues

Bone may contain the largest quantity of fluoride, but the pineal gland contains the greatest concentration of fluoride. The half life of fluoride in the body is about 20 years. The likely and probable harm to the pineal gland and melatonin production should be of serious concern to the CDC. Other tissues should be reviewed by the CDC.

V. CONGRESS HAS NOT AUTHORIZED THE CDC TO PROVIDE GUIDANCE ON THE DOSAGE OR CONCENTRATION OF FLUORIDE ADDED TO PUBLIC WATER SYSTEMS. [98]

A. The CDC does Not have an Approval Process for Fluoridation.[99]

B. The CDC does Not have Authorization to Recommend Unapproved and Therefore Illegal Drugs, such as Fluoridation. [100]

C. The CDC does Not have Empirical Data or Randomized Controlled Trials on Safety or Efficacy of Fluoridation at any Concentration. [101]

D. The CDC does Not have RCTs or Scientific Evidence to Support the Claim that Fluoridation is One of the Ten Great Public Health Achievements of the 20th Century. [102]

E. The FDA has Not Relinquished Drug Approval to the CDC or EPA.[103]

VI. CONGRESS HAS NOT APPROVED THE FDA/EPA MOU[104] AND THE MOU RELATES TO FOOD, NOT DRUGS.

A. The MOU (Appendix P, 225-79-2001) Between the EPA and the FDA is an Agreement as to How the "Food" Regulation Authority of the FDA Will Be Harmonized With the "Water" Regulation Authority of the EPA.

The MOU does not give up any **FDA** authority to EPA or CDC regarding regulation of drugs. The **FDA** has stated to Congress that fluoride when used in the mitigation or prevention of disease is a drug subject to FDA regulation.[105] When bulk fluoride raw ingredients are added to drinking water to create a "fluoride and water" drug with intent to prevent or mitigate dental disease (tooth decay or dental caries), it is a drug subject to **FDA** regulation. Fluoride is recommended by the CDC and others to prevent and control dental caries (i.e. tooth decay) which the CDC calls an "infectious, multifactorial disease;"[106] however, dental caries are not considered highly contagious or generally life threatening.

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[98] Appendix 113 CDC FOI 3 17 11
[99] Appendix 113 CDC FOI 3 17 11
[100] Appendix 113 CDC FOI 3 17 11
[101] Appendix 113 CDC FOI 3 17 11
[102] Appendix 113 CDC FOI 3 17 11
[103] Appendix 84 FDA FOI 6 10
[104] Appendix 1 EPA/FDA MOU
[105] Appendix 4 Calvert
[106] Appendix 21 CDC 8-17-01

MOU 225-79-2001 is an agreement to resolve conflicting legal authorities granted to the EPA and FDA. The conflicting EPA and FDA legal authorities are described in this MOU at 2-3. This MOU only seeks to resolve FDA authority over food in (FFDCA 201(f) (21 U.S.C. 321(f))), FFDCA 402 (21 U.S.C. 341)), FFDCA 406 (21 U.S.C. 346)), FFDCA 409 (21 U.S.C. 348)), and FFDCA 410 (21 U.S.C. 349)).MOU at 2.

However, the FDA has separate authority over drugs. FFDCA 201(g)(1) (21 U.S.C. 321(g)(1) and FFDCA 501 et seq. (21 U.S.C. 351 et seq.) The term "drug" is defined in 21 U.S.C. 321(g)

> *"(1) articles recognized in the official United States pharmacopoeia, official homeopathic pharmacopoeia of the United States, or official national formulary, or any supplement to any of them; and (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in human beings or other animals;"*

B. The FDA CDER Denial[107] Specifically References the MOU Number 225-79-2001 Statement[108] (MOU) Which References Foods and Never References Drugs:

> *"all substances in water used in food are added substances subject to the provisions of the Act, but no substances added to a public drinking water system before the water enters a* ***food processing establishment*** *will be considered a food additive."* Emphasis added.

1. The MOU in section I(H) states*: "protect the pubic from, inter alia, the adulteration of* ***food*** *by* ***food*** *additives and poisonous and deleterious substances."*

2. The MOU under "Intent B." states: "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."

3. The MOU under section II Background defines "Food" and references the word **"food" fourteen times** in this section alone, including the statement*, "to include any substance the intended use of which results or may reasonable (sic) 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."*

WASW charges that fluoride is highly toxic, defined as a poison by law, and is a substance "not generally recognized as safe." Neither the concentration nor safety after addition is an exemption or stipulation. The MOU is clearly referencing food and not drugs. The use of public water to dilute a drug does not provide for transfer of oversight

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[107] Appendix 22 FDA Petition Denial Sauerheber
[108] Appendix 1 MOU

regulatory authority to the EPA.

4. The MOU under section IIIB describes the **FDA's** responsibilities:

> "2 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."

WASW charges the **FDA** with failure to provide a senior toxicologist to the EPA as agreed in the MOU. Failure to do so has contributed to serious irreparable harm to the public. The above MOU statement is clearly referencing food processing establishments and not drug manufacturing establishments. For example, a soup company uses water which has had chlorine added before the water enters the soup processing establishment, the label on the soup container does not need to list the chlorine ingredient.

5. The FDA CDER denial is correct that the MOU is in regards to **additives** for the disinfection of water; however, **drugs** added to water must still be approved by the FDA CDER. An additive is intended to treat water. A drug is intended to treat people. The fluoridated water drug is intended to treat disease in people, not for the treatment or disinfection of water and is defined as a drug, not an additive.

6. The FFDCA does not authorize the FDA CDER to delegate drug regulatory authority.

7. The EPA could not enter into an MOU with the FDA which requires the EPA to violate the SDWA.

8. The MOU relates to and applies to foods, not drugs.

C. The MOU Stipulates Areas of Agreement Between the EPA and FDA. Fluoride Is a Drug and Not an Additive.

The MOU recognizes:

> *"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*;[109]

The addition of fluoridation raw compounds, especially the contaminated toxic waste product scrubbings of the phosphate fertilizer companies to public water, does cause harm to health and the environment.

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[109] Appendix 1 MOU

"*B. That the scope of the additives problem in terms of the health significance of these contaminants in drinking water is not fully known*;[110]

The diluted final fluoridated water drug product's risks are not fully known; however, enough risk of ingesting fluoride is known that regulatory oversight is essential. Water districts are forcing the drug into everyone without consent, without empirical evidence of safety, without any drug regulatory oversight of efficacy or safety, with negligible food oversight, and inadequate water oversight.

"*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*;"[111]

The FDA CDER denial is precisely one of the public's concerns. The FDA points the authority finger for fluoridation at the EPA and the EPA points the authority finger at the FDA. The public is left in harm because no regulatory authority accepts responsibility for the fluoride forced into about 225,000,000 people without their consent and without regulatory oversight.

"*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*"[112]

Regulatory authority placed in one agency is appropriate for additives to treat water. Delegating **drug** regulatory authority for the manufacturing and marketing of drugs to treat people to the EPA is beyond FDA's authority and beyond the capability of the EPA.

The **EPA** has jurisdiction to require the removal of the naturally occurring fluoride contaminant from drinking water if the level exceeds the MCL. **EPA** is not permitted to authorize addition of fluoride to drinking water under the SDWA – if it is being added for "preventive health care purposes." As pointed out elsewhere, 42 USC 300g-1(b)(11) states:

"No national primary drinking water regulation may require the addition of any substance for preventive health care purposes unrelated to contamination of drinking water."

Circumventing Congress, the EPA delegated to the National Sanitation Foundation (NSF) the right to regulate fluoride chemical purity. In effect, the NSF is assumed to provide purity evaluation of the fluoridation chemicals. The NSF has set itself up in part as a sham FDA.[113] In brief summary: the people rely on Congress, Congress has authorized the FDA to regulate drugs and the FDA relies on the EPA to do what the SDWA prohibits. Water systems and state public health agencies rely on the EPA who has turned over testing to the NSF, which is not obliged to release testing data

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[110] Appendix 1 MOU
[111] Appendix 1 MOU
[112] Appendix 1 MOU
[113] http://fluoride-class-action.com/sham

and which does not test the efficacy or safety of the fluoride chemical and has no oversight.[114] Meanwhile the CDC promotes and in effect markets the unapproved drug claiming, without careful scientific review, efficacy and assumes EPA evaluates safety.

The CDC in effect suggests that pharmaceutical grade fluoride drugs are lower quality than the waste product scrubbings of the phosphate fertilizer companies.[115] The CDC web site (probably water treatment personnel rather than pharmacologists) suggest pharmaceutical grade fluoride might increase impurities apparently because AWWA and NSF/ANSI standards are higher than pharmaceutical standards. The CDC is flawed because the FDA drug approval process places liability and responsibility on the manufacturer rather than patient. The AWWA and NSF/ANSI do not have liability or responsibility to disclose testing of purity nor oversight. USP is stricter with maximum exposure levels rather than relative contaminant source. Sodium fluoride used in water systems is listed in the USP and fluorosilicic acid and sodium fluorosilicate are substantially similar.

The CDC is flawed claiming "Fluoride Additives Are Not Different From Natural Fluoride."[116] The references provided by the CDC do not support the CDC's claim. For example, Whitford (2008) compared NaF with H2SiF6 and not naturally occurring calcium fluoride. And Finney (2006) evaluated the dissolution and intermediates of hexafluorosilicic acid and not naturally occurring calcium fluoride. No study provided by the CDC examines the toxicology, safety, or efficacy of natural calcium fluoride with hexafluorosilicic acid or sodium fluoride.

The EPA has jurisdiction over the removal of excess fluoride if it occurs naturally in drinking water. Naturally occurring fluoride is often calcium fluoride, which is less toxic than the silicofluorides or sodium fluoride artificially added to drinking water. The EPA is prohibited by the SDWA from adding any substance to water with the intent to prevent disease and therefore the EPA does not and did not appropriately evaluate the safety or efficacy of fluoridation. No law provides the EPA with jurisdiction over the addition of substances which are used with the intent to treat, mitigate, prevent, or cure human disease. The FDA CDER is charged by Congress in the FFDCA to regulate substances intended to prevent disease.

The CDC has no authority to recommend unapproved misbranded adulterated and contaminated drugs.

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[114] On July 7, 1988, by Notice in the Federal Register (53 FR, 25586),
[115] http://www.cdc.gov/fluoridation/fact_sheets/engineering/wfadditives.htm#9 accessed 4/10/11
[116] http://www.cdc.gov/fluoridation/fact_sheets/engineering/wfadditives.htm#9 accessed 4/10/11

VII. CONGRESS HAS NOT AUTHORIZED THE DIVISION OF NUTRITION PROGRAMS AND LABELING OFFICE OF NUTRITIONAL PRODUCTS, LABELING AND DIETARY SUPPLEMENTS CENTER FOR FOOD SAFETY AND APPLIED NUTRITION TO BRAND THE WATER FLUORIDATION DRUG AND REGULATE FLUORIDE AS A FOOD OR DIETARY SUPPLEMENT.

A. A Conflict Exists Between Fluoride Defined by Congress as a Drug[117] and FDA's Bottled Water Rule at 21 CFR 165.110(b)(4)(ii).

1. The regulation of fluoride concentration is not the same as drug approval, for example with dosage and label. *"Bottled water packaged in the United States to which fluoride is added shall not contain fluoride in excess of levels in Table 2. . . .."*[118] Individual consumption of water is not the same as "average" consumption, and concentration is not the same as dosage. Only limiting concentration is not adequate drug regulatory oversight.

2. 21 CFR 165.110(b)(4)(ii) does not exempt manufacturers from FDA CDER drug approval but does limit the concentration for those who chose to fluoridate bottled water. Drug regulatory approval for the addition of a drug to bottled water and marketing the drug is still required.

3. The FFDCA law is superior to FDA rules.

> *"...power to issue regulations is not power to change the law..."*
> *US v. New England Coal and Coke Company 318 F.2d 138 (1963).*

> *"Administrative agency may not, under guise of its rulemaking power, abridge or enlarge its authority or act beyond powers given it by statute which is source of its power; administrative regulations that alter or amend statute or enlarge or impair its scope are void." San Bernardino Valley Audubon Soc. V. City of Moreno Valley, 51 Cal.Rptr.2d. 897 (1996, Cal.App. 4th Dist).*

The U.S. Supreme Court has confirmed it is Congress and the language of the statute that controls the jurisdiction of the FDA Act, not a statement by an agency or another governmental entity. FDA v. Brown & Williamson, (529 U.S. 120 (2000)).

B. Fluoride is a Poison, Not a Food. Fluoride is Exempt from Poison Laws when Regulated as a Drug and not Exempt as a Food.

1. Fluoridation products such as sodium fluoride are considered lethal at about 5 mg/Kg BW, and as such, fit within federal poison laws and[119] which is in

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[117] *21 U.S.C. 321 CHAPTER II—DEFINITIONS (g)(1)(A) AND (B)*
[118] 21 CFR 165.10(b)(4)(ii)(C)
[119] http://www.law.cornell.edu/uscode/uscode15/usc_sec_15_00001261----000-.html

contrast to naturally occurring calcium fluoride found naturally in water and considered lethal at about 5,000 mg/Kg BW.[120]

2. The **EPA** regulates safety guidelines of maximum contaminant levels existing in water of a generally safer form of fluoride. The EPA has no authority to regulate the addition of any substance to water with health related purposes other than for disinfectants.

3. Washington State Law defines a poison as (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."[121] Sixty grains is 3,889 mg. 15 mg of silicofluoride or hydrogen fluoride is considered by some to be lethal for children.[122] Highly Toxic Poisons such as arsenic, fluoride and strychnine are exempt from poison laws[123] when used as drugs, but are NOT exempt when used as foods. If fluoride is not a drug, then it is a poison without exemption.

Fluoride is a poison and when used as a drug is exempt from poison laws but not exempt when used as a food or nutrient. There is no provision in Federal or State laws to permit the CDC or EPA from adding poisons to water without exemption as a drug and approved by the FDA CDER.

> *"RCW 69.40.030 Placing poison or other harmful object or substance in food, drinks, medicine, or water — Penalty.*
>
> *(1) Every person who willfully mingles poison . . . in any food, drink, medicine, . . . and every person who willfully poisons any spring, well, or reservoir of water, is guilty of a class B felony and shall be punished by imprisonment in a state correctional facility for not less than five years or by a fine of not less than one thousand dollars."*

4. Federal Law[124] and some states, such as Oregon[125] define a highly toxic substance (poison) as a substance which causes serious illness or death at 50 mg/Kg of body weight or less. The toxicity of fluoride at 5 mg/Kg BW is less than 50mg/Kg BW and therefore fluoridation compounds are poisons and are exempt from poison laws as drugs, but NOT exempt as foods. Poisoning water is illegal and possession of an unapproved drug is illegal.[126] Federal laws are strict regarding labeling of the container and fluoridated water is not appropriately labeled.[127]

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[120] Merck Index, 9th Edition, Merck and Co., Inc., Rahway, N.J. 1976, p 1663.

[121] RCW 69.38.010

[122] "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." SOURCE: 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."

[123] RCW 69.38

[124] http://www.law.cornell.edu/uscode/uscode15/usc_sec_15_00001261----000-.html

[125] *If Death with 50mg/Kg or less oral then "Highly toxic" ORS 453.005 (8);* "The word "Poison" for any hazardous substance which is defined as "highly toxic" in ORS *453.005 (Definitions for ORS 453.005 to 453.135)*;

[126] For example Idaho TITLE 37 CHAPTER 1 IDAHO FOOD, DRUG AND COSMETIC ACT 37-115. "PROHIBITED ACTS. The following acts and the causing thereof within the state of Idaho are hereby prohibited: (a) The manufacture, sale, or delivery, holding or offering for sale of any food, drug, device, or cosmetic that is adulterated or misbranded;

[127] http://www.law.cornell.edu/uscode/uscode15/usc_sec_15_00001261----000-.html

5. The toxicity of fluoride rules it out as being a food. Further, mother's milk usually has an undetected level of fluoride.[128] In this case, nature sets a reasonable example for the FDA CDER, HHS, CDC and EPA to protect infants. The first aim of the Federal Caustic Poison Act is the protection of children.[129]

6. A caffeine comparison. Caffeine is sold as an additive in both foods and drugs. An estimated lethal dose of caffeine is 150-200 mg/Kg/day. The FDA has concerns ingesting fluoride at 0.25 mg toothpaste and in 1963 an adult ingesting 2 mg[130] of fluoride. 2 mg for an adult would be about 0.03 mg/kg/day, significantly below the EPA's proposed RfD of 0.08 mg/kg/day and CDC's 0.7 ppm in water.[131] Caffeine is not mass medicated without patient consent, label or dosage. The manufacturing of caffeine is not the contaminated waste product of manufacturing. The analogy with caffeine breaks down, because caffeine is much less toxic than fluoride.

7. Pro-fluoride professionals fail to appreciate the FFDCA requires the FDA CDER to protect the public from misguided experiments of highly toxic poisons used with the intent to prevent disease. Focusing on a disease of the poor without fully evaluating the risks of a drug can cause the poor more harm and harm to the entire population. All drugs have risks.

8. When fluoride exists in water it is called a contaminant and regulated by state agencies regulating contaminants in water such as the Board of Pharmacy[132] (as a poison), Department of Health,[133] Agriculture[134] and Board of Health. Most states have signed an agreement to enforce the SDWA which prohibits the addition of substances to water for the prevention of disease, but the EPA fails to enforce the SDWA. When the fluoride contaminant is added to water with the intent to prevent disease, then the approval from the FDA CDER is required and in the case of Washington State, the Board of Health and Board of Pharmacy have primary intrastate jurisdiction.

C. The MOU at H. The FDA is to Protect the Public from Poisons Added to Foods, Such as Poisons Added to Bottled Water.

Section H of the EPA-FDA MOU states:

> *"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."*

Either as food or drug, the **FDA** has regulatory oversight jurisdiction. Either with direct supervision or indirect supervision through the EPA, the **FDA** has ultimate regulatory oversight jurisdiction of food and drugs. The chain of command for food and

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[128] NRC 2006 page 27
[129] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1760461/
[130] Appendix 3
[131] Estimating half of fluoride exposure comes from water, about 5 glasses of 0.7 ppm fluoridated water would plus other exposure would exceed 2 mg/day, the level of EPA concern in 1963.
[132] RCW 69.04.730
133 RCW 69.41.010
134 RCW 69.04.006, RCW 69.04.001

drug regulation goes from Congress to the **FDA**. Regardless of any delegation, agreement, or assistance the FDA may use, Congress holds the **FDA** ultimately responsible for food and drugs. In effect, the EPA assists the **FDA** to ensure the public water is not adulterated by poisons to the same standards as though the FDA were doing direct supervision. If the EPA is not adequately regulating poisons or drugs being added to the water, the **FDA** must take regulatory action. The CDC and EPA need to refer manufacturers of drugs to the FDA for NDA.

D. Fluoride is Not a Food.

Foods, as with any substance, may be toxic in large amounts, but are not defined as toxic by law. Fluoride is highly toxic and a poison and Whitford (1996) considered as little as 15 mg could be lethal for a child.[135] Washington State Statute[136] defines a poison as any substance which causes violent sickness or death with less than 60 grains (3,889 mg). A determination of dosage is the jurisdiction of the FDA CDER. After a dosage is determined, current individual exposure must be determined which must include serum and urine fluoride levels. Only then can a determination be made as to whether a concentration of fluoride from an additional source, such as fluoridated public water, fluoridated bottled water, supplements and fluoride chewing gum is needed to make up anyone's deficiency.

1. The **FDA** in 1963 more succinctly stated the same concept:

> *"Above 2 milligrams per day of total intake of fluorides can cause tooth mottling in sensitive persons. It would be impossible to state a safe amount for supplementation by an individual without knowledge of the amount of fluorides already being consumed by him from such sources as drinking water and food grown in soils that are rich in fluorides."*[137]

The EPA exclusion of major sources of fluoride intake when they determined an RfD for fluoride is bogus science and a sham. Any reference dose with intent to prevent disease must be protective of all, not to the 90th percentile.

2. Foods do not require prescriptions for purchase at a pharmacy.

3. Foods are not listed as drugs in the Pharmacopiea or as poisons.

4. The absence of fluoride in the diet does not cause any disease, whereas the lack of a vitamin or essential mineral does.

5. Foods are not "forced" into competent adults.

6. Minerals and nutrients added to food are listed in food ingredients, for example, Vitamin D in milk. Fluoride is not listed in a manufacturer's ingredients,

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[135] 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." .

[136] RCW 69.38.010

[137] Appendix 3

such as canned foods and beverages made with fluoridated water.

7. Foods do not cause pathology at the same dosage which causes benefit. "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."[138]

E. Fluoride is Not a Dietary Supplement.

1. *"A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains one or more "dietary ingredients."*[139]

Neither the CDC nor EPA has demonstrated that any or all people have an inadequate intake of fluoride and need supplementation. On the contrary, even without fluoridation many show signs of excess fluoride ingestion.

2. Fluoride is not regulated as a supplement, and there is no "Supplement Facts" panel on products containing fluoride.

3. Supplements do not require prescriptions and are not exempt from poison laws.

F. The Public is at Risk because HHS and EPA Regulate Concentration of Fluoride in Public Water Rather than Dosage from Total Exposure.

Dosage from all sources should be determined rather than a relative contribution of fluoride from water. Determining RfD from a relative dose of water and 0.01 mg/kg/day from food and not including other sources of fluoride such as toothpaste, is like two doctors prescribing the same drug for the same patient at the same time. Both CDC and EPA must use total exposure and not relative exposure when determining safety and efficacy.

1. The NRC (2006 page 44) reported, *"Heller et al. (1999, 2000) estimated that a typical infant less than 1 year old who drinks fluoridated water containing fluoride at 1 mg/L would ingest approximately 0.08 mg/kg/day from water alone."*

2. The NRC (2006 page 44) reported*, "Ten percent of the infants at 3 months old exceeded an intake of 1.06 mg/day."* A 5 kg infant would exceed 0.2 mg/kg/day, far exceeding the EPA RfD of 0.08 mg/kg/day.

3. Contaminated fluoridation raw products are injected into public water to create a concentration of about 1 ppm of fluoride ion, proposed to change to 0.7 ppm and no other drug (substance to treat humans) is dispensed based on concentration in water. If everyone drank the same amount of water dispensing for everyone would still

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[138] 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

[139] www.fda.gov/AboutFDA/Transparency/Basics ucm192949.htm Accessed 11/12/10

be problematic because not everyone's kidney's work the same and not all genetics are the same.

4. The dosage of fluoride received by the patient depends on their body size and the amount of water consumed.

3. The NRC (2006) *reported "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

"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.

HHS, FDA CDER, CDC, EPA must be protective of everyone, 100%, not the 90th or 99th percentiles because fluoride is not an essential element and is an elective unapproved drug. At least the label should give patients clear concise information on dosage and side effects. When government agencies use police powers to medicate everyone with an illegal drug, then they are responsible for the dosage and risks for everyone, 100%, not to one standard deviation, but everyone. If HHS/CDC and EPA want physician responsiblity for each patient and recommend and encourage the forced administration to each person, then HHS/CDC and EPA must also encourage appropriate warnings and dosages for each and every person. Cautions could include advice for infants and those with kidney disorders, etc.

In Appendix B, Table B-4, page 376, the NRC (2006) lists water consumption at the 99th percentile with several groups close to 4-5 liters of water a day and one group at the 99th percentile is 5.356 L/day, and individuals in that group were over 5.356 L/day. What are the serum fluoride concentrations of these individuals? Are they in risk of brain, cancer, thyroid, or fluorosis damage? Have they been warned not to drink so much water? HHS/CDC EPA must answer the questions of what is not enough fluoride (if inadequacy exists), adequate, and excess fluoride concentrations for the teeth, serum urine, and other body tissues, water and total exposure.

HHS, FDA CDER, CDC and EPA must also consider the sources of fluoride exposure. The graph below (NRC 2006 p 49 Figure 2-1) shows that although water is the predominant source of fluoride for infants, other sources contribute a significant amount of fluoride, about half. HHS/CDC dropping fluoride concentration in water from 1 ppm to 0.7 ppm only reduces total exposure by about 15% which still leaves infants and sensitive subpopulations at risk of harm.

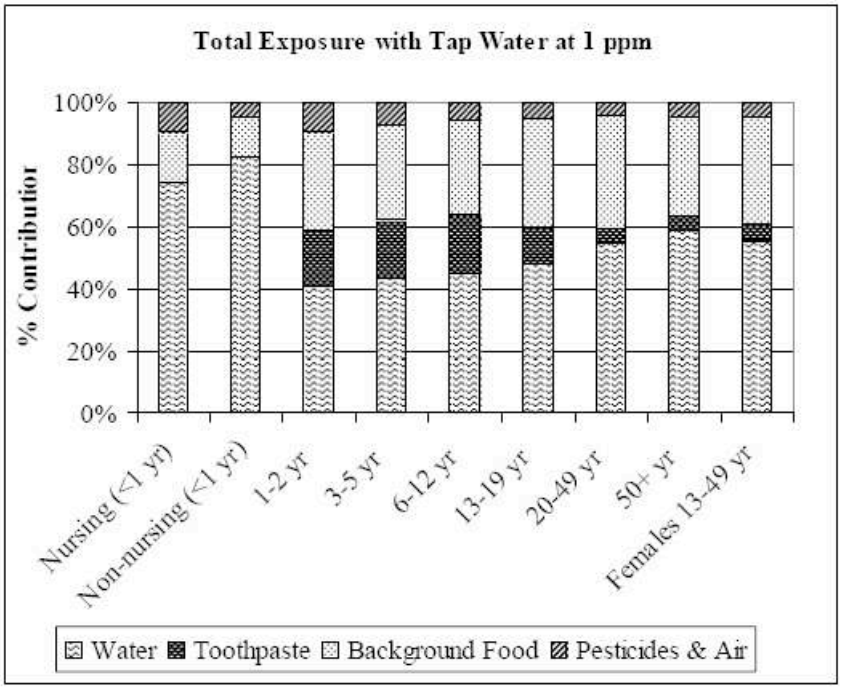

FIGURE 2-1 Source contribution to total inorganic fluoride exposure, including fluoride at 1 mg/L in tap water. The estimated chronic inorganic fluoride exposures from the various routes are presented in Tables 2-9 and 2-10. No fluoride supplement is included for any population subgroup. The total exposures as presented in Table 2-11 for the population subgroups are: 0.030 mg/kg/day (nursing infants), 0.087 mg/kg/day (non-nursing infants), 0.066 mg/kg/day (1-2 years old), 0.060 mg/kg/day (3-5 years old), 0.040 mg/kg/day (6-12 years old), 0.028 mg/kg/day (13-19 years old), and 0.031 mg/kg/day for adults (20 to 50+ years old) and women of child-bearing age (13-49 years old).

VIII. WITH GUIDANCE AND SUPPORT FROM HHS/CDC AND EPA, PUBLIC WATER SYSTEMS ARE MANUFACTURING THE MISBRANDED, ADULTERATED, ILLEGAL FLUORIDATED WATER DRUG AND FOR THE SAFETY OF THE PUBLIC HHS, EPA, AND FDA CDER ARE RESPECTFULLY ORDERED TO STOP AND TAKE IMMEDIATE REGULATORY ENFORCEMENT ACTION.

A. Fluoride: a Protected Illegal Drug.

The chemicals used to make the fluoridated water drug are generally the polluted contaminated scrubbings of the phosphate manufacturing process. Currently a shortage exists in the USA and our governments purchase the contaminated toxic waste from China and Japan and force us to drink what those countries prohibit their people from drinking. Of interest is the difficulty in dissolving the fluoride from China. Perhaps the fluoride from China contains more calcium fluoride which is less toxic and does not dissolve as well in water. If so, then the toxic fluoride waste from China may be less toxic than the toxic fluoride waste made in the USA.

The public is not permitted to know the other contaminants in the fluoride compounds being injected into their water. The National Sanitation Foundation is a private company and will not release the testing reports of the chemicals. Therefore, the EPA hides behind the NSF and the public is left in harm.

B. Most Developed Countries No Longer Fluoridate or Recommend Fluoride Supplements, in Part Because Their Drug Regulatory Agencies have Not Approved Fluoride for Ingestion for the Prevention of Dental Caries.

C. 'Contaminants' in Drinking Water are Not Desired.

Contaminants are bad, not good, which is why they are called contaminants. Contaminants, like fluoride, should not be intentionally increased.

D. Fluoridated Water Drugs Contribute to an Aggregate Excess Fluoride Exposure for Some Individuals and Subpopulations.

To understand population exposure is helpful but does not determine individual patient exposure to the fluoride drug. Some individuals absorb more fluoride than others from their mouth, stomach, intestines, lungs and skin. Some individual's kidneys are better than others at removing fluoride. To determine what a dosage is doing in a patient, the desired, normal, and current concentration of each patient's, serum, plasma, urine, hair, or bone measurements need to be used and evaluated by the FDA CDER.

What level of **serum fluoride** is "normal?" The jury is still out. Historically controls in studies have ranged up to 0.22 ppm[140] Taves reporting "normal" of 0.13 ppm[141] and 0.15 ppm by Singer.[142] These "normal" levels can be roughly compared to the 8 IQ point loss when comparing serum levels between two villages of 0.04 ppm and

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[140] Appendix 68
[141] Taves DR, Normal Serum Fluoride Concentrations, Nature 211, 192-193 (09 July 1966). Appendix 102
[142] As reported by Taves DR, Normal Serum Fluoride Concentrations, Nature 211, 192-193 (09 July 1966).

0.08 ppm by Xiang (2010) and higher bone tumors in people with 0.07 ppm. The historical "normal" is not protective. In vitro studies are finding damage down to 0.002 ppm. Perhaps mother's milk at no detectable fluoride level is optimal for infants and adults.

E. Determining Risk and Safety.

Determining the risk of a naturally occurring contaminant and a drug should be quite different. The EPA should look for "proof" available of reasonable harm of contaminants existing in water. The FDA CDER should approach the risk/safety question from the other end of the paradigm, what is the "proof" of safety.

With fluoridation, the EPA needs to put on the FDA CDER thinking cap and demand "proof" of safety from the fluoridation drug manufacturers. States rely on the EPA to assure the safety of fluoridation.[143]

[143] Appendix 11 and 12.

IX. FLUORIDE'S LACK OF BENEFIT

A. Current scientific literature is generally finding little or no effectiveness from fluoridation.[144] [145] [146] [147] [148] [149] [150] [151] [152] [153] [154] [155] [156] [157] [158] [159] [160] [161]

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[144] http://www.slweb.org/colquhoun.html and www.ada.org

[145] " Fluorosis prevalence increased significantly with higher water fluoride levels; however, caries prevalence did not decline significantly." Hong L, Levy S, Warren J, Broffit B. (2006). Dental caries and fluorosis in relation to water fluoride levels. *ADEA/AADR/CADR Conference*, Orlando Florida, March 8-11, 2006.

[146] "No fluoride, socioeconomic status or beverage variables were significantly associated with lesion progression." Warren JJ, Levy SM, Broffitt B, Kanellis MJ. (2006). Longitudinal study of non-cavitated carious lesion progression in the primary dentition. *Journal of Public Health Dentistry* 66(2):83-7.

[147] "In the present study, fluoridated water did not seem to have a positive effect on dental health, as it might have been expected in a community with the respective caries prevalence." Meyer-Lueckel H, et al. (2006). Caries and fluorosis in 6- and 9-year-old children residing in three communities in Iran. *Community Dentistry and Oral Epidemiology* 34:63-70

[148] "The WHO data do not support fluoridation as being a reason for the decline in dental decay in 12 year olds that has been occurring in recent decades." Neurath C. (2005). Tooth decay trends for 12 year olds in nonfluoridated and fluoridated countries. *Fluoride* 38:324-325

[149] "Our analysis shows no convincing effect of fluoride-intake on caries development." Komarek A, et al. (2005). A Bayesian analysis of multivariate doubly-interval-censored dental data. *Biostatistics* 6:145-55.

[150] "Levels in fluoridated and non-fluoridated areas were similar. " Harding MA, et al. (2003). Dental erosion in 5-year-old Irish school children and associated factors: a pilot study. *Community Dental Health* 20(3):165-70.

[151] "There was no statistically significant difference between DMFT in municipalities of the same size, regardless of the presence or absence of fluoride in the water supply..." Sales-Peres SH, Bastos JR. (2002). [An epidemiological profile of dental caries in 12-year-old children residing in cities with and without fluoridated water supply in the central western area of the State of Sao Paulo, Brazil]. *Cadernos de Saude Publica* 18: 1281-8

[152] Water fluoridation status of the children's area of residence did not have a significant effect on Early Childhood Caries (ECC) at the 0.1 level of significance in the unadjusted logistic regression analysis, nor was it found to be a confounder of the effect of race/ethnicity on ECC prevalence in the multivariable model." Shiboski CH, et al. (2003). The association of early childhood caries and race/ethnicity among California preschool children. *Journal of Public Health Dentistry* 63(1):38-46

[153] "[E]ven a longitudinal approach did not reveal a lower caries occurrence in the fluoridated than in the low-fluoride reference community." Seppa L. et al. (2002). Caries occurrence in a fluoridated and a nonfluoridated town in Finland: a retrospective study using longitudinal data from public dental records. *Caries Research* 36: 308-314

[154] The magnitude of [fluoridation's] effect is not large in absolute terms, is often not statistically significant and may not be of clinical significance." 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*

[155] "[R]esults of recent large-scale studies in at least three countries show that, when similar communities are compared and the traditional DMFT index of dental caries is used, there is no detectable difference in caries prevalence. This has been demonstrated for schoolchildren in the major cities of New Zealand, Australia, the US and elsewhere." Diesendorf, M. et al. (1997). New Evidence on Fluoridation. *Australian and New Zealand Journal of Public Health*. 21: 187-190

[156] Higher fluoride proportions appeared to be associated with lower dfs + DFS, with an estimated difference between fluoridated and non-fluoridated groups of 0.65 decayed or filled surfaces per child, but this association was not statistically significant. The effects of fluoridation on the other outcomes were small and not statistically significant." Domoto P, et al. (1996). The estimation of caries prevalence in small areas. *Journal of Dental Research* 75:1947-56

[157] "Children attending centers showed no significant differences (in baby bottle tooth decay) 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

[158] The fluoride incorporated developmentally – that is, systemically into the normal tooth mineral – is insufficient to have a measurable effect on acid solubility." Featherstone JDB, M.Sc., Ph.D. , Cover Story; J American Dental Association, Vol. 131, July 2000, p. 890.

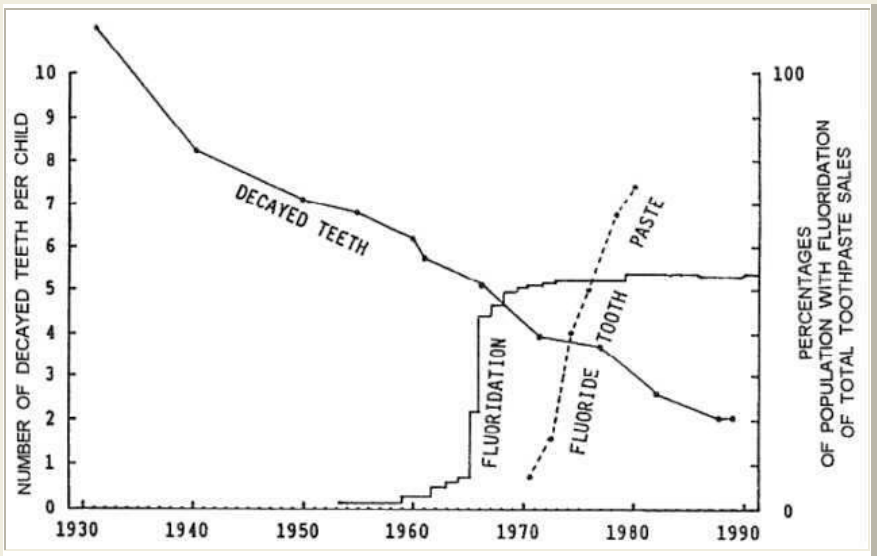
[159] Centers for Disease Control; MMWR Weekly Report. 1999;48:933-940. "Fluoride's caries-preventive properties initially were attributed to changes in enamel during tooth development because of the association between fluoride and cosmetic changes in enamel and a belief that fluoride incorporated into enamel during tooth development would result in a more acid-resistant mineral. However, laboratory 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."

[160] "It is no longer acceptable to use fluoride supplements on large populations, even if the caries rate is higher than average." Limeback H. "A re-examination of the pre-eruptive and post-eruptive mechanism of the anticaries effects of fluoride: is there any anti-caries benefit from swallowing fluoride?" Community Dentistry and Oral Epidemiology 27: 62-71, 1999.

[161] "In 1970, during a meeting in Switzerland on fluoride research, I was astounded to hear the statement from a European cariologist of great reputation that the mechanism of action of fluoride against dental caries was entirely topical! At that time I believed, along with the majority of American caries researchers, that fluoride worked because it became incorporated into enamel – especially developing enamel – to increase its resistance to acid demineralization. We thought that where this could not be accomplished preeruptively by water fluoridation, we ought to try to achieve the same goal posteruptively by short-term regimens of very highconcentration fluoride solutions and gels. I thought that my European

[162] Studies finding benefit are frequently historical and flawed for lack of controlling confounding factors and unknowns.[163] [164] [165] The NIH (National Institute of Health) and Surgeon General's report suggest efficacy estimates based on randomized controlled trials under ideal circumstances are preferred; however, no one disputes that in the case of fluoridation those types of studies would be difficult and have never been done, but they could be done. Therefore, a greater degree of caution and margin of safety must be used to protect public health and a reasonable margin of safety, 10, is essential.

Graph H[166] is one of the two most important graphs on efficacy the CDC should fully and carefully consider.



http://www.fluoride-journal.com/98-31-2/312103-f.htm
1997 ISFR Published 1998 Graph H

Graph H provides a six decades "perspective" of decredasing dental caries. Caries have decreased consistently regardless of fluoridation of public water or

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colleague was very poorly informed.
Now, twelve years later, I continue to be impressed by the wisdom of his assertion. Probably it was not completely correct; absolute statements about biological processes rarely are. However, each year since then the evidence has continued to accumulate to support the hypothesis that the anti-caries mechanism of fluoride is mainly a topical one."
12. Fejerskov O. et al. "Rational use of fluorides in caries prevention". Acta

[162] "As a direct consequence any method which places particular emphasis on incorporation of bound fluoride into dental enamel during formation may be of limited value. Therefore, there is limited scientific data to support the assertion that systemic fluoride treatment should be initiated from shortly after birth." Fejerskov O. et al. "Rational use of fluorides in caries prevention". Acta Odontol. Scand. 1981, 39:241-249.

[163] Confounding factors such as delay in tooth eruption are not included in studies. See Komarek A, et al. Biostatistics. 2005 Jan;6

[164] McDonagh, M., P. et al 2000a. A Systematic Review of Public Water Fluoridation. NHS Centre for Reviews and Dissemination, U. of NY

[165] Leroy R, et al. (2003). The effect of fluorides and caries in primary teeth on permanent tooth emergence. Community Dentistry and Oral Epidemiology31(6):463-70

[166] Appendix 23 Colquhoun J, WHY I CHANGED MY MIND ABOUT WATER FLUORIDATION Full Article (Permission at Appendix 24) http://www.fluoride-journal.com/98-31-2/312103.htm

fluoridated toothpaste. Dental caries declined by more than half before fluoridation became common. One or more unknown confounding factor(s), we shall call the "Major Unknown" wiped out more than half of dental caries from 1930 to 1970 when the a significant number of 5 year olds who had been fluoridated all their lives should have started to show significant caries reduction.

The "Major Unknown" appears to have rolled on until 2000 when dental cavities were reported at about 1.2 per 12 year old child. (Graphs "A" and "B" below)

Until dental caries research identifies and controls for the "Major Unknown," caries research efficacy is suspect. And it would be unwise to assume all communities, families and individuals were reducing dental caries at the same rate at the same time. Assuming cause-effect when measuring a moving variable, declining dental caries, with one or more extremely strong unknowns, is problematic and uncertain if not hopeless.

The chance the "Major Unknown" abruptly stopped decreasing dental caries at the same time fluoridation started, is a leap of faith, but not impossible. Overlay this USA data in Graph H, with Graph A and B showing nonfluoridated and fluoridated countries with the same dental caries endpoint of prevalence, removes the possibility fluoridation caused the significant reduction in dental caries in developed countries. Fluoridation did not reduce dental caries before fluoridation started, nor did fluoridation reduce caries in non-fluoridated countries the same as fluoridated countries. Fluoridation's benefit, if any, is not detected in the public at large.

B. Comparing Nations Does Not Find Benefit from Fluoridation. Current Effectiveness Studies Concur, Little or No Detectable Benefit from Fluoridation. [167] [168] [169] [170] [171] [172] [173] [174] [175] [176] [177]

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[167] "The aim of this paper is to review publications discussing the declining prevalence of dental caries in the industrialized countries during the past decades...[T]here is a general agreement that a marked reduction in caries prevalence has occurred among children in most of the developed countries in recent decades."
SOURCE: Petersson GH, Bratthall D. (1996). The caries decline: a review of reviews. *European Journal of Oral Science* 104: 436-43"

[168] "The regular use of fluoridated toothpastes has been ascribed a major role in the observed decline in caries prevalence in industrialized countries during the last 20 to 25 years, but only indirect evidence supports this claim." Haugejorden O. (1996). Using the DMF gender difference to assess the "major" role of fluoride toothpastes in the caries decline in industrialized countries: a meta-analysis. *Community Dentistry and Oral Epidemiology* 24: 369-75

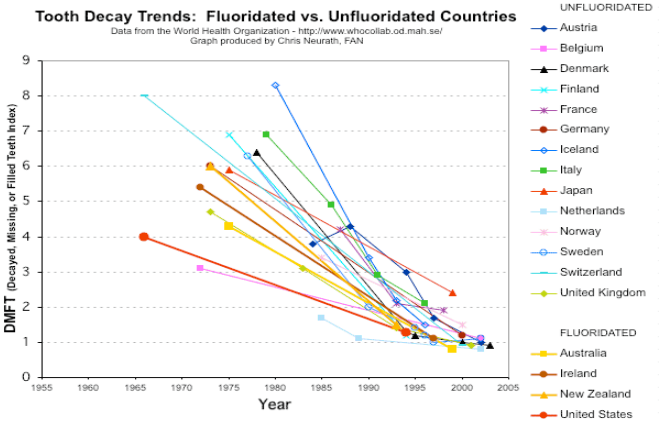
[169] "The marked caries reduction in many countries over the last two decades is thought to be mainly the result of the widespread and frequent use of fluoride-containing toothpaste... There seem to be no other factors which can explain the decline in dental caries, which has occurred worldwide during the same period, in geographic regions as far apart as the Scandinavian countries and Australia/New Zealand." Rolla G, Ekstrand J. (1996). *Fluoride in Oral Fluids and Dental Plaque*. In: Fejerskov O, Ekstrand J, Burt B, Eds. Fluoride in Dentistry, 2nd Edition. Munksgaard, Denmark. p 215

[170] "Although difficult to prove, it is reasonable to assume that a good part of the decline in dental caries over recent years in most industrialized countries, notably those Northern European countries without water fluoridation, can be explained by the widespread use of fluoride toothpastes. This reduction in caries has not been paralleled by a reduction in sugar intake..." Clarkson BH, Fejerskov O, Ekstrand J, Burt BA. (1996). *Rational Use of Fluoride in Caries Control*. In: Fejerskov O, Ekstrand J, Burt B, Eds. Fluoride in Dentistry, 2nd Edition. Munksgaard, Denmark. p 354

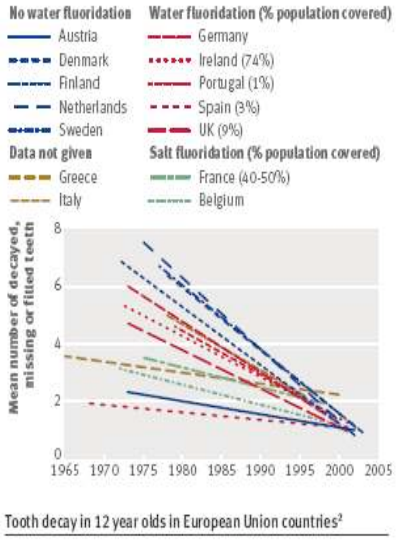
[171] "During the past 40 years dental caries h as been declining in the US, as well as in most other developed nations of the world... The decline in dental caries has occurred both in fluoride and in fluoride-deficient communities, lending further credence to the notion that modes other than water fluoridation, especially dentrifices, have made a major contribution." Leverett DH. (1991). Appropriate uses of systemic fluoride: considerations for the '90s. *Journal of Public Health Dentistry* 51: 42-7

[172] "In most European countries, the 12-year-old DMFT index is now relatively low as compared with figures from 1970-1974. WHO (World Health Organization) data relating to availability of fluoride in water and toothpaste appear reliable. However, these data did not explain differences between countries with respect to the DMFT index of 12-year-olds." Kalsbeek H, Verrips GH. (1990). Dental caries prevalence and the use of fluorides in different European countries. *Journal of Dental Research* 69(Spec Iss): 728-32

Graph A published in Fluoride and graph B[178] published in the BMJ, show a consistent decline in decay over several decades. Regardless of whether the country has natural or artificially fluoridated water, fluoridated salt or no fluoridated products at all, decay rates are similar. Clearly, other factors (such as socioeconomics) are more relevant than the fluoride concentration in water. Proponents of fluoridation suggest non-fluoridated communities benefit in a "halo" effect" from fluoridated communities; however, it is unreasonable to suggest non-fluoridated Europe benefits from fluoridated USA public water.



Graph A Neurath Graph[179]



Graph B Cheng Graph[180]

From 1930 to 1970, dental caries went form about 11 DMFT to about 5 DMFT. (Graph H two pages earlier). From 1970 to 2000 the trend continued in the USA and in

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[173] "The most striking feature of some industrialized countries is a dramatic reduction of the prevalence of dental caries among school-aged children." Binus W, Lowinger K, Walther G. (1989). [Caries decline and changing pattern of dental therapy] [Article in German] *Stomatol DDR* 39: 322-6

[174] "The current reported decline in caries tooth decay in the US and other Western industrialized countries has been observed in both fluoridated and nonfluoridated communities, with percentage reductions in each community apparently about the same." Heifetz SB, et al. (1988). Prevalence of dental caries and dental fluorosis in areas with optimal and above-optimal water-fluoride concentrations: a 5-year follow-up survey. *Journal of the American Dental Association* 116: 490-5"

[175] "(D)uring the period 1979-81, especially in western Europe where there is little fluoridation, a number of dental examinations were made and compared with surveys carried out a decade or so before. It soon became clear that large reductions in caries had been occurring in unfluoridated areas. The magnitudes of these reductions are generally comparable with those observed in fluoridated areas over similar periods of time." Diesendorf, D. (1986). The Mystery of Declining Tooth Decay. *Nature* 322: 125-129

[176] "Even the most cursory review of the dental literature since 1978 reveals a wealth of data documenting a secular, or long term, generalized decline in dental caries throughout the Western, industrialized world. Reports indicate that this decline has occurred in both fluoridated and fluoride-deficient areas, and in the presence and absence of organized preventive programs." Bohannan HM, et al. (1985). Effect of secular decline on the evaluation of preventive dentistry demonstrations. *Journal of Public Health Dentistry* 45: 83-89

[177] "The decline in caries prevalence in communities without fluoridated water in various countries is well documented. The cause or causes are, at this time, a matter of speculation." Leverett DH. (1982). Fluorides and the changing prevalence of dental caries. *Science* 217: 26-30

[178] "Graphs of tooth decay trends for 12 year olds in 24 countries, prepared using the most recent World Health Organization data, show that the decline in dental decay in recent decades has been comparable in 16 non-fluoridated countries and 8 fluoridated countries which met the inclusion criteria of having (i) a mean annual per capita income in the year 2000 of US$10,000 or more, (ii) a population in the year 2000 of greater than 3 million, and (iii) suitable WHO caries data available. *The WHO data do not support fluoridation as being a reason for the decline in dental decay in 12 year olds that has been occurring in recent decades."* Neurath 2005. [178] (Graph A)[178] British Medical Journal published a similar graph and report in 2007. (Graph B)[178]

[179] http://www.fluoridealert.org/health/teeth/caries/who-dmft.html Appendix 94 & Cheng 98

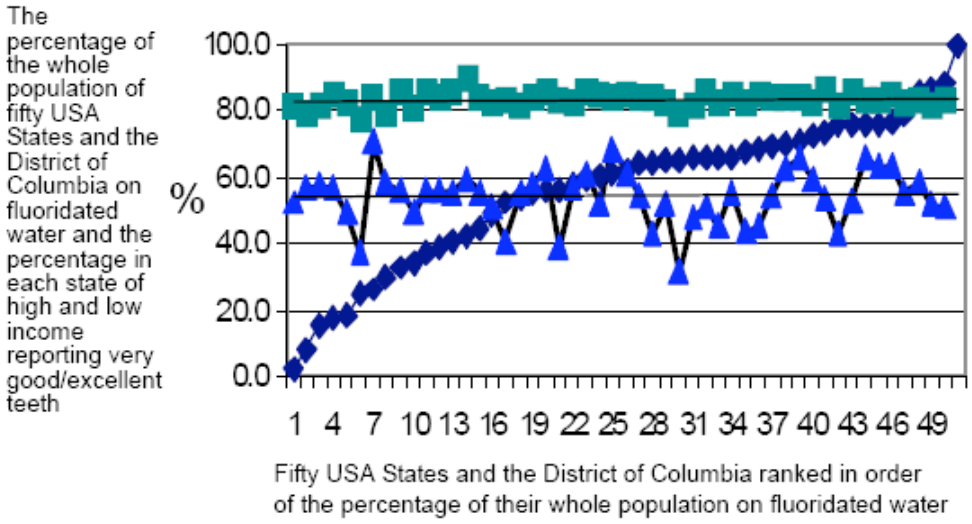
[180] Chen et al, BMJ 5 October 2007 Appendix 98

both fluoridated and nonfluoridated developed countries, further dropping dental caries from about 5 in fluoridated communities and about 6 or 7 in non-fluoridated communities to just over 1 DMFT. The caries decline in non-fluoridated communities was actually greater over the last 30 years. Fluoridation made no apparent difference in the decline of dental caries over 70 years, unless one argues that fluoridated countries had less of a decline in dental caries.

After 40 years of significant fluoridation in the USA, we should be able to detect the effectiveness of fluoridation in the public at large. Suggestions that the ubiquitous halo effect benefits neighboring communities[181] and countries is without substance.

C. Comparing 50 USA States[182] Does Not Find Benefit From Fluoridation.

Ranking 50 US states based on the percentage of residents receiving fluoridation (Graph C below) and plotting the low income segment of the population reporting very good/excellent teeth (lower blue line Graph C) and the high income segment reporting very good to excellent teeth (upper horizontal green line Graph C), finds about 53% of the poor and 82% of the wealthy have very good to excellent teeth regardless of fluoridation. A state could fluoridate 0% or 100% of their population without significant change to decay for either rich or poor.[183] [184] [185] [186]



Graph C

Over time, dental caries has dropped regless of fluoridation of public water.

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[181] http://www.cdc.gov/fluoridation/benefits.htm The Halo Effect: Quantifying the diffused benefit from water fluoridation in the United States Griffin SO, Gooch BF, Lockwood SA, Tomar SL. *Community Dent Oral Epidemiol* 2001;29:120–129.

[182] Appendix 30 Osmunson http://www.fluorideresearch.org/404/files/FJ2007_v40_n4_p214-221.pdf

[183] National Survey of Children's Health. http://mchb.hrsa.gov/oralhealth/portrait/1cct.htm.

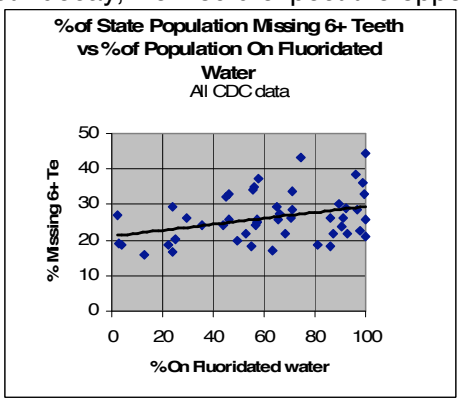
[184] http://www.cdc.gov/oralhealth/waterfluoridation/fact_sheets/states_stats2002.htm

[185] The National Survey of Children's Health 2003. Rockville, Maryland: U.S. Department of Health and Human Services, 2005

[186] U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau

Ranking states on the increasing percentage of population fluoridated finds an increasing trend in the percentage of individuals with six or more teeth missing.

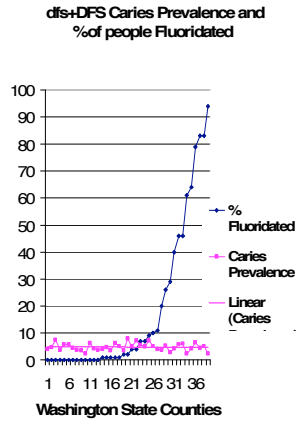
Graph D, below, comparing states shows an increase in loss of six or more teeth with a higher percentage of the population on fluoridated water.[187] If fluoridation significantly reduced tooth decay, we would expect the opposite to occur.



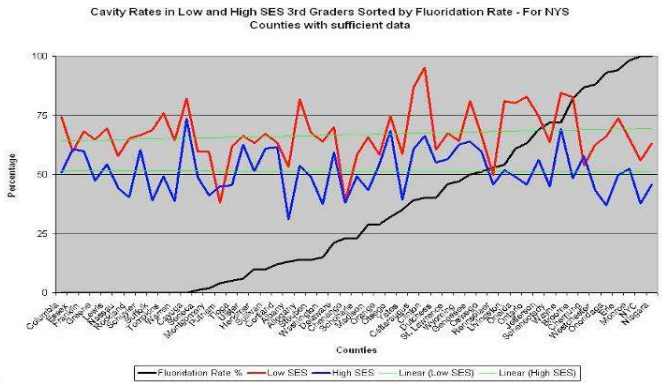
Graph D

D. Comparing Counties in Washington State or New York State Does Not Find Benefit From Fluoridation.

Lourox in 1996[188] reported data on counties in Washington State (Graph E –by Osmunson, uses Lourox data). With 46% of public water users fluoridated, no significant reduction in dental decay could be detected in the fluoridated areas. In spite of the lack of fluoridation's benefit, the Department of Health and other Public Health officials aggressively promoted fluoridation. As of 2008, 59% of public water users in Washington State are fluoridated.



Graph E



Graph F, New York Counties & Fluoridation

[187] "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

[188] Leroux, et al Univ. WA, J Dent Res 1996

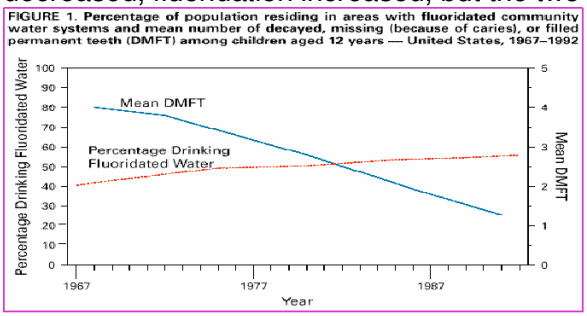
Comparing counties in New York State (Graph F) finds no detectable benefit from fluoridation (blue line is low socioeconomic residents, the red line is high, and the black line is the percentage of people in each county on fluoridated water).

Current epidemiological effectiveness comparisons[189] [190] [191] between Washington State with 59% of the population receiving fluoridated water and Oregon's 19%[192] find Oregon having similar or better dental health with a third the percentage of population fluoridated (confounding factors similar or in Washington's favor).[193] [194]

E. Cavities have been Reduced Regardless of Fluoridation.

Part of the support for the alleged effectiveness from fluoridation is the Graph G below.[195] An increase in the percentage fluoridated as well as a drop in DMFT (Decayed, Missing, Filled Teeth) during the same time is not disputed; however, the two events are not related as fluoride promoters have claimed.

It is statistically improbable - if not impossible - for a random 17% increase of population to be treated with fluoride, causing a 70% drop in caries incidence for the entire population. To achieve those stunning results, fluoridation projects would have had to target specific high-risk individuals rather than random communities. Decay rates decreased, fluoridation increased, but the two events are not related.



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.

Graph G

HHS[196] suggests dental decay has decreased in the USA and we agree. However, HHS/CDC provides low quality, biased and poor research suggesting community fluoridation is responsible for the decline in caries. Just because the two events have happened, does not mean they are related. Many factors such as socioeconomics, vitamin supplements, year around fresh produce, tooth brushing, flossing, antibiotics and unknowns increased or are confounding along with fluoridation.

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[189] http://www.doh.wa.gov/cfh/Oral_Health/Documents/SmileSurvey2005FullReport.pdf
[190] http://www.oregon.gov/DHS/ph/oralhealth/docs/databook.pdf#search='Oregon%20Decay%20experience'
[191] BRFSS 2002 http://www.dhs.state.or.us/dhs/ph/chs/brfs/02/orahea/dentvisi.shtml
http://apps.nccd.cdc.gov/brfss/display.asp?state=WA&cat=OH&yr=2004&qkey=6610&grp=0&SUBMIT4=Go Sample size OR 3509 and WA 12,926 2004 data
[192] http://www.cdc.gov/oralhealth/waterfluoridation/fact_sheets/states_stats2002.htm
[193] National Survey of Children's Health. http://mchb.hrsa.gov/oralhealth/portrait/1cct.htm
U.S. Department of Health and Human Services, http://www.fluoridationcenter.org/papers/2002/cdcmmwr022102.htm
[194] http://quickfacts.census.gov/qfd/states/41000.html
[195] CDC MMWR, October 22, 1999
[196] http://www.hhs.gov/news/press/2011pres/01/pre_pub_frn_fluoride.html

Only the FDA CDER and perhaps the NAS have the competent procedures and experts to make a determination of efficacy of fluoride use with the intent to prevent disease. HHS/CDC is outside Congressional authority to promote an unapproved drug.

F. Research Finding Little or No Benefit from Fluoridation.

1. *"It is remarkable... that the dramatic decline in dental caries which we have witnessed in many different parts of the world has occurred without the dental profession being fully able to explain the relative role of fluoride in this intriguing process."*[197]

2. *"A very marked decline in caries prevalence [in Europe] was seen in children and adolescents...The number of edentulous adults in Europe has also been declining considerably."*[198] 99% of Europe is fluoridation free and limited use of fluoride salts.

3. *"The caries attack rate in industrialized countries, including the United States and Canada, has decreased dramatically over the past 40 years."* (regardless of fluoridation).[199]

4. *"Since the 1960s and 70s, however, a continuous reduction (in tooth decay) has taken place in most 'westernized' countries, it is no longer unusual to be caries-free. . . It is difficult to get a full picture of what has happened, as the background is so complex and because so many factors may have been involved both directly and indirectly. In fact, no single experimental study has addressed the issue of the relative impact of all possible factors, and it is unlikely that such a study can ever be performed."*[200]

5. *"Caries prevalence data from recent studies in all European countries showed a general trend towards a further decline for children and adolescents. . . The available data on the use of toothbrushes, fluorides and other pertinent items provided few clues as to the causes of the decline in caries prevalence."*[201]

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[197] Aoba T, Fejerskov O. (2002). Dental fluorosis: chemistry and biology. *Critical Review of Oral Biology and Medicine* 13: 155-70

[198] Reich E. (2001). Trends in caries and periodontal health epidemiology in Europe. *International Dentistry Journal* 51(6 Suppl 1):392-8

[199] Fomon SJ, Ekstrand J, Ziegler EE. (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"

[200] "Since the 1960s and 70s, however, a continuous reduction (in tooth decay) has taken place in most 'westernized' countries, it is no longer unusual to be caries-free... During the decades of caries decline, a number of actions have been taken to control the disease, and the literature describes numerous studies where one or several factors have been evaluated for their impact. Still, it is difficult to get a full picture of what has happened, as the background is so complex and because so many factors may have been involved both directly and indirectly. In fact, no single experimental study has addressed the issue of the relative impact of all possible factors, and it is unlikely that such a study can ever be performed." Bratthall D, Hansel-Petersson G, Sundberg H. (1996). Reasons for the caries decline: what do the experts believe?" *European Journal of Oral Science* 104:416-22

[201] "Caries prevalence data from recent studies in all European countries showed a general trend towards a further decline for children and adolescents...The available data on the use of toothbrushes, fluorides and other pertinent items provided few clues as to the causes of the decline in caries prevalence." Marthaler TM, O'Mullane DM, Vrbic V. (1996). The prevalence of dental caries in Europe 1990-1995. ORCA Saturday afternoon symposium 1995. *Caries Research* 30: 237-55

G. Experts Disagree on Factors for Dental Caries Reduction and Find Fluoridation Unnecessary.

The Centers for Disease Control promotes substances, with education, "markets", advises, recommends, collects data, but does not determine the safety, efficacy, toxicology, exposure, dosage, or ethics of substances. The CDC promotes fluoride as a "major factor in the overall decline in recent decades in the prevalence and severity of dental caries in the United States and other economically developed countries."[202] For this alleged multinational effectiveness, the CDC repeatedly uses historical references. A repeated CDC reference is the "anecdotal" historical report of Bratthall et al. 1996, which questioned a group of experts for their opinion *on "Reasons for the caries decline: what do the experts believe?" "A main finding of our study was that there was a very large variation in how the experts graded the impact of various possible factors. In fact, only in the evaluation of "fluoride toothpaste" was there a clear, positive agreement among experts."*[203]

The CDC's claim that fluoridation is one of the ten greatest public health achievements of the 20th Century is not supported by the CDC's own listed reference. In fact, a review of original studies in 2007 by Pizzo found fluoridation in industrialized communities unnecessary.[204] The Washington Department of Health and Board of Health do not determine the safety of fluoridation and erroneously rely on the CDC and EPA to determine the safety and efficacy of fluoridation.[205]

H. IAOMT Reports No Discernible Health Benefit with Fluoridation.

The International Academy of Oral Medicine and Toxicology reports "no discernible health benefit with fluoridation."[206] Many good scientists are opposed to fluoridation.[207] The Environmental Protection Agency scientists through their union have

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[202] http://www2.nidcr.nih.gov/sgr/sgrohweb/chap7.htm

[203] The CDC also references Horowitz and Ismail 1996, Johnston 1994, Ripa 1990, Stookey and Beiswanger 1995, however all these reviewed topical application of fluoride, not the addition of fluoride to water. http://www2.nidcr.nih.gov/sgr/sgrohweb/chap7.htm

[204] Pizzo G, et al, Community water fluoridation and caries prevention: a critical review. Clin Oral Investig. 2007 Feb 27.

[205] Appendix 11 and 12

[206] www.IAOMT.org; Kentucky fluoridated for over 50 years has the highest tooth loss of any state. 2002 CDC MMWR; www.fortwayne.com/mld/newssentinel/7521679.htm?template=contentModules/printstory.jsp http://www.enquirer.com/editions/2002/10/06/loc_special_report.html; http://www.fluoridealert.org/f-boston.htm http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=13678102&query_hl=1 http://www.nhregister.com/site/news.cfm?newsid=14472801&BRD=1281&PAG=461&dept_id=517515&rfi=8&xb=kasan

[207] Over 3,500 professionals have signed their name in opposition to fluoridation. A few scientists opposed to fluoridation include: Kenji Akiniwa, DDS; Phillip Allen, MD, Harvard Medical School, '54; Vinod Barot, PhD; James Beck, MD,; W. Dexter Bellamy, PhD; Miklos Bely, PhD; Shlomi Ben-Arush; Larry Bowden DMD; Laurie Brett, DDS; John Brawner, MD; Chris Bryson (author "The Fluoride Deception"); Albert Burgstahler, PhD, Editor, Fluoride, co-author, "Fluoridation: The Great Dilemma" ; Adolf Butenandt (Nobel Laureate for Chemistry, 1939); Gladys Caldwell (deceased) (co-author of "Fluoridation and Truth Decay"); Noel Campbell; Arid Carlsson, PhD (Nobel Laureate in Medicine, 2000); Robert Carton, PhD, former risk assessment specialist at the US EPA; N. J. Chinoy, (deceased) (past Vice-President of the International Society for Fluoride Research); John Colquhoun, PhD (deceased); Michael Connett FAN; Paul Connett, PhD, Executive Director of the Fluoride Action Network; Ronnie Cummins, Executive Director of Organic Consumers Association; Stephen A. Dean; Lynn H. Ehrle; Nick Dienel, MD; Mark Diesendorf, PhD; Mike Dolan, PhD; Sam Epstein, MD (author of the "Politics of Cancer"); Hans von Euler-Chelpin (Nobel Laureate for Chemistry, 1929); Dr Doug. N. Everingham, Former Federal Health Minister, Australia; Fred B. Exner, MD (deceased) (co-author "The American Fluoridation Experiment"); Rich Fischer, DDS, Past President of the International Academy of Oral Medicine and Toxicology; Richard G. Foulkes, MD (former advisor of the Ministry of Health, British Columbia); Mike Godfrey, MD; Dorothy Goldin-Rosenberg, PhD; Edward Goldsmith, (former editor and publisher of The Ecologist); Anne-Lise Gotzsche (author "The Fluoride Question: Panacea or Poison?"); Barry Groves, PhD; Ella Haley, PhD; Joseph Hensley, MD (State senator from Tennessee); Walter Rudolf Hess (Nobel Laureate for Medicine, 1949); W. Robert Hetrick, PhD; Corneille Jean-François Heymans (Nobel Laureate for Medicine, 1938); Sir Cyril Norman Hinshelwood (Nobel Laureate for Chemistry, 1956); William Hirzy, PhD (Vice-President of the Union representing professionals at EPA Washington, DC, HQ.; C. Vyvyan Howard; Bob Isaacson, PhD; Antone G. Jacobson, PhD; Jackie Jacobson, PhD; Tushar Kant Joshi; Emily A. Kane, DNM, AK, author "Managing Menopause Naturally"; Jong-Chul Kim, Editor, Green Review, South Korea; Stephen M. Koral, DMD; David Kennedy, DDS, Past President IAOMT; Lennart Krook, PhD; Linda Langness, PhD; Todd Lawson DMD; Evie Lawson DO; John R. Lee, MD; Joshua Lederberg (Nobel Laureate for Medicine, 1958); Hardy Limeback, DDS, PhD; Lewis McKinley, PhD (co-author: "Fluoridation: the Great Dilemma."; Peter Mansfield, MD; William Marcus, PhD; Joseph Mercola, MD; Henry Micklem, PhD;

said fluoridation no longer reduces tooth decay, if it ever did.

I. Cessation of fluoridation has not been shown to usually result in an increase in dental decay.[208] (See also Appendix 71)

The CDC claims, *"When fluoridation is withdrawn and there are few other fluoride exposures, the prevalence of caries increases"* however, the CDC's own references do not accurately support the CDC's unqualified statement. For example, the CDC reference states: *"In spite of discontinued water fluoridation, no indication of an increasing trend of caries could be found in Kuopio"*.[209]

J. Potential Benefit of Ingesting Fluoride Through Age 8.

In some places the CDC, IOM (Institute of Medicine), and NRC (National Research Council) suggest potential benefits from fluoridation would be during the development of the tooth up to eight years of age. The level of fluoride in saliva is so minor as to have minimal effect on oral bacteria. Researchers report the potential cariostatic benefit from fluoride is "topical and not systemic."[210] When carefully evaluated, the CDC comments are clearly conflicting and not in agreement with current published studies. Proponents suggest *"studies prove water fluoridation continues to be effective in reducing tooth decay by 20-40%"* [211] when in fact biostatisticians find the same studies show no significant benefit.[212]

Peter Montague, PhD, editor of Rachel's Environmental biweekly; Raul A. Montenegro, PhD; Deborah E. Moore, PhD; Jeffrey Morris, PhD; Phyllis Mullenix, PhD; William P. Murphy (deceased) (Nobel Laureate for Medicine, 1934); Tohru Murakami, DDS; Ralph Nader; Giulio Natta (Nobel Laureate for Chemistry, 1963); Pierce Noble; Bill Osmunson, DDS, MPH; Geoff Pain, PhD; Gilles Parent (co-author); Richard J. Perry, PhD; James Presley, PhD; Alan Price, PhD; Sir Robert Robinson (deceased) (Nobel Laureate for Chemistry, 1947); Perry Roehl, PhD; Paul Ruben, DDS,; Andrew Rynne, MD; Mageswari Sangaralingam ; Albert Schatz (deceased) PhD (co-discoverer of streptomycin); Nikolai Semenov (deceased) (Nobel Laureate for Chemistry, 1956); Richard Shames, MD, author "Feeling Fat, Fuzzy or Frazzled?"; John Shonerd, DO; Bruce Spittle; Caroline Snyder, PhD; Anna Strunecka; James B. Sumner PhD (deceased) (Nobel Laureate for Chemistry, 1946); A.K. Susheela, PhD; James Sumner PhD (deceased) (Nobel Laureate in Chemistry...); Philip Sutton, DDS (deceased) (author of "The Greatest Fraud: Fluoridation); Hugo Theorell (deceased)(Nobel Laureate for Medicine, 1955); Kathleen Thiessen, PhD; Artturi Virtanen (deceased) (Nobel Laureate for Chemistry, 1945); George Waldbott, MD (author "A Struggle with Titans;" co-author "The American Fluoridation Experiment," and co-author, "Fluoridation: The Great Dilemma"); Glen Walker, (author, "Fluoridation: Poison on Tap"); Alan Watson; Susan Willis, PhD; Mae W. Woo, DDS; John Yiamouyiannis, PhD (deceased) (author of The Aging Factor); Philip E. Zanfagna, MD (deceased) (co-author of "Fluoridation and Truth Decay"); Rudolf Ziegelbecker; Dr.techn. Rudolf Ziegelbecker, jun.; Sam Ziff, Loty Zilberman,

[208] Appendix 92 Komarek et al, A Bayesian analysis of multivariate doubly-interval-censored dental data, Biostat. 2005 6 pp 145-155; Armfield & Spencer, 2004 Community Dental Oral Epidemiology; See www.slweb.org
Kunzel W, Fischer T. (2000). Caries prevalence after cessation of water fluoridation in La Salud, Cuba. Caries Research 34: 20-5.
Kunzel W, Fischer T, Lorenz R, Bruhmann S. (2000). Decline of caries prevalence after the cessation of water fluoridation in the former East Germany. Community Dentistry and Oral Epidemiology 28: 382-9. Seppa L, Karkkainen S, Hausen H. (2000). Caries Trends 1992-1998 in Two Low-Fluoride Finnish Towns Formerly with and without Fluoridation. Caries Research 34: 462-468.
Burt BA, et al. (2000). The effects of a break in water fluoridation on the development of dental caries and fluorosis. J Dent Res.79(2):7619.
Maupome G, Clark DC, Levy SM, Berkowitz J. (2001). Patterns of dental caries following the cessation of water fluoridation. Community Dentistry and Oral Epidemiology 29: 37-47.
Shiboski CH, et al. (2003). The association of early childhood caries and race/ethnicity among California preschool children. Journal of Public Health Dentistry 63(1):38-46.

[209] Kugel (sp) and Fischer 1997, Seppä et al. 1998 "In spite of discontinued water fluoridation, no indication of an increasing trend of caries could be found in Kuopio. The mean numbers of fluoride varnish and sealant applications decreased sharply in both towns between 1992 and 1995. In spite of that caries declined. CONCLUSIONS: These findings suggest that the decline of caries has little to do with professional preventive measures performed in dental clinics." and Stephen et al.

[210] Pizzo G, et al, Community water fluoridation and caries prevention: a critical review. Clin Oral Investig. 2007 Feb 27.

[211] http://www.ada.org/prof/resources/positions/statements/fluoride_community_effective.asp 7/13/06

[212] Komarek, Biostatistics. 2005; NRC 2006; Spencer et al 1996; de Liefde 1998

K. Measured Cost for Dental Treatment is Not Lower in Fluoridated Communities.

Research used by the CDC of dental cost savings with fluoridation are based on estimates of assumptions rather than measured costs. Assuming a reduction in dental decay and no adverse effects, the estimated cost savings of fluoridation is estimated between $19-$38 for every dollar spent on fluoridation.

Measured cost of dental treatment is not lower in fluoridated communities.[213] Certainly if fluoridation were to reduce dental decay by 15-40% without adverse effects as some claim, the cost for dental treatment should be lower. One published study by Maupome[214] has compared costs for dental treatment comparing fluoridated and non-fluoridated communities. Moupome reported about a half percent cost reduction in dental treatment in fluoridated communities, enough to cover fluoridation equipment repairs but not chemicals or instulation of equipment. Comparing the two largest communities, children had higher dental costs in the fluoridated community.

Another study of measured costs only used low socioeconomic patients and failed to correct or control for completed versus uncompleted treatment, utilization, or adverse elective proceedures.

If fluoridation reduced dental costs, the evidence over 50 years should have repeatedly been published but is lacking.

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[213] Maupome JPHD, 2007. Data collected in 1995

[214] Maupome JPHD 2007 Another study recently published reported huge medicare savings in the fluoridated communities. However, the author did not permit us review of the public data and confounding factors such as completion of treatment, cosmetic repair for dental fluorosis, costs for fractured teeth and other confounding factors were not reported or included in a poverty treatment program.

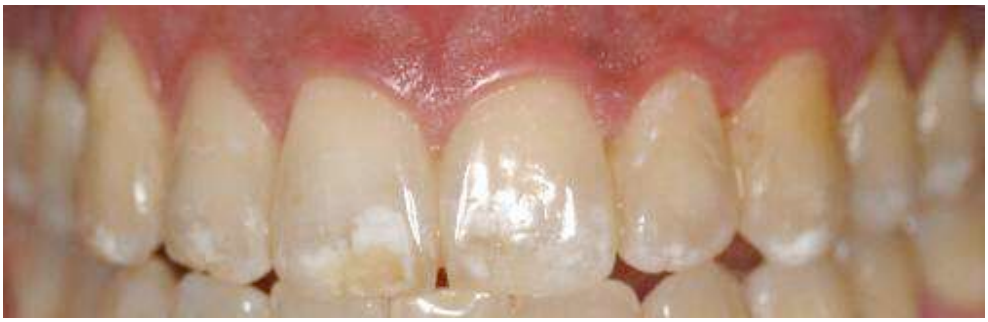
X. EVIDENCE OF FLUORIDE HARM AT LOW LEVELS

> The EPA defines *Functional developmental toxicology definition. . . Structural abnormalities . . . Malformations and variations – A malformation is usually defined as a permanent structural change that may adversely affect survival, development, or function. The term teratogenicity is used in these Guidelines to refer only to malformations. The term variation is used to indicate a divergence beyond the usual range of structural constitution that may not adversely affect survival or health."*[215]

We use the term "teratogenicity" and "variation" in keeping with the EPA definition. Although dental fluorosis would not be considered causing death, there should not be dispute that structural abnormality and altered growth are always evident (altered growth is the intent of ingesting fluoride), and only in severe dental fluorosis would functional deficit become evident.

A. HARM TO TEETH: American Academy of Pediatrics recommends NO prescription fluoride before age 6 months and not more than one cup of fluoridated water (0.25mg) 6 months to 3 years of age. Pediatrics May 1998 Vol. 95, Number 5 RE9511

1. Dental fluorosis is a biomarker, a sign that patient ingested too much fluoride when that part of the tooth enamel was developing under the gums. Depending on the amount of excess fluoride, the tooth can appear with white or brown spots, areas, lines, or streaks and the efficat can be either a variation or teratogenicity. The treated fluorosis cases below do not show pitting but were an adverse effect to health significant enough for the patient to demand significant costly treatment.



Some patients consider the damage to be significant enough to seek treatment. Treatment costs are between $1,000 and $3,000 per tooth. Frequently 10 to 20 teeth are treated and the average life span of a veneer is 15 years. Lifetime costs can be expected to be up to $100,000. Compensation for this damage, both treated and untreated, should be considered.

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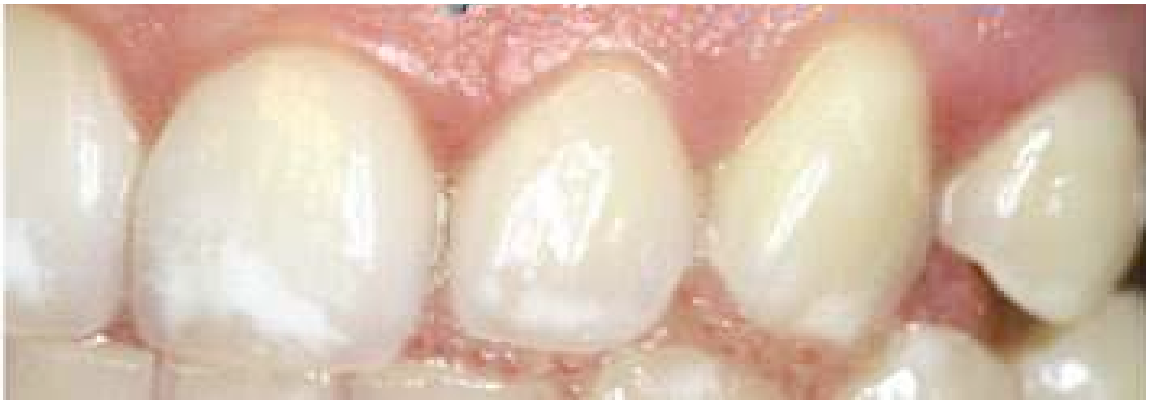
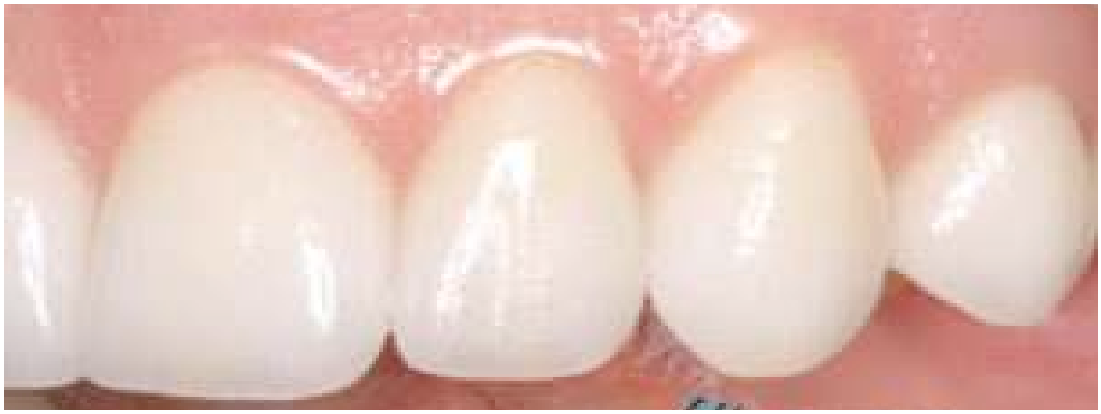
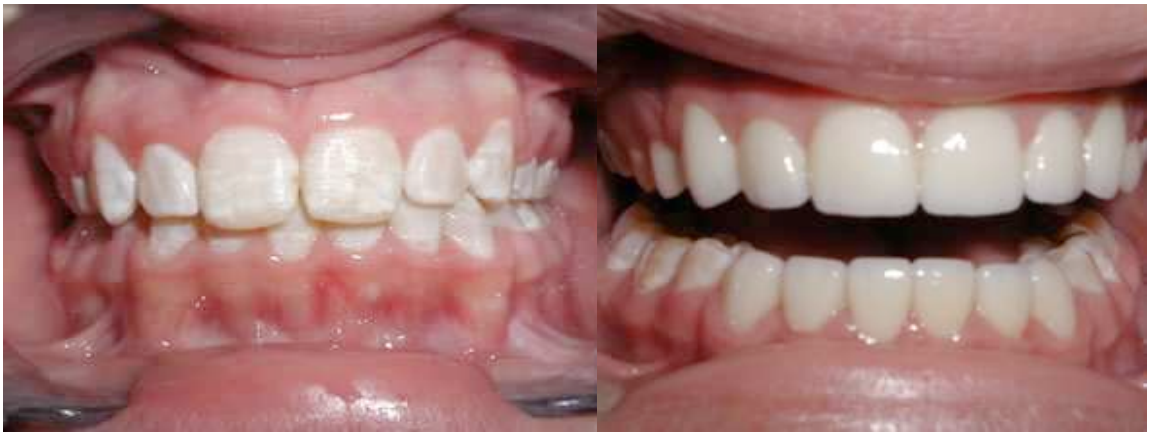
[215] http://www.epa.gov/raf/publications/pdfs/DEVTOX.PDF p 3 Accessed 4/16/11

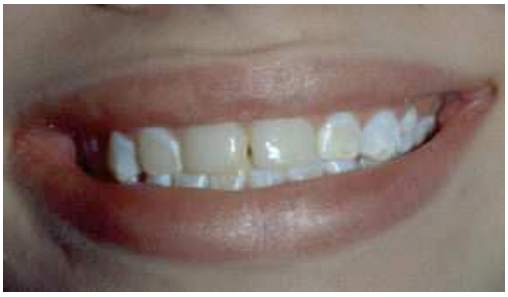


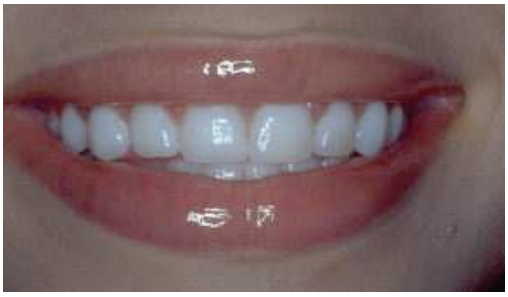


Photos and treatment above by Dr. Soileau.



Photos and treatment above by Dr. Markus. Note, this young man chose not to have his back teeth treated.





Photos and treatment above by Dr. Radz.

Is dental fluorosis a sign of actual "damage" or simply a cosmetic blemish? For example, is obesity a cosmetic problem or a sign of actual damage? Promoters of fluoridation do not consider this type of "light to moderate" effect as actual "damage" and neither the CDC nor the EPA RfD takes these cases into account. However, if someone scratched or sprayed paint on your car, with or without intent, compensation for those "cosmetic" damages would be expected. Cosmetic damage is actual damage and fluoridated water contributes to the total fluoride exposure. Many are now ingesting too much fluoride from many sources and paying many thousands of dollars for repairs.

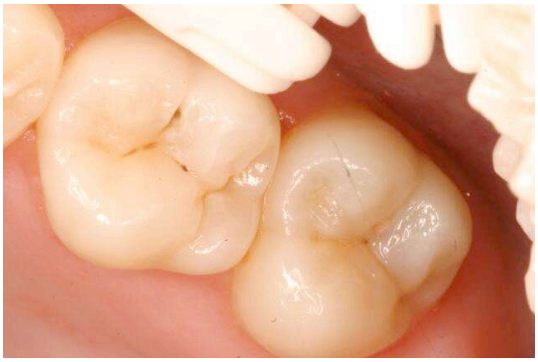
Proponents of fluoridation often work with low income children and not with those wealthy enough to seek treatment for their fluoride damaged teeth. Proponents may claim fluoridation is not damage, but patients paying for repairs do not agree.

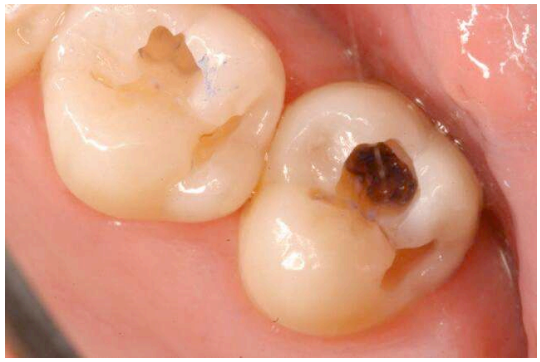
The discoloration induced by fluorosis can cause significant embarrassment and stress to the impacted child, resulting in adverse effects on esteem, emotional health, and career success. Dental fluorosis is a biomarker, a highly confident indication the person was exposed to too much fluoride while those parts of the tooth were developing. For example, the front two teeth are starting to develop at birth. All of the pictures above have enamel which was being formed during the first year and more of life. Those patients as infants ingested too much fluoride and were harmed. The EPA's RfD would not protect those patients as infants nor prevent their dental damage.

Providing warnings, cautions and advice to public water users is prudent to reduce excess ingestion of fluoride.

2. The "Fluoride Bomb:" Functional Deficit

The "Fluoride Bomb" is a clinical term used by dentists when they see a well developed tooth which on the surface looks strong with a slight amount of decay in a pit (demonstrated by picture below on left). On opening the pit, the tooth appears "bombed out" inside (picture on the right below). Clinically, teeth in fluoridated areas seem to appear more dense, harder or stronger. A confounding factor for fluoridation studies is the potential difficulty in diagnosing decay at the same size in subjects and controls. "Frank" caries viewed at the surface in a fluoridated cohort maybe more difficult to detect than a nonfluoridated cohort. Correcting for the confounding factor of the "fluoride bomb" in dental research has not been done. A fluoride/caries study might demonstrate the difficulty in diagnosis more than a benefit of injesting fluoride.



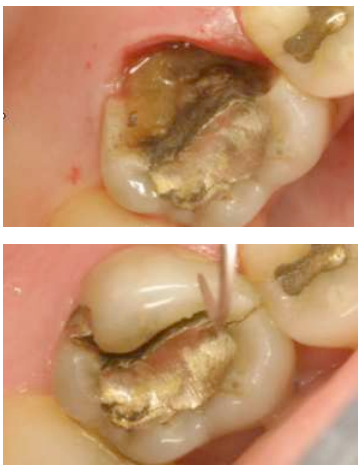


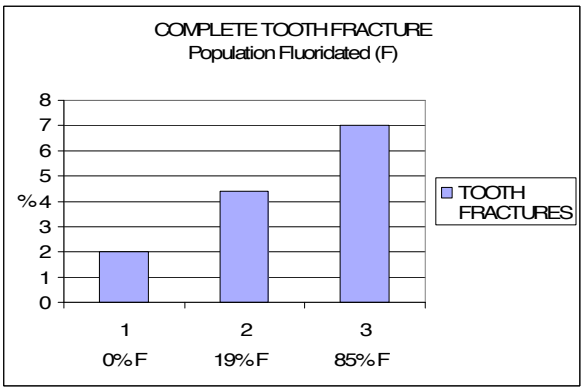
Further research is needed on the "fluoride bomb" and the number of decay or filled teeth in a study may reflect the difficulty in diagnosing dental caries.

3. Complete Cusp Fracture:[216] Functional Deficit

Calcified tissue becomes harder with fluoride. A possible adverse effect from harder teeth is increased tooth fractures. No good studies are found evaluating the increased aggregate exposure of fluoride to tooth fractures. However, three independent studies are of interest and further study is needed. Each study recorded the number of visits to the dental offices for complete cusp fractures. When the three areas are compared, the community which never had fluoridation had 2% of visits with complete cusp fractures, over 4% in the area with 19% of the population fluoridated and about 7% of visits where 85% of the population is fluoridated. (See Graph and pictures below)

Again, complete cusp fractures, fractured and chipped teeth may be one reason for the lack of significant reduction in dental expenses with fluoridation. Further research is needed.





[216] Appendix 30 Osmunson http://www.fluorideresearch.org/404/files/FJ2007_v40_n4_p214-221.pdf

Dental Fluorosis Rates Are Increasing, a Sign of Excess Fluoride Exposure

4. "A nine percentage point increase in the prevalence of very mild or greater fluorosis was observed among children and adolescents aged 6-19 years when data from 1999-2002 were compared with those from the NIDR 1986-1987 survey of school children (from 22.8% in 1986-1987 to 32% in 1999-2002)." Centers for Disease Control and Prevention (CDC, 2005) Surveillance for dental caries, dental sealants, tooth retention, edentulism, and enamel fluorosis—United States, 1988-1994 and 1999-2002. Morbidity and Mortality Weekly Report Surveillance Summaries 54:1-43.

5. "The prevalence of fluorosis in permanent teeth in areas with fluoridated water has increased from about 10-15% in the 1940s to as high as 70% in recent studies..." Marshall TA, et al. (2004). Associations between Intakes of Fluoride from Beverages during Infancy and Dental Fluorosis of Primary Teeth. Journal of the American College of Nutrition 23:108-16.

6. "There is compelling evidence that the prevalence of dental fluorosis has increased in the United States and Canada in recent years." Warren JJ, Levy SM. (2003). Current and future role of fluoride in nutrition. Dental Clinics of North America 47: 225-43

7. "[T]he prevalence of dental fluorosis in the United States has increased during the last 30 years, both in communities with fluoridated water and in communities with nonfluoridated water." Fomon SJ, Ekstrand J, Ziegler EE. (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.

8. "Current studies support the view that dental fluorosis has increased in both fluoridated and non-fluoridated communities. North American studies suggest rates of 20 to 75% in the former and 12 to 45% in the latter." Locker, D. (1999). Benefits and Risks of Water Fluoridation. An Update of the 1996 Federal-Provincial Subcommittee Report. Prepared for Ontario Ministry of Health and Long Term Care.

9. "Systemic F-exposure to children has increased. Mild dental fluorosis is now more common than one would predict on the basis of Dean's findings in the late 1930s and early 1940s: in fluoridated and non-fluoridated communities. Several recent studies report prevalence rates in the 20 and 80 percent range in areas with fluoridated water." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford.

10. "[A] few cases of more severe fluorosis can be found now in some communities. Because the prevalence of fluorosis is now higher than 50 years ago, we can conclude that fluoride availability... has increased in North American children." Rozier RG. (1999). The prevalence and severity of enamel fluorosis in North American children. Journal of Public Health Dentistry 59:239-46.

11. "There is a growing body of evidence which indicates that the prevalence and, in some cases, the severity of dental fluorosis is increasing in both fluoridated and non-fluoridated regions in the U.S... This trend is undesirable for several reasons: (1) It increases the risk of esthetically objectionable enamel defects; (2) in more

severe cases, it increases the risk of harmful effects to dental function; (3) it places dental professionals at an increased risk of litigation; and (4) it jeopardizes the perception of the safety and, therefore, the public acceptance of the use of fluorides." Whitford GM. (1990). The physiological and toxicological characteristics of fluoride. Journal of Dental Research 69(Special Issue):539-49.

12. "It is illogical to assume that tooth enamel is the only tissue affected by low daily doses of fluoride ingestion." Dr. Hardy Limeback, Head of Preventive Dentistry, University of Toronto. (2000). Why I am now Officially Opposed to Adding Fluoride to Drinking Water.

13. "Common sense should tell us that if a poison circulating in a child's body can damage the tooth-forming cells, then other harm also is likely." Colquhoun J. (1997). Why I changed my mind about Fluoridation. Perspectives in Biology and Medicine 41:29-44.

14. Like bones, a child's teeth are alive and growing. Fluorosis is the result of fluoride rearranging the crystalline structure of a tooth's enamel as it is still growing. It is evidence of fluoride's potency and ability to cause physiologic changes within the body, and raises concerns about similar damage that may be occurring in the bones." Environmental Working Group, "National Academy Calls for Lowering Fluoride Limits in Tap Water", March 22, 2006.

15. "It seems prudent at present to assume that the ameloblasts are not the only cells in the body whose function may be disturbed by the physiological concentrations of fluoride which result from drinking water containing 1 ppm" Groth, E. (1973), Two Issues of Science and Public Policy: Air Pollution Control in the San Francisco Bay Area, and Fluoridation of Community Water Supplies. Ph.D. Dissertation, Department of Biological Sciences, Stanford University, May 1973.

16. "The safety of the use of fluorides ultimately rests on the assumption that the developing enamel organ is most sensitive to the toxic effects of fluoride. The results from this study suggest that the pinealocytes may be as susceptible to fluoride as the developing enamel organ." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 176.

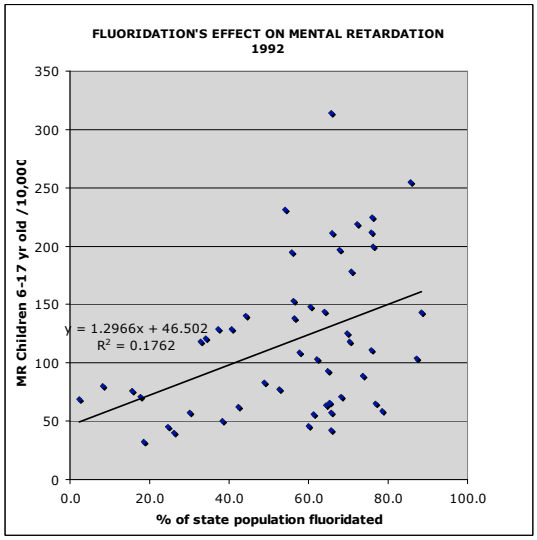
17. "A linear correlation between the Dean index of dental fluorosis and the frequency of bone fractures was observed among both children and adults." Alarcon-Herrera MT, et al. (2001). Well Water Fluoride, Dental fluorosis, Bone Fractures in the Guadiana Valley of Mexico. Fluoride 34(2): 139-149.

B. Likely and Possible Harm to the Brain and IQ from Fluoride: Teratogenicity, Altered Growth and Functional Deficit

1. The unpublished graph below[217] plots the 50 US states on the percent of whole state population fluoridated and mental retardation reported in 1992.

[217] Although this data was from 1992, that is the latest state survey of mental retardation we can find. More current studies use special education rates and the graphs are similar. Certainly MR data must be available but was not found to date. http://apps.nccd.cdc.gov/giscvh/map.aspx

As the percent of the populations on fluoridated water increases a tripling of mental retardation is found. This graph is consistent with half a standard deviation drop in IQ, about 8 IQ points and consistent with the studies below.



"The effects of excessive fluoride intake during pregnancy on neonatal neurobehavioral development and the neurodevelopment toxicity of fluoride were evaluated. . . The results showed that the urinary fluoride levels of mothers from the high fluoride group were higher than those of the control group. There were significant differences in the neonatal behavioral neurological assessment score and neonatal behavioral score between the subjects in the endemic fluoride areas and the control group. There were also significant differences in the non-biological visual orientation reaction and biological visual and auditory orientation reaction between the two groups. It is concluded that fluoride is toxic to neurodevelopment and that excessive fluoride intake during pregnancy can cause adverse effects on neonatal neurobehavioral development." For mother's in the "high fluoride group the urinary fluoride level averaged 3.58±1.47 mg/L, . . . the control group (1.74±0.96 mg/L)"

Table 2. Neurobehavioral assessment scores of neonates from high fluoride group and control group (mean±SD)

Group	Number of neonates	Total NBNA score	Behavioral capability	Passive muscle tension	Agonistic muscle tension	Primary reflection	General reaction
High fluoride	44	36.48±1.09*	10.05±0.84*	7.89±0.32	6.80±0.70*	5.89±0.32	5.84±0.37
Control	47	38.28±1.10*	11.34±0.56*	7.87±0.34	7.40±0.68*	5.89±0.31	5.79±0.41

*Statistically significant.

http://apps.nccd.cdc.gov/nohss/FluoridationV.asphttp://pubs.usgs.gov/circ/2004/circ1268/htdocs/table05.html http://www.cdc.gov/mmwR/preview/mmwrhtml/00040023.htm

Table 3. Scores of various neurobehavioral capabilities of neonates (mean±SD)

Group	Number of neonates	Total score of behavioral capability	Tolerance to light	Tolerance to clicking sounds	Directional reaction to non-biological audition	Directional reaction to non-biological vision	Directional reaction to biological vision and audition	Placebo
High fluoride	44	10.05±0.94*	1.95±0.21	1.93±0.26	1.95±0.21	0.98±0.63*	1.09±0.64*	1.99±0.17
Control	47	11.34±0.56*	1.98±0.15	1.89±0.31	1.98±0.15	1.66±0.52*	1.77±0.48*	1.98±0.15

*Statistically significant.

Li J, li Y, Shao QL, Wu CY, EFFECTS OF HIGH FLUORIDE LEVEL ON NEONATAL NEUROBEHAVIORAL DEVELOPMENT, Fluoride April-June 2008, 41(2)165-170 [Translated by Bin Li and published with the concurrence of the Chinese Journal of Endemiology 2004 Sep;23(5):463-5.] Appendix 39 Full Article. Note: Subject wells 1.7-6.0 mg F/L and control wells 0.5-1.0 mg F/L and subject urine samples were 3.58 mg F/L ±1.47 and controls 0.18-2.6 mg F/L statistically significant ($p<0.01$)

2. "This paper presents a systematic literature review conducted to investigate whether fluoride exposure has increased the risk of low intelligence quotient (IQ) scores in China over the past 20 years. . . . Children who live in a fluorosis area have five times higher odds of developing low IQ than those who live in a nonfluorosis area or a slight fluorosis area." SOURCE: Tang QQ, DuJ, Ma HH, Jiang SJ, Zhou XJ, Fluoride and children's intelligence: a meta-analysis, Biol Trace Elem Res. 2008 Winter: 126(1-3):115-20 Appendix 42 Full Abstract.

3. "We found that exposure to fluoride (F) in urine was associated with reduced Performance, Verbal, and Full IQ scores before and after adjusting for confounders. The same pattern was observed for models with F in water as the exposure variable.... The individual effect of F in urine indicated that for each mg increase of F in urine a decrease of 1.7 points in Full IQ might be expected." SOURCE: Rocha-Amador D, et al. (2007). Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. Cadernos de Saude Publica 23(Suppl 4):S579-87.

4. "These negative correlations between IQ and urinary As and between IQ and urinary fluoride indicate that exposure to high levels of As or fluoride, or both, could affect children's intelligence... This study indicates that exposure to fluoride in drinking water is associated with neurotoxic effects in children." SOURCE: Wang SX, et al. (2007). Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. Environmental Health Perspectives 115(4):643-7.

5. "In agreement with other studies elsewhere, these findings indicate that children drinking high F water are at risk for impaired development of intelligence." SOURCE: Trivedi MH, et al. (2007). Effect of high fluoride water on intelligence of school children in India. Fluoride 40(3):178-183.

6. "Based on the findings of this study, exposure of children to high levels of fluoride may carry the risk of impaired development of intelligence." SOURCE: Seraj B, et al. (2006). [Effect of high fluoride concentration in drinking water on children's intelligence]. Journal of Dental Medicine 19(2):80-86.

7. In 2006, more than 20 of the human studies finding brain damage with higher exposures of fluoride had not been published in English. The 2006 NRC

Report said, “A few epidemiologic studies of Chinese populations have reported IQ deficits in children exposed to fluoride at 2.5 to 4 mg/L in drinking water. Although the studies lacked sufficient detail for the committee to fully assess their quality and relevance to U.S. populations, the consistency of the results appears significant enough to warrant additional research on the effects of fluoride on intelligence.” SOURCE: National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA’s Standards. National Academies Press, Washington D.C. p. 6. Those studies of US populations have not been done.

8. “Conclusion: High fluoride burden has a definite effect on the intellectual and physical development of children.” SOURCE: Wang S, et al. (2005). Effects of coal burning related endemic fluorosis on body development and intelligence levels of children. Journal of Applied Clinical Pediatrics 20(9): 897-898.

9. “In our study, it was shown that the average IQ of children in a fluoride endemic area was somewhat lower than the control, but the result was not significant ($P>0.05$). The rate of children with “low” IQs, however, was elevated as compared to the control, and this was very statistically significant... Our study showed that, within the fluoride endemic area, the average IQ of children suffering from dental fluorosis is clearly lower than those that show no signs of the disease, and this result is very significant ($P <0.01$). This IQ difference of 8.12 suggests that children suffering from dental fluorosis might be particularly sensitive to excess fluoride, and that the manifestation of this is not limited to the typical symptoms of fluorosis, but, more seriously, also disrupts intellectual development.” SOURCE: Li Y, et al. (2003). The effects of endemic fluoride poisoning on the intellectual development of children in Baotou. Chinese Journal of Public Health Management 19(4):337-338.

10. “Higher drinking water fluoride levels were significantly associated with higher rates of mental retardation (IQ <70) and borderline intelligence (IQ 70-79)... In endemic fluorosis areas, drinking water fluoride levels greater than 1.0 mg/L may adversely affect the development of children’s intelligence.” SOURCE: Xiang Q, et al. (2003a). Effect of fluoride in drinking water on children’s intelligence. Fluoride 36: 84-94.

11. “As an additional part of our investigation of an association between fluoride in drinking water and children’s intelligence in two villages of Sihong County, Jiangsu Province, China, we have now determined blood lead levels of children in that study... The results show there is essentially no difference between the two villages in blood lead concentrations of the children... These results thus make it very unlikely that the differences in IQ of the children living in Wamiao and Xinhuai are the result of differences in exposure to lead rather than to fluoride.” SOURCE: Xiang Q, et al. (2003b). Blood lead of children in Wamiao-Xinhuai intelligence study. Fluoride 36: 198-199.

12. “After controlling by significant confounders, urinary fluoride correlated positively with reaction time and inversely with the scores in visuospatial organization. IQ scores were not influenced by fluoride exposure. An increase in reaction time could affect the attention process, also the low scores in visuospatial organization could be affecting the reading and writing abilities in these children.” SOURCE: Calderon J, et al. (2000). Influence of fluoride exposure on reaction time and visuospatial organization in children. Epidemiology 11(4): S153.

13. “In terms of IQ ranking, the high fluoride groups showed significant deficits as compared to control ($P<0.01$)... Conclusion: When fluoride and iodine levels in

excess of national standards for drinking water are present in the same area and ingested together, the harmful effects of fluoride are more pronounced, and the resulting damage compounded." SOURCE: Hong F, et al. (2001). A study of fluorine effects on children's intelligence development under different environments. Chinese Primary Health Care 15: 56-57.

14. "The IQ of the 60 children in the high-fluoride area was significantly lower than that of the 58 children in the low-fluoride area... More children in the high-fluoride area were in the retardation or borderline categories of IQ than children in the low fluoride area. An inverse relationship was also present between IQ and the urinary fluoride level. Exposure of children to high levels of fluoride may therefore carry the risk of impaired development of intelligence." SOURCE: Lu Y, et al (2000). Effect of high-fluoride water on intelligence of children. Fluoride 33:74-78,

15. "Within the seven categories of the scores, there were significantly more borderline and low IQs in the high F area (13/60) than in the low F area (2/58) ($p<0.01$)." Report on the Intellectual Ability of Children Living in High-Fluoride Water Areas, Liu S, et al, Chinese Journal of Control of Endemic Diseases 2000;15(4)231-2. Fluoride 41(2)144-147

16. "A study of intelligence quotient (IQ) in China was conducted using Wickler's Intelligence Quotient Table for preschool children, in 4-7 year-old children, 147 from a district with high level of fluoride and 83 from a control area. High F intake had a significant influence on IQ of preschool children. Operation IQ was mainly affected." SOURCE: Wang G, et al. (1996). Research on intelligence quotient of 4-7 year-old children in a district with a high level of fluoride. Endemic Diseases Bulletin 11:60-62.

17. "In Shanxi Province, China, children living in the endemic fluoride village of Sima located near Xiaoyi City had average IQ significantly lower than children living to the north in the nonendemic village of Xinghua." SOURCE: Zhao LB, et al (1996). Effect of high-fluoride water supply on children's intelligence. Fluoride 29: 190-192.

18. "The intelligence was measured of 907 children aged 8-13 years living in areas which differed in the amount of fluoride present in the environment. The Intelligence Quotient (IQ) of children living in areas with a medium or severe prevalence of fluorosis was lower than that of children living in areas with only slight fluorosis or no fluorosis. The development of intelligence appeared to be adversely affected by fluoride in the areas with a medium or severe prevalence of fluorosis. A high fluoride intake was associated with a lower intelligence." SOURCE: Li XS. (1995). Effect of Fluoride Exposure on Intelligence in Children. Fluoride 28:189-192.

19. "We made an investigation in 157 children, aged 12-13, born and grew up in a coal burning pattern endemic fluorosis area and an experiment on excessive fluoride intake in rat. The results showed: (1) Excessive fluoride intake since early childhood would reduce mental work capacity (MWC) and hair zinc content: (2) The effect on zinc metabolism was a mechanism of influence on MWC by excessive fluoride intake..." SOURCE: Li Y, et al. (1994). [Effect of excessive fluoride intake on mental work capacity of children and a preliminary study of its mechanism] Hua Hsi I Ko Ta Hsueh Hsueh Pao. 25:188-91.

20. "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. The subject group of children from the high fluoride, high iodine zone have an average IQ of 76.67±7.75, which was somewhat less than the control (IQ = 81.67 ±11.9), though the different is not significant (P>0.05). However, the percentage of subject children in the low range (16.67%) is higher than the control, suggesting that a high iodine, high fluoride environment also has a definite negative influence on child intellectual ability." SOURCE: Yang Y, et al. (1994). Effects of high iodine and high fluorine on children's intelligence and the metabolism of iodine and fluorine. Chinese Journal of Pathology 15(5):296-8.

21. "The results of this study show that the children living in high fluoride areas have lower IQs than the children from the non-endemic area. Also, there were many more children from the endemic area with an IQ score ranking of below the borderline low level as compared to the control; in the endemic area, there were 18 such subject, or 30% of the total, while in the non-endemic area there were only 7, or a rate of 11.5%. The difference between the two groups is significant. The overall distribution shows marked difference, with the scores in control group on average one rank higher than the control... In summary, although diminished intellectual ability can result from a multitude of factors (both innate and acquired) that influence neural development and cell division in the cerebrum, the comparison conducted in this study of two areas where the other environment factors are basically the same shows clear differences in IQ, and it's probable that this difference is due to a high fluoride environment. It is not clear whether the underlying mechanism is fetal exposure to fluoride resulting from the poisoning of the mother or intake of fluoride after birth (in either case causing a disruption nerve cell development leading to mental deficits); this matter awaits further study." SOURCE: Guo XC, et al. (1991). A preliminary exploration of IQ of 7-13 year old pupils in a fluorosis area with contamination from burning coal. Chinese Journal of Endemiology 10:98-100.

22. "The results of this study indicate that there is significant difference between the intellectual ability of the 7 – 14 year old children from the endemic area and those of the control, and moreover that the average IQ of the children from the endemic area is clearly lower. In the endemic region, the children in the 80-89 range and below make up more than 25% of the total, while in the control range only 18% of the children fall into that range, demonstrating that high fluoride has a direct connection with the intellectual development of children." SOURCE: Chen YX, et al. (1991). Research on the intellectual development of children in high fluoride areas. Chinese Journal of Control of Endemic Diseases. 6(supplement):99-100. Chen, et al. Research on the intellectual development of children in high fluoride areas. Fluoride 41(2):120–4. 2008

23. "The significant differences in IQ among these regions suggests that fluoride can exacerbate central nervous lesions and somatic developmental disturbance caused by iodine deficiency. This may be in keeping with fluoride's known ability to cause degenerative changes in central nervous system cells and to inhibit the activities of many enzymes, including choline enzymes, causing disturbance of the nerve impulse." SOURCE: Lin Fa-Fu; et al (1991). The relationship of a low-iodine and high-fluoride environment to subclinical cretinism in Xinjiang. Iodine Deficiency Disorder Newsletter Vol. 7. No. 3.

24. "By testing of the intellectual ability of 447 elementary school students ranging in age from 9 to 10 ½, it was discovered that both high and low fluoride had an effect on child intelligence. Fluoride levels greater than 2.0 mg/L or less than 0.2 mg/L can disrupt intellectual development." SOURCE: Qin LS, Cui SY. (1990). The

influence of drinking water fluoride on pupils IQ, as measured by Rui Wen's standards. Chinese Journal of the Control of Endemic Diseases 5:203-204. Fluoride 41(2)115-119 Appendix 44 Full Article

25. "The effect of a harmful environment containing both high fluoride and low iodine on the development of child mental ability has yet to be reported on. To investigate this question, the authors used the Wechsler Intelligence Test to determine the IQs of a total of 329 eight- to fourteen-year-old children living in nine high fluoride, low iodine villages and seven villages that had only low levels of iodine. We discovered that the IQs of children from high fluoride, low iodine villages were clearly lower than those from the villages with low iodine alone." SOURCE: Ren Da-Li. (1989). An investigation of intelligence development of children aged 8-14 years in high-fluoride and low-iodine areas. Chinese Journal of Control of Endemic Diseases 4:251. Fluoride 41(4)319-320 Appendix 34 Full Article

26. "The effects of excessive fluoride intake during pregnancy on neonatal neurobehavioural development and the neurodevelopment toxicity of fluoride were evaluated. Ninety-one normal neonates delivered at the department of obstetrics and gynecology in five hospitals of Zhaozhou County, Heilongjiang province, China were randomly selected from December 2002 to January 2003. The subjects were divided into two groups (high fluoride and control) based on the fluoride content in the drinking water of pregnant women. The results showed that the urinary fluoride levels of mothers from the high fluoride group were higher than those of the control group. There were significant differences in the neonatal behavioral neurological assessment score and neonatal behavioral score between the subjects in endemic areas and the control group. There were also significant differences in the non-biological visual orientation reaction and biological visual and auditory orientation reaction between the two groups. It is concluded that fluoride is toxic to neurodevelopment. Excessive fluoride intake during pregnancy can cause adverse effects on neonatal neurobehavioural development." SOURCE: Li J, Yao L, Shao Q-L. (2004). Effects of high-fluoride on neonatal neurobehavioural development. Chinese Journal of Endemiology 23:464-465. (Same study as published in Fluoride and used above to illustrate urine F concentration levels Appendix 39)

27. "The levels of neurotransmitters and receptors in brain tissue of aborted fetuses from areas of endemic fluorosis were tested. The results showed that in 10 subjects from a high fluoride area ranging in age from 5 to 7 months, the levels of norepinephrine, 5-hydroxyltryptamine, and α1-receptor were lower and the level of epinephrine higher as compared with levels seen in the control fetuses from a non-fluorosis endemic area; each of these results was statistically significant ($P<0.05$). Other monoamine neurotransmitters and metabolic products, such as dopamine, 5-hydroxy-indole acetic acid, and 3,4-dihydroxybenzoic acid showed no significant differences ($P>0.05$). The results suggest that the accumulation of fluoride in the brain tissue can disrupt the synthesis of certain neurotransmitters and receptors in nerve cells, leading to neural dysplasia or other damage." SOURCE: Yu Y, et al. (1996). Changes in neurotransmitters and their receptors in human foetal brain from an endemic fluorosis area. Chinese Journal of Endemiology 15:257-259. Fluoride 41(2)134-138 Appendix 48 Full Article

28. "Fifteen therapeutically aborted fetuses at the 5^{th}-8^{th} gestation month from the endemic fluorosis area were compared with those from the non-endemic area. Stereological study of the brains showed that the numerical density of volume of the neurons and the undifferentiated neuroblasts as well as the nucleus-cytoplasm ratio of the neurons were increased. The mean volume of the neurons was reduced. The

numerical density of volume, the volume density and the surface density of the mitochondria were significantly reduced. The results showed that chronic fluorosis in the course of intrauterine fetal life may produce certain harmful effects on the developing brain of the fetus." SOURCE: Du L. (1992). [The effect of fluorine on the developing human brain]. Chung-hua Ping Li Hsueh Tsa Chih. 21:218-20. Fluoride 41(4)327-330 Appendix 33 Full Article

29. "Fluoride can pass through the blood-brain barrier and accumulate in brain tissue, thus in our study the brain tissue of the fetuses from the fluoride endemic area showed higher fluoride levels than the control. The mechanisms involved are not yet clear. Besides increased amounts of fluoride, the brain tissue of the endemic subjects also showed nerve cells with swollen mitochondria, expanded granular endoplasmic reticula, grouping of the chromatin, damage to the nuclear envelope, a lower number of synapses, fewer mitochondria, microtubules, and vesicles within the synapses, and damage to the synaptic membrane. These changes indicate that fluoride can retard the growth and division of cells in the cerebral cortex. Fewer mitochondria, microtubules, and vesicles within the synapses could lead to fewer connections between neurons and abnormal synaptic function, influencing the intellectual development after birth. These questions await further research." SOURCE: Han H, et al. (1989). The effects of fluorine on human fetus. Chinese Journal of Control of Endemic Diseases 4:136-138.

30. "The results of the NCTB (neurobehavioral core test battery) testing show the exposed groups with significant differences for various indices as compared to the reference standards and the control, with particular deficits in attention, auditory retention, and physical dexterity and acuity as well as abnormal emotional states. This is consistent with the symptoms of endemic fluoride poisoning, suggesting occupational exposure to fluoride has a harmful effect on the higher functions of the central nervous system, negatively influencing both cognitive and autonomic functioning. There is a definite relationship between the damage caused by fluoride and the level of exposure. The correlation analysis shows that, with the exception of visual retention and digit symbol testing, serum fluoride is negatively correlated with all relevant indices, further demonstrating the cause and effect relationship between occupational fluoride exposure and neurobehavioral function; these tests can be used as early indicators to help protect the health of workers exposed to fluoride as part of their jobs." SOURCE: Guo Z, et al. (2001). Study on neurobehavioral function of workers occupationally exposed to fluoride. Industrial Health and Occupational Disease 27:346-348.

31. "Sulfuryl fluoride exposure over the year preceding examination was associated with significantly reduced performance on the Pattern Memory Test and on olfactory testing... CONCLUSIONS: Occupational sulfuryl fluoride exposures may be associated with subclinical effects on the central nervous system, including effects on olfactory and some cognitive functions." SOURCE: Calvert GM, et al. (1998). Health effects associated with sulfuryl fluoride and methyl bromide exposure among structural fumigation workers. American Journal of Public Health 88:1774-80.

32. "Although the blood-brain barrier is relatively impermeable to fluoride, it does not pose an absolute barrier and fluoride has the ability to enter the brain. The literature was examined to assess the quality of the evidence for cerebral impairment occurring due to exposure to fluoride from therapeutic or environmental sources. Several surveys of persons chronically exposed to industrial fluoride pollution reported symptoms related to impaired central nervous system functioning with impaired

cognition and memory. Examination of individual case reports showed the evidence for aetiological relationships between symptoms and fluoride exposure to be of variable quality. The evidence was seen as being suggestive of a relationship rather than being definitive. The difficulties with concentration and memory described in relation to exposure to fluoride did not occur in isolation but were accompanied by other symptoms of which general malaise and fatigue were central. Possible mechanisms whereby fluoride could affect brain function include influencing calcium currents, altering enzyme configuration by forming strong hydrogen bonds with amide groups, inhibiting cortical adenylyl cyclase activity and increasing phosphoinositide hydrolysis." SOURCE: Spittle B. (1994). Psychopharmacology of fluoride: a review. International clinical psychopharmacology 9:79-82. (Full article at http://www.fluoridefreefairbanks.org/localweb/Psychopharmocology%20of%20fluoride.pdf)

33. "Epidemiological investigations reveal that high fluoride and low iodine have strong adverse effects on the intelligence quotient (IQ) of children. . . we first report on the proteomic changes in brain proteins in offspring rats . . . The identified proteins are mainly related with cellular signaling, energy metabolism, and protein metabolism and provide a valuable clue to explore the mechanism underlining the neurotoxicity of high fluoride and low iodine." SOURCE: Ge Y et al, Proteomic analysis of brain proteins of rats exposed to high fluoride and low Iodine, Arch Toxicol. 2010 Apr 3 www.ncbi.nlm.nih.gov/pubmed/20364248

34. "Overall, these results suggest that moderate intoxication with sodium fluoride has potentially deleterious effects on learning and memory." SOURCE: Chioca LR, et al. (2007). Subchronic fluoride intake induces impairment in habituation and active avoidance tasks in rats. European Journal of Pharmacology Oct 25; [Epub ahead of print]

35. "The results of the present study indicate that perinatal exposure to sodium fluoride (NaF), at dose levels below those associated with gross malformations and/or overt neurotoxic effects, produces both short and long term sex and dose specific neurobehavioural alterations in rat offspring." SOURCE: Bera I, et al. (2007). Neurofunctional effects of developmental sodium fluoride exposure in rats. European Review for Medical and Pharmacological Sciences 11(4):211-24.

36. "Additional animal studies designed to evaluate reasoning are needed. These studies must be carefully designed to measure cognitive skills beyond rote learning or the acquisition of simple associations, and test environmentally relevant doses of fluoride." SOURCE: National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p. 187.

37. "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." SOURCE: 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: 201-208.

38. "Fluoride intoxicated animals also performed poorly in motor co-ordination tests and maze tests. Inability to perform well increased with higher fluoride concentration in drinking water." SOURCE: Bhatnagar M, et al. (2002). Neurotoxicity of fluoride: neurodegeneration in hippocampus of female mice. Indian Journal of Experimental Biology 40: 546-54.

39. “Administration of sodium fluoride with drinking water produced both behavioural and dental toxicities and not lethality in the present study. A suppression of spontaneous motor activity, a shortening of rota-rod endurance time, a decreased body weight gain and food intake, a suppression of total cholinesterase and acetylcholinesterase activities and dental lesion were observed in test animals.” SOURCE: Ekambaram P, Paul V. (2001). Calcium preventing locomotor behavioral and dental toxicities of fluoride by decreasing serum fluoride level in rats. Environmental Toxicology and Pharmacology 9(4):141-146.

40. “The main results showed that the learning capability of mice drinking higher concentration of fluoride presented remarkable deterioration.” SOURCE: Zhang Z, et al. (2001). [Effects of selenium on the damage of learning-memory ability of mice induced by fluoride]. Wei Sheng Yan Jiu. 30(3):144-6.

41. “Learning and memory abilities of high-fluoride exposed groups were significantly lower than that of the control group, while the brain ChE activities of high-fluoride exposed groups were significantly higher. Conclusions: High fluoride concentration in drinking water can decrease the cerebral functions of mice. Fluoride is a neurotoxicant.” SOURCE: Sun ZR, et al. (2000). Effects of high fluoride drinking water on the cerebral functions of mice. Chinese Journal of Epidemiology 19: 262-263.

42. “The main results are as follows: the learning ability of mice drinking high concentration of fluoride presented remarkable deterioration... The results suggested that the impairment on the learning capability induced by fluorosis may be closely related with the pathological changes of synaptic structure in the brain of mice.” SOURCE: Zhang Z, et al. (1999). [Effect of fluoride exposure on synaptic structure of brain areas related to learning-memory in mice] [Article in Chinese]. Wei Sheng Yan Jiu 28(4):210-2.

43. “Sodium fluoride treatment suppressed spontaneous motor activity but no change was observed in the motor coordination of these animals. A suppression of spontaneous motor activity suggests that fluoride has, by a central action, inhibited motivation of these animals to exhibit locomotor behavior.” SOURCE: Paul V, et al. (1998). Effects of sodium fluoride on locomotor behavior and a few biochemical parameters in rats. Environmental Toxicology and Pharmacology 6: 187–191.

44. “In this experiment, the freeze response to auditory stimuli in the pups showed significant delay, indicating that relatively high doses of fluoride can negatively influence the development of auditory nerves. Guan Zhizhong et al[8] report that the offspring of rats exposed to fluoride have retarded cerebral development and exhibit changes in neural cell ultrastructure. The results of the present experiment suggest that the effects of high doses of fluoride on the behavior development of the offspring are visible primarily as slight delays in response times, particularly with regard to motor and coordination function and well as muscle strength. The measurement of the thickness of the cerebral cortex of offspring on day 21 revealed that the 25 mg/L group had a significantly thinner cerebral cortex as compared to the control; this histological analysis indicates that fluoride slows the growth of brain cells.” SOURCE: Wu N, et al. (1995). Research on the abnormal behavior of rats exposed to fluoride. Chinese Journal of Control of Endemic Diseases 14(5):271.

45. “This study demonstrates a link between certain fluoride exposures and behavioral disruption in the rat. The effect on behavior varied with the

timing of exposure during CNS development. Behavioral changes common to weanling and adult exposures were different from those after prenatal exposures... Experience with other developmental neurotoxicants prompts expectations that changes in behavioral function will be comparable across species, especially humans and rats... [A] generic behavioral pattern disruption as found in this rat study can be indicative of a potential for motor dysfunction, IQ deficits and/or learning disabilities in humans." SOURCE: Mullenix P, et al. (1995). Neurotoxicity of Sodium Fluoride in Rats. Neurotoxicology and Teratology 17:169-177.

46. " When rats were treated 6 hr a day for 5 mo. with HF concentrations of 3, 1, 0.5, and 0.1 mg/m-3, it caused functional changes in the CNS, as shown by the condition reflex method and the measurement of chronaxy. There was inhibition of the blood alkaline phosphatase activity and pathomorphological changes in the CNS, bone and tooth tissues and internal organs. The extent of the changes depended on the concentration of HF. The maximum allowable concentration of HF for the air at working places presently accepted, 0.5 mg/m-3, is too high." SOURCE: Vishnevskii VL, El Nichnykh LN. (1969). (A toxicological and morphological characterization of the action of different concentrations of inhaled hydrogen fluoride on the body.). Tr Tsentr Nauchno-Issled Proektn-Konstr In. 2: 143-147.

47. "General malaise, asthenia, and apathy developed to a marked degree in the monkeys exposed to the BeF2 (beryllium fluoride) aerosol, and in those under the heaviest BeHPO4 exposure. The monkeys retreated to the furthest corner of their cages and paid no attention to light flashed at them. They remained in this withdrawn and listless condition until death. Monkeys which inhaled the BeSO4 aerosol faired best of all." SOURCE: Schepers GWH. (1964). Biological action of beryllium: Reaction of the monkey to inhaled aerosols. Industrial Medicine and Surgery 33: 1-16.

48. "Lipids and phospholipids, phosphohydrolases and phospholipase D, and protein content have been shown to be reduced in the brains of laboratory animals subsequent to fluoride exposure. The greatest changes were found in phosphatidylethanolamine, phosphotidylcholine, and phosphotidylserine. Fluorides also inhibit the activity of cholinesterases, including acetylcholinesterase. Recently, the number of receptors for acetylcholine has been found to be reduced in regions of the brain thought to be most important for mental stability and for adequate retrieval of memories. It appears that many of fluoride's effects, and those of the aluminofluoride complexes are mediated by activation of Gp, a protein of the G family. G proteins mediate the release of many of the best known transmitters of the central nervous system. Not only do fluorides affect transmitter concentrations and functions but also are involved in the regulation of glucagons, prostaglandins, and a number of central nervous system peptides, including vasopressin, endogenous opioids, and other hypothalamic peptides. The AlFx binds to GDP and ADP altering their ability to form the triphosphate molecule essential for providing energies to cells in the brain. Thus, AlFx not only provides false messages throughout the nervous system but, at the same time, diminishes the energy essential to brain function. Fluorides also increase the production of free radicals in the brain through several different biological pathways. These changes have a bearing on the possibility that fluorides act to increase the risk of developing Alzheimer's disease. Today, the disruption of aerobic metabolism in the brain, a reduction of effectiveness of acetylcholine as a transmitter, and an increase in free radicals are thought to be causative factors for this disease. More research is needed to clarify fluoride's biochemical effects on the brain." SOURCE: National Research

Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p. 186.

49. "Studies of rats exposed to NaF or AlF3 have reported distortion in cells in the outer and inner layers of the neocortex. Neuronal deformations were also found in the hippocampus and to a smaller extent in the amygdala and the cerebellum. Aluminum was detected in neurons and glia, as well as in the lining and in the lumen of blood vessels in the brain and kidney. The substantial enhancement of reactive microglia, the presence of stained intracellular neurofilaments, and the presence of IgM observed in rodents are related to signs of dementia in humans. The magnitude of the changes was large and consistent among the studies." SOURCE: National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p. 187.

50. "In the present study, levels of glutathione and activities of catalase, GSH-PX, and SOD were significantly decreased, whereas lipid peroxide levels were enhanced in the brain of adult rats by treatment with NaF, As2O, or NaF + As2O3, in agreement with earlier reports." SOURCE: Chinoy NJ, et al. (2004). Biochemical effects of sodium fluoride and arsenic trioxide toxicity and their reversal in the brain of mice. Fluoride 37: 80-87.

51. "The histology of the cerebral hemisphere was altered by NaF and/or Arsenic trioxide [As2O3] treatment for 30 days, wherein the effect by As2O3 was greater than by NaF treatment. This result is in agreement with others... The reduced brain acetylcholinesterase (AChE) enzyme activity observed in the present study corroborates data of others in rats exposed for three months to arsenic trioxide and in the brain of NaF-treated mice and rats as compared to controls... The DNA and RNA levels in the cerebral hemisphere were significantly lower in NaF and/or As2O3-treated mice in the present study, which could affect brain function. The ingestion of the antidotes vitimans C and E as well as calcium phosphate, either indivdually or in combination, during the 30-day withdrawal period resulted in significant recovery, probably due to the antioxidant-properties of vitamins C and E and modulation of fluoride-induced toxicity in rats by calcium." SOURCE: Shah SD, Chinoy NJ. (2004). Adverse effects of fluoride and/or arsenic on the cerebral hemisphere of mice and recovery by some antidotes. Fluoride 37: 162-171.

52. "Superoxide dismutase (SOD) activity and the malondialdehyde (MDA) content in the brain of the combined high fluoride and low iodine group were significantly higher during and at the end of the 90-day period than in the control group, but the SOD/MDA ratio in this high fluoride and low iodine group was consistently lower than in the control group. These results suggest that [oxidative] stress from high fluoride and low iodine is one of the causes of reduction in learning and memory in offspring rats." SOURCE: 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: 201-208.

53. "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." SOURCE: 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: 201-208.

54. "Recently, we have detected the alterations of nicotinic acetylcholine receptors (nAChRs) in rat brains and PC12 cells affected by fluoride toxicity... [O]xidative stress, including protein oxidation of the receptors and lipid

peroxidation in cellular membrane, might be a mechanism of the deficit of the receptors." SOURCE: Shan KR, Qi XL, Long YG, Wang YN, Nordberg A, Guan ZZ. (2004). Decreased nicotinic receptors in PC12 cells and rat brains influenced by fluoride toxicity—a mechanism relating to a damage at the level in post-transcription of the receptor genes. Toxicology 200: 169–177.

55. "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 (potassium iodine) is the optimal concentration for the antagonistic action with this influence from fluorosis." SOURCE: 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. 33:158-61.

56. "These findings suggest that selective decreases in the number of nAChRs may play an important role in the mechanism(s) by which fluoride causes dysfunction of the central nervous system." SOURCE: Chen J, Shan KR, Long YG, Wang YN, Nordberg A, Guan ZZ. (2003). Selective decreases of nicotinic acetylcholine receptors in PC12 cells exposed to fluoride. Toxicology 183: 235-42.

57. "These neurotoxic changes in the brain suggested that there was a direct action of fluoride upon the nerve tissue which was responsible for central nervous system problems such as tremors, seizures, and paralysis indicating brain dysfunction seen at the two highest doses." SOURCE: Shashi A. (2003). Histopathological investigation of fluoride-induced neurotoxicity in rabbits. Fluoride 36: 95-105.

58. "CONCLUSION: Fluoride may go through the blood-brain barrier and accumulate in rat hippocampus, and inhibit the activity of cholinesterase." SOURCE: Zhai JX, et al. (2003). [Studies on fluoride concentration and cholinesterase activity in rat hippocampus]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 21:102-4.

59. "Light microscopic study of hippocampal sub-regions demonstrated significant number of degenerated nerve cell bodies in the CA3, CA4 and dentate gyrus(Dg) areas of sodium fluoride administered adult female mice. Ultrastructural studies revealed neurodegenerative characteristics like involution of cell membranes, swelling of mitochondria, clumping of chromatin material etc, can be observed in cell bodies of CA3, CA4 and dentate gyrus (Dg)." SOURCE: Bhatnagar M, et al. (2002). Neurotoxicity of fluoride: neurodegeneration in hippocampus of female mice. Indian Journal of Experimental Biology 40: 546-54.

60. "The DNA damage in pallium neurons in rats of the fluoride group was much more serious compared with those of the control group...Sodium fluoride could induce DNA damage and apoptosis in rats brain." SOURCE: Chen J, Chen X, Yang K, Xia T, Xie H. (2002). [Studies on DNA damage and apoptosis in rat brain induced by fluoride]. Zhonghua Yu Fang Yi Xue Za Zhi 36: 222-224.

61. "In order to investigate the molecular mechanism(s) underlying brain dysfunction caused by chronic fluorosis, neuronal nicotinic acetylcholine receptors (nAChRs) in the brain of rats receiving either 30 or 100 ppm fluoride in their drinking water for 7 months were analyzed in the present study employing ligand binding and Western blotting... Since nAChRs play major roles in cognitive processes such as learning and memory, the decrease in the number of nAChRs caused by fluoride toxicity may be an important factor in the mechanism of brain dysfunction in the disorder." SOURCE: Long YG, Wang YN, Chen J, Jiang SF, Nordberg A, Guan ZZ. (2002).

Chronic fluoride toxicity decreases the number of nicotinic acetylcholine receptors in rat brain. Neurotoxicology and Teratology 24:751-7.

62. "These results suggest that fluoride enhances oxidative stress in the brain, thereby disturbing the antioxidant defense of rats. Increased oxidative stress could be one of the mediating factors in the pathogenesis of fluoride toxicity in the brain." SOURCE: Shivarajashankara YM , et al. (2002). Brain lipid peroxidation and antioxidant systems of young rats in chronic fluoride intoxication. Fluoride 35: 197-203.

63. "Rats exposed to 100 ppm fluoride showed significant neurodegenerative changes in the hippocampus, amygdala, motor cortex, and cerebellum... These histological changes suggest a toxic effect of high-fluoride intake during the early developing stages of life on the growth, differentiation, and subcellular organization of brain cells in rats." SOURCE: Shivarajashankara YM , et al. (2002). Histological changes in the brain of young fluoride-intoxicated rats. Fluoride 35: 12-21.

64. "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."
SOURCE: Chen J, Chen X, Yang K. (2000). [Effects of selenium and zinc on the DNA damage caused by fluoride in pallium neural cells of rats]. Wei Sheng Yan Jiu. 29: 216-7.

65. "This study therefore shows that both brain and muscle are affected by fluoride with inhibition of some enzymes associated with free-radical metabolism, energy production and transfer, membrane transport, and synaptic transmission, but with an enhanced activity of XOD." SOURCE: Lakshmi Vani M, Pratap Reddy K. (2000). Effects of fluoride accumulation on some enzymes of brain and gastrocnemius muscle of mice. Fluoride 33: 17-26.

66. "There is a tendency for neurone apoptosis in chronic fluorosis in rats. It is most evident with changes in pathology. It is not likely that only one form of neurone damage exist in the process of chronic fluorosis. There are recessive changes and apoptosis in the process at the same time." SOURCE: Lu XH, et al. (2000). Study of the mechanism of neurone apoptosis in rats from the chronic fluorosis. Chinese Journal of Epidemiology 19: 96-98.

67. "Over uptake of fluoride for a long term could cause potential increase in the level of oxidative stress in the brain tissue." SOURCE: Shao Q, Wang Y, Guan Z. (2000). [Influence of free radical inducer on the level of oxidative stress in brain of rats with fluorosis]. Zhonghua Yu Fang Yi Xue Za Zhi 34:330-2.

68. "It was concluded that aluminium interferes with the metabolism of the neuronal cytoskeleton and that this interference is potentiated by fluoride." SOURCE: van der Voet GB, et al. (1999). Fluoride enhances the effect of aluminium chloride on interconnections between aggregates of hippocampal neurons. Archives of Physiology and Biochemistry 107:15-21.

69. "[T]he thickness of post-synaptic density (PSD) was decreased, and the width of synaptic cleft was remarkably increased. The results suggested that the impairment on the learning capability induced by fluorosis may be closely related with the pathological changes of synaptic structure in the brain of mice." SOURCE: Zhang Z,

et al. (1999). [Effect of fluoride exposure on synaptic structure of brain areas related to learning-memory in mice] [Article in Chinese]. Wei Sheng Yan Jiu 28:210-2.

70. "The results demonstrate that the contents of phospholipid and ubiquinone are modified in brains affected by chronic fluorosis and these changes of membrane lipids could be involved in the pathogenesis of this disease." SOURCE: Guan ZZ, Wang YN, Xiao KQ, Dai DY, Chen YH, Liu JL, Sindelar P, Dallner G. (1998). Influence of chronic fluorosis on membrane lipids in rat brain. Neurotoxicology and Teratology 20: 537-542.

71. "While the small amount of AlF in the drinking water of rats required for neurotoxic effects is surprising, perhaps even more surprising are the neurotoxic results of NaF at the dose given in the present study [1.0 ppm F]... The results of the present study indicate that more intensive neuropathological evaluations of F effects on brain may prove to be of value... In summary, chronic administration of AlF and NaF in the drinking water of rats resulted in distinct morphological alterations in the brain, including effects on neurons and cerebrovasculature." SOURCE: Varner JA, et al. (1998). Chronic administration of aluminum-fluoride and sodium-fluoride to rats in drinking water: Alterations in neuronal and cerebrovascular integrity. Brain Research 784: 284-298.

72. "These results indicate that fluoride may penetrate the blood brain barrier, interact with AChE located on cell membranes, and interfere with their physiological functions and thus induce the neurotoxicities." SOURCE: Zhao XL, Wu JH. (1998). Actions of sodium fluoride on acetylcholinesterase activities in rats. Biomedical and Environmental Sciences 11(1):1-6.

73. "The metabolism of brain phospholipid might be interfered by fluoride accumulated in brain tissue, which is related with the degeneration of neuron. The changes of brain phospholipid could be involved in the pathogenesis of chronic fluorosis." SOURCE: Guan Z, Wang Y, Xiao K. (1997). [Influence of experimental fluorosis on phospholipid content and fatty acid composition in rat brain]. Zhonghua Yi Xue Za Zhi. 77: 592-6.

74. "Neuronal abnormalities were observed in the NaF treated animals- especially in the deeper cell layers... The NaF treatment also produced distortions of cells and, in some rats, cell losses could be demonstrated in particular brain regions. Both AlF3 and NaF induced vascular inclusions, although of a different character..." SOURCE: Issacson R, et al. (1997). Toxin-induced blood vessel inclusions caused by the chronic administration of aluminum and sodium fluoride and their implications for dementia. Annals of the New York Academy of Science 825: 152-166.

75. "Coenzyme Q content of brain tissue in rats fed with fluorine-containing water decreased at early stage of fluorosis, but increased significantly at late stage. It is speculated that changes in content of coenzyme Q could correlate with changes in free radical levels induced by fluorine." children and a preliminary study of its mechanism] Hua Hsi I Ko Ta Hsueh Hsueh Pao. 25(2):188-91.

76. "The results reported here indicate that fluoride has a specific effect on the synthesis of proteins in the brain which may lead to degenerative changes in the form of ballooning degeneration of neurons, various degrees of loss of nisal substance, and changes in the purkinje cells of the cerebellar cortex. Such changes

would provide a plausible explanation for some of the diverse neruological complaints in arms and legs such as numbness, muscle spasms and pains, tenaniform convulsions, and spastic paraplegia, encountered in patients with skeletal fluorosis." SOURCE: Shashi A, et al. (1994). Effect of long-term administration of fluoride on levels of protein, free amino acids and RNA in rabbit brain. Fluoride 27: 155-159

77. "The neurotoxic effect of fluoride on lipid content of brain was assessed in rabbits during experimental fluorosis... Fluoride exerts an inhibitory effect on the free fatty acids in brain of both sexes. The relevance of these results in experimental fluorosis is discussed." SOURCE: Shashi A. (1992). Studies on alterations in brain lipid metabolism following experimental fluorosis. Fluoride 25:77-84.

Water with fluoride at 1 ppm is only part of the total fluoride exposure. Although studies often have fluoride concentrations higher than fluoridated water, many studies are within the total exposure of subpopulations in theUSA.

Those discounting studies finding harm, will suggest none are high quality randomized controlled trials. We agree there are no high quality studies of either efficacy, safety or harm and until quality studies are done, MCLG of fluoride in water should be zero.

C. Likely and Possible Harm to the Thyroid from Fluoride

1. According to the US National Research Council, *"several lines of information indicate an effect of fluoride exposure on thyroid function."*

2. Fluoride's potential to impair thyroid function is perhaps best illustrated by the fact that—up until the 1970s—European doctors used fluoride as a thyroid-suppressing medication for patients with HYPER-thyroidism (over-active thyroid). Fluoride was utilized because it was found to be effective at reducing the activity of the thyroid gland - even at doses as low as 2 mg/day.

3. Today, many people living in fluoridated communities are ingesting doses of fluoride (1.6-6.6 mg/day) that fall within the range of doses (2 to 10 mg/day) once used by doctors to reduce thyroid activity in hyperthyroid patients.

4. "**Thyroid Function Suppression** Fluoride was widely used, especially in Europe, to suppress over-active thyroid function with doses in the range of 2.3-4.5 mg/day. Exposure doses in the U.S. were estimated to be 1.6-6.6 mg/day as published in 1991. Exposures are probably higher today, with increased water fluoridation since 1991, meaning the virtual epidemic of depressed thyroid function in America might be tied to excessive fluoride exposures."

5. While it may be that the thyroid in a patient with hyperthyroidism is particularly susceptible to the anti-thyroid actions of fluoride, there is concern that current fluoride exposures may be playing a role in the widespread incidence of HYPO-thyroidism (under-active thyroid) in the U.S.

6. Hypothyrodisim, most commonly diagnosed in women over 40, is a serious condition with a diverse range of symptoms including: fatigue, depression, weight gain, hair loss, muscle pains, increased levels of

"bad" cholesterol (LDL), and heart disease.. The drug (Synthroid) used to treat hypothyroidism is now one of the top five prescribed drugs in the U.S.

7. As recommended by the US National Research Council: "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."

8. Fluoride & the Thyroid - US National Research Council (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. 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." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 223.

9. "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." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 224.

10. "several lines of information indicate an effect of fluoride exposure on thyroid function." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 197.

11. "it is difficult to predict exactly what effects on thyroid function are likely at what concentration of fluoride exposure and under what circumstances." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 197.

12. "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." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 218.

13. "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." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 218.

14. "The recent decline in iodine intake in the United States could contribute to increased toxicity of fluoride for some individuals." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 218.

15. "Intake of nutrients such as calcium and iodine often is not reported in studies of fluoride effects. The effects of fluoride on thyroid function, for

instance, might depend on whether iodine intake is low, adequate, or high, or whether dietary selenium is adequate." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 222.

16. 1854 - Maumene feeds sodium fluoride to a dog and causes a goitre to appear [also spelled goiter]. He is the first to consider fluorides as a cause of goiter. Suggests that high fluoride in water might cause endemic struma (goiter). (NOTE: The amount of fluoride given was 20 to 120 mg Na F-/day, for four months - Buergi, 1984 claims that a "cumulative dose of 10 g" was given.) Maumené E -"Experiencé pour déterminer l'action des fluores sur l'economie animale" Compt Rend Acad Sci (Paris) 39:538-539 (1854)

17. 1869 - First experiments with sodium fluoride, showing inhibitory effects on glycolysis [a thyroid hormone - associated event] in isolated muscle tissue, are published by Nasse.(see also: 1937 Litzka) Nasse O - "Beitraege zur Physiologie der contractilen Substanz" Pfluegers Archiv fuer Physiologie 2: 97-121 (1869)

18. 1917/1918 - McKay, the dentist who investigated the cause of 'mottled teeth' - later to be renamed 'dental fluorosis', writes in the "Dental Cosmos" that enamel conditions in children with 'mottled teeth' are identical to those reported by Prof. Greves in Holland as being due to thyroid dysfunction (goitre). Greves reports that when rats were given water from the Utrecht area, goitre and mottled enamel developed

19. Gautier - Bull Soc Chim 13:909 (1913), cited in: Kraft K -"Beiträge zur Biochemie des Fluors I.Über den Antagonismus zwischen Fluor und Thyroxin." Hoppe-Seglers Z.Physiol. Chem 245:58 -65 (1937)

20. 1919 -1921 - Ignorant of McKay's work, Goldemberg (Argentina) investigates the areas then commonly referred to as "goiterous waters" ('Kropfwaesser'), and reviews the work by others (Repin, Gautier, Clausmann, McCarrison, Parhou and Goldstein, Pighini, Christiani, Cahages, Houssay, Tappeiner, Schulz, Brandt and Pisotti). His findings convince him that the world-wide occurrence of goiter and cretinism is NOT due to iodine deficiency as commonly believed, but is the result of excessive fluoride intake from air, food and water. [Jod Basedow] He conducts animal experiments to test his hypothesis and reports that 2 to 3 mgs of NaF- daily for 6 to 8 months produced a 5 to 6-fold increase in the size of the thyroid gland. He calls the condition 'cretinisme fluorique'. McKay, FS - "Progress of the year in the investigation of mottled enamel with special reference to its association with artesian water" J Natl Dental Assn 5:721 (1918)

21. 1923 - Pighini causes goiters in rats, dogs and chicken by giving them fluoridated water from a goiterous area. When sodium fluoride was administered, the same histological changes in the thyroid were seen as are produced in endemic goitre. Pighini G -"Il gozzo endemico e la sua etiologia in funzionie disfunzionitiroidee" Publicato per cura dell'Institute Sieroterapico, Milano p.41 (1923), also cited in Roholm K - "Fluoride Intoxication, London, C.K. Clarke and Co, (1937) (F- inhibits thyroid function/cause of goiter.)

22. 1926 - Goldemberg is the first to take medical advantage of the now much-observed iodine-fluoride antagonism. He deliberates that, because fluoride was the reason behind iodine deficiency/goitre areas, it would therefore also reduce the high iodine levels in Basedow patients and begins to use fluorides to effectively cure Basedow's disease - hyperthyroidism caused by excessive iodine consumption. Goldemberg publishes extensively between 1921 and 1935 on his findings of applying fluorides as anti-thyroid medication. Goldemberg L -"Action physiologique des fluorures" Compt Rend Soc Physiol (Paris) 95:1169 (1926); Goldemberg L - La Semana Med 28:628 (1921) - also cited in Wilson RH, DeEds F - "The Synergistic Action Of Thyroid

On Fluoride Toxicity" Endocrinology 26:851 (1940) Goldemberg L - Compt Rend Soc Biol (Paris) 104:1031 (1930)

23. 1927 - Gorlitzer von Mundy (Austria) reports that daily intake of 3 mgs of fluoride in rabbits and rats leads to goiter and cretinism-like conditions. Gorlitzer von Mundy V - J. Physiol.et Path gen 25:1 (1927) (3 mg NaF- fluoride intake in rabbits and rats results in goiter and cretinism-like conditions)

24. 1930 - Christiani publishes on the changes in thyroid function from fluoride injections.

[Earlier, in 1925, Christiani and Gautier became the first to use the term 'fluorosis'. They called it "La Fluorose" and "Cachexie fluorique", using these terms to describe "fluoride intoxication" (not yet described as "dental fluorosis"...), as induced by fluoride emissions from a Swiss aluminum smelter. LINK] Cristiani H - "Alteration de la glande thyroide dans l'intoxication fluoree" Compt Rend Soc Biol 103:554-556 (1930)

25. 1932 - Gorlitzer von Mundy (Austria) publishes findings on 1500 experiments using fluoride to inhibit thyroid function in mice and metamorphosis in tadpoles.

26. NOTE: As it had been shown that metamorphosis in tadpoles was regulated by thyroid hormones, one had to show inhibition of metamorphosis to satisfy claims that a medication was an "anti-thyroid". This test was known as the "Gudernatsche Tadpole Test".

i. Gorlitzer von Mundy V - Arch f. exper.Path 165 (1932)

27. Gorlitzer von Mundy V - "Die Beinflussung des Stoffwechsels durch die Halogenwasserstoffsäuren im Tierexperiment, mit besonderer Berücksichtigung der Fluorwasserstoffsäure" Arch Exp Pathol 165:443- 461 (1932)

28. (describes his 1500 investigations on fluoride use in inhibition of metamorphosis in tadpoles, mice experiments, etc., many pictures)

i. Gorlitzer von Mundy V - "Ein neuer Weg zur Behandlung der Thyreotoxikose mit Fluorwasserstoffsäure" Med Klin 21:&17-719(1932)

29. (reports on the first successful use of baths containing HF in the treatment of hyperthyroidism) Gorlitzer von Mundy V - Wien Klin Wschr 48 (1933)

30. Gorlitzer von Mundy V - Med. Klin.47:911 (1952), cited in Gorlitzer von Mundy, V - "Einfluss von Fluor und Jod auf den Stoffwechsel, insbesondere auf die Schilddrüse" Münch Med Wochensschr 105:182-186 (1963)

31. Gorlitzer von Mundy, V - "Einfluss von Fluor und Jod auf den Stoffwechsel, insbesondere auf die Schilddrüse" Münch Med Wochensschr 105:182-186 (1963);

32. also in Gordonoff, T. - Fluor und die Schilddrüse, Toxikology des Fluors Basel/Stuttgart, pp.111-123(1964)

33. 1932 - Machoro (Italy) uses sodium fluoride in the successful treatment of hyperthyroidism. Machioro - Riforma Med p.1436 (1932); Ref. Zbl.68, p.515 (1932); also cited in Purjesz et al, 1931

34. 1932 - Wilhelm May (Germany) also starts fluoride therapy in the treatment of hyperthyroidism, using calcium fluoride tablets, topical ointments, etc. May W - "Antagonismus zwischen Jod und Fluor im Organismus" Klin Wochenschr 14:790-792 (1935)

35. Orlowski W- "Sur la valeur therapeutique du sang animal du bore et du fluor dans la maladie de Basedow" La Presse Medicale 42:836-837 (1932)

36. Phillips PH - “The manifestations of scurvy-like symptoms induced by ingestion of sodium fluoride”J Biol Chem 100:29 (1933)

37. 1934 - Purjesz and colleagues (Poland) give chicken eggs high in fluoride to hyperthyroid patients and achieve lowering of body temperature, of pulse and BMR, as well as weight gain; report that most of the fluoride is found in liver; no fluoride is found in the blood of healthy people. Purjesz B, Berkessy L, Gönczi K, Kovacs-Oskolas M - “Über die biologische Speicherung der halogenen Elemente in Hühnereiern und im tierischen Organismus” Arch Exp Pathol Pharmakol 176:578-582 (1934) (describes accumulation of fluoride in chicken eggs; gave such eggs to Basedow patients and achieved lowering of body temperature, pulse and BMR, as well as weight gain; found that most of the fluoride was found in liver; found NO fluoride in the blood of healthy people -> 1934)

38. 1934 - Chang, Phillips, et al. report that in the thyroid of cows fed fluoride for a long time, the fluoride content increased to 240 times as much. [Note: in the original text it states 24 times, however, Dr. Phillips later corrected the text figures in a communication with Wilson & DeEds -> see: 1940] Chang CY, Phillips PH, Hart EB, Bostedt G - J Dairy Sci 17:695 (1934)

39. Phillips PH, Lamb AR -“”Histology of certain organs and teeth in chronic toxicosis due to fluorine” Arch Path 17:169 (1934)

40. 1935 - Phillips et al. (USA) report that fluoride and thyroid have synergistic effects on fluorosis in chicken.

41. 1935 - Phillips et al. conduct studies in rats and find the same results: fluoride and thyroid have synergistic toxic effects. Phillips PH, English HE, Hart EB - “The influence of sodium fluoride upon the basal metabolism of the rat under several experimental conditions” Am J Physiol 113:441-449 (1935) [First evidence that fluoride mimicks TSH. Also, when 5.2mg of NaF (2.34 F-) was added to diet of rats fed desiccated thyroid, effects were dramatically potentiated leading to rapid weight loss and death: F- and thyroid have synergistic effects...]

42. Phillips PH, English H, Hart NB -“The augmentation of fluorosis in the chick by feeding desiccated thyroid” J Nutrition 10:399 (1935), cited in:Harris NO, Hayes RL -“A tracer study of the effects of acute and chronic exposure to sodium fluoride on the thyroid iodine metabolism of rats” J Dent Res 34:470-477 (1955) (F- and thyroid have synergistic effects)

43. Phillips PH - “Further studies on the effects of NaF administration upon the basal metabolic rate of experimental animals” Am J Physiol 117:155-159(1936) (F- and thyroid have synergistic effects)

44. 1936 - Phillips conducts further animal experiments and verifies the 1935 findings. Phillips PH, Edens RJ - “Fluorgehalt d. Schilddrüse in Fällen von Hyperthyreoase” Madison Diskussion, Biblioth.d Forsch. Knoll (in May, 1950)

45. 1937 - Litzka (Germany) discusses the mode of action of fluorides in treating patients with hyperthyroidism: fluoride antagonizes thyroid hormone effects/glycolysis in liver and influences glycolysis in skeletal muscle. Litzka G - “Die experimentellen Grundlagen der Behandlung des Morbus Basedow und der Hyperthyreose mittels Fluortyrosin” Med Wochenschr 63:1037-1040 (1937)

46. (discusses the basis of the use of fluorides in anti-thyroid medication, documents activity on liver, skeletal muscle, inhibition of glycolysis, etc.) Litzka G - “Erfolgskontrolle bei Behandlung der Schilddrüsenüberfunktion” Z. klin. Med.131:791-799 (1937); Litzka G - “Die antithyreotoxische Wirkung des Fluortyrosins” Arch. exp. Pathol. u. Pharmakol. 183:436-458 (1936); Litzka G -“Fluortyrosine” Klin Wochenschr. 15:1568-1569 (1936)

47. 1937 - Wilhelm May reports further on his fluoride therapy,

including the use of sodium fluoride ointments (up to one year-therapy), and Fluorotyrosin (6 to 8 - week therapy). Also reports on findings that two other common medications given in the treatment of hyperthyroidism - Solvitren and Tyronorman - had been found to contain fluoride, in fact double the amount used in Fluorotyrosin. Further May reports that the traditional areas where people had been sent for “natural therapy” (‘Kur’) were found to contain higher amounts of fluoride in the water. May W - “Eine neue interne Behandlung der Hyperthyreosen einschließlich des Morbus Basedow” Diskussionsvortrag, Verhandlungen der Deutschen Gesellschaft für innere Medizin, 49.Kongress, Wiesbaden, March 15-18, 1937, München(1937); May W, Schwartz E - Fortschr Med 28:9 (1932); also cited in: Kraft K -“Beiträge zur Biochemie des Fluors I. Über den Antagonismus zwischen Fluor und Thyroxin” Hoppe-Seglers Z.Physiol. Chem 245:58 -65 (1937)

48. May W - “Behandlung the Hyperthyreosen einschliesslich des schweren genuinen Morbus Basedow mit Fluor” Klin Wochenschr 16:562-564 (1937)

49. May W - “Eine neue interne Behandlung der Hyperthyreosen einschliesslich des Morbus Basedow” Verhandlungen der Deutschen Gesellschaft fuer Innere Medizin, 49. Kongress, Wiesbaden March 15 - 18, 1937, publ. Munich (1937)

50. 1937 - Kraft (Knoll AG, Germany) investigates inorganic sodium fluoride and organic fluoride compounds fluorobenzoic acid and fluorotyrosine and reports that all fluoride compounds inhibit thyroid hormones. It is a matter of amplification - the fluoride component is essential. Kraft K - “Beiträge zur Biochemie des Fluors I.Über den Antagonismus zwischen Fluor und Thyroxin.” Hoppe-Seglers Z.Physiol. Chem 245:58 -65 (1937)

51. 1939 - Steyn (South Africa) first reports on his findings of fluoride-induced goiter. Steyn DG - “Water poisoning in man and animal, together with a discussion on urinary calculi” Onderstepoort J Vet Sci Animal Ind 12:167-230 (1939)

52. 1939 - May H, Litzka G - “Über die Hemmung des Tumorwachstums durch Fluortyrosine” Z. Krebsforschung 48:376 - 382 (1939)

53. 1940 - Wilson and DeEds (USA) report dental fluorosis in rats as a result of the synergistic action of fluoride and thyroid hormones. Results are described as “strikingly clearcut”. Wilson RH, DeEds F -“The Synergistic Action Of Thyroid On Fluoride Toxicity” Endocrinology 26:851 (1940).

54. May R - “Untersuchungen über den Fluorgehalt des Trinkwasseres in bayerischen Kropfgebieten verschiedener Endemiestärke” Z. Ges. Exp. Med 107:450 (1940)

55. 1941 - Wilson (UK) reports in the Lancet on his findings that mottling of teeth is prevalent in the same areas in the UK which had previously been prevalent with goitre. Wilson DC -“Fluorine in aetiology of endemic goitre” Lancet I:211-213 (1941)

56. 1941 - Schwarz (Germany) prepares fluoride/iodide anti-thyroid medications and combines with sedatives. Schwarz - Med. Klin. 5 (1941);cited in May, 1950

57. 1942 - Euler & Eichler (Germany) report that the chronic administration of organic fluoride compounds (fluorotyrosine) cause the same defects in bone as inorganic fluorides, although no dissociation takes place, ascribing effects to the whole molecule.

58. 1942 - Euler & Eichler further report that the chronic administration of organic fluoride compounds cause the same defects in teeth as inorganic fluorides. Identical crystal formation is seen, although no soluble (free) fluoride is observed, leading the authors to the conclusion that such crystals declared by others to contain “calcium fluoride” [see: fluoroapatite] could not be such. The organic compounds did not

dissolve. Euler H, Eichler - “Ueber die Wirkung von Fluor in organischer Binding auf das Zahnsystem der Ratte” Arch exper Path 199:179-187 (1942); also Dtsch Zahn Hk 9(1) (1942)

59. May W - “Die Behandlung der Hyperthyeosen mit Fluortyrosine” Deutsch Med Wochenschr 68:164 (1942)

60. 1944 - The editorial in the Journal of the American Dental Association (JADA) acknowledges that “...drinking water containing as little as 1.2 to 3ppm of fluorine will cause such developmental disturbances...as goitre”. Hatfield JD, Shrewsbury CL, Andrews FN, Doyle LP - “Iodine-fluorine relationship in sheep nutrition” J Anim Sci 3:71-77 (1944)

61. 1946 - The Atomic Energy Commission (Department of Pharmacology & Toxicology - headed by Harold Carpenter Hodge, incomprehensibly at the same time also head of the International Association for Dental Research (IADR) - acknowledges the German findings that all fluoride compounds - organic or inorganic - inhibit thyroid hormone activity, and declares this issue a research priority. No further research into this issue is conducted, however.

62. 1947 - Casterra uses Knoll’s “K17”, later to be renamed “Capacin”, in the successful treatment of 500 hyperthyroid patients. Casterra H - “Erfahrungen mit einem neuen organischen Fluorpräparat bei Hyperthyreosen” Das Deutsche Gesundheitswesen 2(22):704-705 (1947)
(describes use of Knoll’s “K 17” - later named Capacin - in successful treatment of over 500 hyperthyroid patients. K 17 => 3-fluoro-4-hydroxyphenylacetic acid)

63. 1948 - Steyn (Africa) finds that fluoride has definite anti-thyroid effects. He investigates the incidence of endemic goiter in the North Western Cape Province in South Africa and reports that his findings “closely agree with the ... 1944 JADA editorial”, and that goiters are actually ‘fluoride-induced’. Steyn DG - “Fluoride and endemic goitre” S Afr Med J 22:525-526 (1948)

64. 1949 - Richard May reports on the highly successful use of the organic fluoride compounds Pardinon (IG Farben) and Capacin (Knoll AG) in the treatment of hyperthyroidism. Up until 1943, 10,000 patients had been cured. May Richard - “Erfahrungen in der Behandlung von Hyperthyreose- und Basedow-Kranken mit einer organischen Fluorverbindung (Fluoroxyphenylessigsäure, ‘Capacin’)” Deutsche Med. Wochenschr.74(12):374-375 (1949)

65. 1949 - Euler et al. test various organic fluoride compounds and find again that all organic fluoride compounds inhibit thyroid hormone activity. Euler H, Eichler O, Hindemith H - “Über die Wirkung einiger organischer Fluoride bei chronischer Darreichung” Arch exp. Path u Pharmakol. Bd.206:75-82 (1949), also cited in: Steyn DG - The problem of dental caries and the fluoridation of public water supplies - Johannisburg (1958)
(All organic fluoride compounds inhibit thyroid function, all compounds act on glycogen/liver - activity only differentiated by amplitude)

66. 1950 - Wilhelm May publishes monograph on the fluoride-iodine antagonism, including over 300 references, detailing the known biochemical findings. [Originally slated for publication in 1944, the lack of paper in Germany prohibits publication until 6 years later.] May W - “Die Basedowsche Krankheit” Aulendorf (1950)

67. 1950 - Richard May reports that between 1935 and 1947 over 5000 hyperthyroid patients had been treated successfully with Pardinon and Capacin in the May clinic alone. May R -“Therapie mit organischen Fluorverbindungen” Med Wochenschr 4:489-490 (1950)

68. 1951 - Kraft K - “Über die Synthese einiger aromatischer Fluorverbindungen” Knoll Research, Chem Ber. 84(2):150-156 (1951)

(describes manufacturing processes of numerous organic fluorides, after it was shown that all organic fluoride compounds displayed stronger anti-thyroid activity than the fluoride ion)

69. May Wilhelm - “Fluor als Therapeuticum” Arzneimittel Forschung 1:33-37 (1951) (Review on fluoride as a therapeutic agent...discusses fluoride Goldemberg’s 1926 use in treatment of whooping cough (-> Pertussin - G(i) proteins), Goldemberg’s prioneering work in 1928 in the treatment of hyperthyroidism, etc..., as well as his son’s - Richard May - decision in 1949 to recommened use of fluoride compounds as an anti-caries prophylaxis...discusses fluoroform as whooping cough (pertussis) medication, difluorophenyl compounds as wound-disinfectants such as “Epidermin”, another fluorophenyl compound called “Fluor-rheumin” against rheumatism, etc.)

70. 1952 - Kraft and Dengel (Germany) investigate yet more fluorophenyl-derived fluoride compounds, all of which lower BMR. Kraft K, Dengel F - “Über die Synthese einiger aromatischer Fluorverbindungen, II. Mitteilung” Chem Ber 85(6):577-582 (1952) (more reports on fluorophenyl/organic fluoride investigations...”in regards to their characteristics in lowering BMR...”)

71. 1952 - Reynolds Metals Corp vs Paul Martin hypothyroidism caused by fluoride is documented. Reynolds Metals Corp vs. Paul Martin et al - Transcript of Record. US Court of Appeals, Ninth District, Nos.14990-14992 (1952) (Court case: Family of three residing near aluminum smelter in Troutdale, Oregon. Litigation of this case revealed muscular pains, general fatigue, arthritis in conjunction with liver and kidney damage, and hypothyroidism.)

72. Gordonoff T, Minder W - “Caries prophylaxis with fluorine as a physiological problem” Schweiz Med Wochenschr. 82:972-973 (1952)

73. 1953 - Wadwhani (India) reports that fluoride concentrated in thyroid gland of rats consuming 0.9mg F- per day. Wadhwani TK -“Metabolism of Fluoride. Absorption, retention, distribution and elimination of fluorine and its effect on the Vitamin C content of different tissues, and on the iodine content of thyroids of rats and monkeys” J Indian Inst Sci (35)354-362 (1953) Fluoride concentrated in thyroid gland of rats consuming 0.9mg F- per day

74. 1954 - Wespi (Italy) reports mottled teeth (‘dental fluorosis’) together with goitre in Italy. Wespi HJ - “Besteht ein Antagonismus zwischen Fluor und Jod?” Praxis 43:616-623 (1954) (Wespi reports both dental fluorosis and goitre in the same patients in Campagnano di Roma and Casamicciola...)

75. 1954 - Jentzer (Switzerland) reports that less than normal amounts of thyroid hormone are deposited in the pituitary gland when rabbits are given fluoride in water - at levels corresponding to that of artificially fluoridated water. Jentzer A -“Action du fluor sur le relais thyroidenhypophysaire demontree par l’iode 131” Bull Schweiz Akad Med Wiss 10:211-220 (1954)
(Less than normal amounts of thyroid hormone are deposited in the pituitary gland when rabbits are given fluoride in water at levels corresponding to that of artificially fluoridated water)

76. 1955 - Benagiano & Fiorentini (Italy) describe the effects of fluoride on thyroid function. They find that the farther away from the toxic dose, the longer it takes for fluoride to cause thyroid changes. (This in accord with May (1950), who found that although it might take months - “sometimes even a year” - even low fluoride amounts would always be successful in lowering iodine levels...May urged the practioner to be patient...) Benagiano A, Fiorentini S -“Richerche sperimentali e cliniche sui rapporrti tra fluore e tirodi” Annali di Stomatol 4:3-16(1955)

77. 1955 - Korrodi, Wegmann, Galetti and Held also verify a fluoride -

iodine antagonism, presuming that the fluoride ion pushes out the iodine in the thyroid gland. Steyn DG, Kieser J, Odendaal WA, Malherbe MA, Synan HW, Sunkel W, Naude CP, Klintworth H, Fisher E - "Endemic goitre in the Union of South Africa and some neighbouring territories" Pretoria:Union of South Africa, Department of Nutrition (March 1955)

78. 1957 - Galetti et al. treat hyperthyroid patients with fluoride at daily doses lower than those estimated being the current average intake in the US, and document a significant reduction in protein-bound iodine, as well as an overall reduction of iodine and a reduction of iodine uptake by the thyroid gland. Galletti PM, Joyet G - "Effect of fluoride on thyroidal iodine metabolism in hyperthyroidism" J Clin Endocrinol 18:1102-1110 (1958)

79. Gordonoff T - "Zum Fluorproblem" Osterr Z Stomatol 54:561:571 (1957)

80. 1959 - Jentzer again shows reduced iodine levels in the pituitary gland under the influence of fluorides. Jentzer, A - "Effet du fluor et du fluor-iod sur la teneur en iode de la thyroide de lapin" Bull Schweiz Akad Med Wiss 15:412-422 (1959). (In rabbits fed 0.05mg F- per day [!] iodine content in thyroid was reduced by 25%. Also showed that the iodine uptake in the pituitary gland was greatly reduced under the influence of fluoride)

81. Steyn DG - "The problem of dental caries and the fluoridation of public water supplies" Johannisburg (1958)

82. 1960 - Gordinoff and Minder describe the results of experiments with radioactive iodine (I131) which show that fluorides remove an iodine atom during the conversion process (T4 to T3). Effects are dose-responsive, meaning the higher the fluoride intake the lower the iodine measurements. Gordonoff T, Minder W - "Fluoride and the thyroid gland" in "World Review of Nutrition and Dietetics" Pitman Medical Co, Vol 2:234-247 (1960)

83. 1959/1960 - Anbar et al (Israel) report in Nature and other journals that fluoroborates and other fluoride compounds inhibit thyroid hormone transport and concentrate in the thyroid gland. [BTW: The first fluoroborate 'safety document' appeared in 1932!] Anbar M, Guttman S, Lewitus Z -" Effect of monofluorosulphanate, difluorophosphate, and F borate ions on the iodine uptake of the thyroid gland" Nature 183:1517 (1959); Anbar M, Guttman S, Lewitus Z- "The accumulation of fluoroborate ions in thyroid glands of rats" Endocrinology 66:888 (1960)(-> fluoroborate concentrates in thyroid gland, inhibits iodide transport.

84. 1962 - Steyn (Africa) reports that drinking water containing "as little as 1 to 2 ppm of fluorine can cause serious disturbances of general health and especially in normal thyroid gland function and in the normal processes of calcium-phosphate metabolism (parathyroid function)."

85. 1962 - Spira reports on the fluorine-induced endocrine disturbances in mental illness. Spira L - "Fluorine-induced endocrine disturbances in mental illness" Folia Psychiat Neurol Jap 16:4-14 (1962) NLM CIT. ID: 62182027

86. 1963 - Gorlitzer von Mundy reports on the [then] current knowledge gained from experiments by Gordonoff with I131 as to how the effects of the enzyme responsible for the T4 to T3 conversion were inhibited if a fluorine ion was absorbed before the conversion from T4 to T3 occurs.

87. Gedalia I, Brand N -"The relationship of fluoride and iodine in drinking water in the occurrence of goiter" Arch Int Pharmacodyn 142:312-5 (1963)

88. 1964 - Ritzel reports on disturbances in T4 metabolism in areas with fluoridated drinking water. Ritzel G - "Thyroxinstoffwechsel und Trinkwasser-fluoridierung" Int Z Vitaminforsch 34:422-426 (1964)

89. Gordonoff T (Ed) - “Fluor und die Schilddrüse”, Toxikology des Fluors (Toxicology of fluorine) Symposium, Ber, Oct.15-17 1962, Schwabe Verlag, Basel/Stuttgart, pp.111-123 (1964)

90. 1964 - Steyn (Africa) - again - reviews the “overwhelming evidence” on the fluoride-iodine antagonism. (Steyn, Maumene, Euler et al., Wadwhani, Wadwhani and Ramaswamy, Chang et al., Littich, Benagiano and Fiorentini, Fiorentini, Feltman, De Eds, Baume and Becks, Orban, Spira, Galetti et al., Gordonoff and Minder, Wilson, Wespi, Goldemberg, Todd, Coton, Gorlitzer, May, Hodenberg, Korrodi et al., Christiani, Jentzer, Grab and Overdisse) Steyn DG - “Chronic fluorine poisoning caused by the drinking of subterranean waters containing excessive quantities of fluorine” in: Gordonoff, T. - Fluor und die Schilddrüse, Toxikology des Fluors Basel/Stuttgart (1964)

91. Steyn DG - “Once More - Fluoridation” Review Chief Research Officer, Division of Life Sciences, Atomic Energy Board, Pretoria, Republic of South Africa, (Emeritus Professor of Pharmacology, University of Pretoria) University of Pretoria NUWE REEKS No.24 (1964)

92. 1964 - Steyn reports on his detailed 1949-1950 experiments on young rats, conducted to determine if there was in fact a fluoride-iodine antagonism. The experiment, which ran for 12 months, showed that the more severe the teeth were mottled, the more severe the thyroid dysfunction. It further showed that iodine supplementation was not likely to prevent the endemic goiter caused by excessive fluoride in drinking water, and that fluoride intake needed to be reduced.

93. Pastan I, Macchia V, Katzen R - “Effect of fluoride on metabolic activity of thyroid slices” Endocrinology 83(1):157-60 (1968)

94. 1969 - Rodesch et al. and Zor et al. independently report that fluoride mimicks TSH. Rodesch F, Neve, P, Willems C, Dumont JE - “Stimulation of thyroid metabolism by thyrotropin, cyclic 3’,5’-AMP, dibutyryl cyclic 3’,5’-AMP and prostaglandin E1” Eur J Biochem 8(1):26-32 (1969)

95. 1969 - Siddiqui show small visible goiters in persons 14 to 17 years of age in India to be connected directly to high fluoride concentrations in drinking water. Siddiqui AH - “Incidence of Simple Goiter in Areas of Endemic Fluorosis in Nalgonda District, Andhra Pradesh, India” Fluoride 2 (4):Pages 192 - 249 (1969)

96. Zor U, Kaneko T, Lowe IP, Bloom G, Field JB - “Effect of thyroid-stimulating hormone and prostaglandins on thyroid adenyl cyclaseactivation and cyclic adenosin 3’-5’-monophosphate.” J Biol Chem 244(19):5189-95. (1969)

97. 1970 - Ahn and Rosenberg confirm that fluoride mimicks TSH. Ahn CS, Rosenberg IN - “Iodine metabolism in thyroid slices - effects of TSH, dibutyril cyclic 3’,5’-AMP, NaF and prostaglandin E1” Endocrinology 86(2):396-405 (1970)

98. 1970 - Burke documents that TSH and fluoride have additive effects. Burke G - “Comparison of thyrotropin and sodium fluoride effects on thyroid adenyl cyclase” Endocrinology 86(2):346-52 (1970)

99. 1971 - Narbutt et al. show that in rats fed sodium fluoride at 0.1 and 1 mg/day there is an increase in the thyroid weights after 4 weeks, irrespective of dosage. Narbutt recommends iodine administration during fluoride prophylaxis. Narbutt B, Romer TE, Grabski J, Szymik N - “Influence of natrium fluoride on the structure of the rat thyroid” Endocrynol Pol 22 (5):445-451 (1971)

100. 1972 - Willems et al. document that sodium fluoride blocks thyroid hormone secretion. Willems C, Van Sande J, Dumont JE- “Inhibition Of Thyroid Secretion By Sodium Fluoride (In Vitro)” Biochimica Et Biophysica Acta 264:197-204 (1972)

101. 1972 - Day and Powell-Jackson study 648 people in 13 mountainous regions in Nepal where the iodine content in the water is low and find a

close relationship between fluoride intake and the incidence of goiter. Day TK, Powell-Jackson PR -"Fluoride, Water Hardness, and Endemic Goitre" Lancet 1:1135-1138 (1972)

102. 1976 - Polish researchers Bobek and Kahl document that rats consuming fluoride in water at 0.1 to 1 mg/day have significantly lowered T4, T3, and free thyroxine index in plasma. They ascribe this to an inhibition of thyroid hormone transport by fluoride. Bobek S, Kahl S, Ewy Z - "Effect Of Long Term Fluoride Administration on Thyroid Hormone Levels In Rats" Endocrinol Exp (Bratisl)10:289-295 (1976)

103. 1976 - Aliev finds that goiter, caries and fluorosis are correlated in Azerbaijan. Aliev Yu M - "Some biogeochemical characteristics of the environment in Azerbaijan, USSR" Gig Sanit (8):103-104 (1976)

104. 1976 - Orgiazzi et al. use fluoride as TSH analogue in assessing "cold nodules". Orgiazzi J, Chopra IJ, Solomon DH, Williams DE - "Comparison of the effect of TSH and fluoride on the adenylate cyclase activity of cold thyroid nodules" Ann Endocrinol (Paris) 37(2):107-8 (1976)

105. Tokar' VI, Savchenko ON - "Effect of inorganic fluorine compounds on the functional state of the pituitary-testis system" Probl Endokrinol (Mosk) 23(4):104-7 (1977)

106. 1978 - In German thyroid medications like "Druesensalbe Fides", "Strumadragees Fides" and "Strumetten" still list calcium fluoride and hydrogen fluoride as active ingredients, and are listed in the 1978 index of the German Federal Association of the Pharmaceutical Industry. ("Schilddruesentherapeutika" in "Rote Liste", Bundesverband der Pharmazeutischen Industrie, e.V., Frankfurt, Germany)

107. 1978 - Maccia et al. use fluoride as TSH analogue (hyperplastic thyroid, hyperfunctioning follicular carcinoma, "cold" nodules). Macchia V, Mandato E, Carella C, Pisano G, Biscaglia G - "The adenylate cyclase-cyclic cAMP-phosphodiesterase system in pathological human thyroid" J Endocrinol Invest 1(4):337-45 (1978)

108. 1978 - Kalderon & Sheth use fluoride as TSH analogue ("cold" nodules). Kalderon AE, Sheth V - "Secretion and adenylate cyclase in thyroid nodules" Arch Pathol Lab Med 102(7):381-86 (1978)

109. 1978 - George Waldbott writes that in most cases of poisoning from fluoridated water in which he had occasion to study the action of the thyroid gland, it's function was low. He cites a case of a 33-year-old male who exhibited typical manifestations of pre-skeletal fluorosis and a basal metabolism rate of -22, indicative of hypothyroidism. Within three months after the man ceased consuming fluoridated water, the thyroid function had returned to normal (BMR=0). In addition, Waldbott writes that "simultaneously, other symptoms associated with low grade fluoride poisoning - including excessive thirst, headaches, blurred vision, arthritis in shoulders, elbows, knees, and gastrointestinal disturbances - also disappeared." [He did not know that the symptoms he ascribed to "low-grade fluoride poisoning" would likewise be considered symptoms of hypothyroidism some 20 years later.] Waldbott, GL; Burgstahler, AW; McKinney, HL - "Fluoridation:The Great Dilemma" Coronado Press (1978)

110. 1979 - Toccafondi et al. use fluoride as TSH analogue in assessing hyperfunctioning nodules (thyroid toxic adenoma). Toccafondi RS, Rotella CM, Tanini A, Fani P, Arcangeli P - "Thyrotrophin-responsive adenylate cyclase activity in thyroid toxic adenoma" Acta Endocrinol (Copenh) 92(4):658-68 (1979)

111. 1979 - Walinder et al. use fluoride as TSH analogue to activate human thyroid tumors (nodules). Walinder O, Karlsson FA, Dahlberg PA - "Adenyl cyclase activity in human thyroid plasma membranes from normal human thyroid tissue

and thyroid adenomas" Acta Endocrinol (Copenh) 92(1):95-104 (1979)

112. 1979 - Hillman et al. find that cattle afflicted with fluorosis develop hypothyroidism.(Fluorosis here caused by mineral supplements.) Hillman D, Bolenbaugh DL, Convey EM - "Hypothyroidism and anemia related to fluoride in dairy cattle" J Dairy Sci 62(3):416-23 (1979)

113. 1982 - Mizukami et al. use fluoride as TSH analogue (adenomatous goiter). Mizukami Y, Matsubara F, Matsukawa S - "Localization of adenylate cyclase and 5'-nucleotidase activities in human thyroid follicular cells" Histochemistry 74(1):9-19(1982)

114. 1983 - Sidora et al. find iodine deficiency and "adaptive amplification of the hypophyseal-thyroid system, not ensuring an absolute compensation in the citizens using drinking water with an 'enhanced' fluorine content as compared to a 'decreased' one, accompanied by an augmented incidence of functional disturbance". Sidora VD, Shliakhta AI, Iugov VK, Kas'ianenko AS, Piatenko VG - "Indices of the pituitary-thyroid system in residents of cities with various fluorine concentrations in drinking water" Probl Endokrinol (Mosk) 29(4):32-5 (1983)

115. Jonderko G, Kita K, Pietrzak J, Primus-Slowinska B, Ruranska B, Zylka-Wloszczyk M, Straszecka J - "Effect of subchronic sodium fluoride poisoning on the thyroid gland of rabbits with normal and increased supply of iodine" Endokrynol Pol 34(3):195-203 (1983)

116. 1983 - Desai et al.(India) report increased incidence of goiter in endemic fluorosis areas. Desai VK, Saxena DK, Bharsar BS, Kantharia SL - "Health survey of residents of villages surrounding fluoride mines in relation to their drinking water fluoride level" Abstracts, 13th Conference ISFR, New Delhi (1983)

117. 1985 - Bachinskii et al. document how fluorides at 2.3 ppm in water cause tension of function of the pituitary-thyroid system that is expressed in TSH-elevated production, a decrease in the T3 concentration [both sure-tell diagnostic signs of hypothyroidism] and more intense absorption of radioactive iodine by the thyroid [as in iodine deficiency]. The results lead to a conclusion that excess of fluorine in drinking water was a risk factor of more rapid development of thyroid pathology. 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. (See abstract I See study) Bachinskii PP, Gutsalenko OA, Naryzhniuk ND, Sidora VD, Shliakhta AI - "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 (1985) (-> reduced T3, increased TSH and I131 uptake)

118. Yu YN. (1985). [Effects of chronic fluorosis on the thyroid gland]. Zhonghua Yi Xue Za Zhi. 65(12):747-9.

119. 1985 - Clark and Gerend use fluoride as TSH analogue in human thyroid cancers. Clark OH, Gerend PL - "Thyrotropin regulation of adenylate cyclase activity in human thyroid neoplasms" Surgery 97(5):539-46 (1985)

120. Monti M, Hedner P, Ikomi-Kumm J, Valdemarsson S - "Erythrocyte metabolism in hyperthyroidism: a microcalorimetric study on changes in the Embden-Meyerhof and the hexose monophosphate pathways" Acta Endocrinol (Copenh) 115(1):87-90(1987)

121. Shashi A. (1988). Biochemical effects of fluoride on thyroid gland during experimental fluorosis. Fluoride 21: 127-130. (See abstract)

122. 1988 - Zhao publishes first results of investigations into mutual interactive effects of fluoride and iodine in goitre and dental fluorosis. Zhao WY -"A preliminary study of the interaction of iodide and fluoride in experimental iodide-goiter and fluorosis" Chung Hua Yu Fang I Hsueh Tsa Chih 22(3):146-8 (1988)

123. 1988 - Guan et al. report on synergistic effects of iodine deficiency and fluoride excess in rat thyroid. Guan ZZ, Zhuang ZJ, Yang PS, Pan S - "Synergistic action of iodine-deficiency and fluorine-intoxication on rat thyroid" Chin Med J (Engl) 101(9):679-84 (1988)

124. 1989 - Tokar' and others in a study on workers exposed to fluorides write that "changes in the pituitary-thyroid axis are caused by disorders of the regulatory chain and fluorine impact on thyroid hormones' metabolism at the level of target cells". (-> G-proteins) Tokar VI, et al. (1989). [Chronic effects of fluorides on the pituitary-thyroid system in industrial workers]. Gig Tr Prof Zabol (9):19-22. (See abstract) Tokar' VI, Voroshnin VV, Sherbakov SV - "Chronic effects of fluorides on the pituitary-thyroid system in industrial workers" Gig Tr Prof Zabol (9):19-22 (1989)

125. 1989 - Ren et al. report more findings on the devastating effects on IQ of fluoride in low iodine areas. Ren DL, Liu Y, An Q - "An investigation of intelligence development of children aged 8-14 years in high-fluoride and low-iodine areas." Chinese J of Control of Endemic Diseases 4:251-254 (1989)

126. 1991 - Lin Fa-Fu et al. report that a low iodine intake coupled with "high" (0.88ppm) fluoride intake excaberates the central nervous lesions and the somatic developmental disturbance of iodine deficiency. The authors considered the possibility that "excess" fluoride ion affected normal de-iodination. Fluorides caused increase of reverse T3 (rT3) and elevated TSH levels, as well as increased I131 uptake (see: Bachinskii et al, 1985). Lin Fa-Fu, Aihaiti, Zhao Hong-Xin, Lin Jin, Jiang Ji-Yong, Maimaiti, and Aiken - "The Relationship of a Low-Iodine and High-Fluoride Environment to Subclinical Cretinism in Xinjiang" ICCIDD Newsletter, Volume 7 Number 3 August (1991)
http://64.177.90.157/science/html/lin_fa-fu.html

127. 1991 - Delemer et al. show that fluoroaluminate (AlF4-) and TSH have additive effects. Delemer B, Dib K, Saunier B, Haye B, Jacquemin C, Correze C - "Alteration of the functional activity of Gs protein in thyrotropin-desensitized pig thyroid cells" Mol Cell Endocrinol 75(2):123-31 (1991)

128. 1993 - Brtko et al. find that fluoride inhibits binding of 125I-T3 to its receptor in rat liver nuclei. Brtko J, Knopp J, Baker ME - "Inhibition of 3,5,3'-triiodothyronine binding to its receptor in rat liver by protease inhibitors and substrates" Mol Cell Endocrinol 93(1):81-6 (1993)

129. 1993 - Desai et al. investigate 22,276 people in India and find dental fluorosis and goitre significantly and positively correlated. Desai VK, Solanki DM, Bansal RK "Epidemiological study of goitre in endemic fluorosis district of Gujarat" Fluoride 26(3):187-190 (1993)

130. 1994 - Tezelmann et al. report that fluoride, by increasing the intracellular cAMP concentration, causes desensitization of the thyroid stimulating hormone receptor (TSHr). No specific thyroid factor(s) other than increased levels of cAMP are required for TSHr desensitization. Tezelman S, Shaver JK, Grossman RF, Liang W, Siperstein AE, Duh QY, Clark OH - "Desensitization of adenylate cyclase in Chinese hamster ovary cells transfected with human thyroid-stimulating hormone receptor" Endocrinology 134(3):1561-9 (1994) (Fluorides cause insensitization (decreased response) of the TSH receptor).

131. 1994 - Yang et al. investigate intelligence in children and report that high iodine and high fluoride exert "severe damage to the human body". Yang Y, Wang X, Guo X - "Effects of high iodine and high fluorine on children's intelligence and the metabolism of iodine and fluorine" Chung Hua Liu Hsing Ping Hsueh Tsa Chih 15(5):296-8 (1994)

132. 1995 - Balabolkin et al. study the thyroid and immune statuses in

workers continuously exposed to fluorine. "...T3 is seen reduced in 51% of the workers. The examinees with 'euthyroid condition' had immune disorders with an allergic tendency (increased number of B-lymphocytes, immunoglobulins A). In workers with subclinical hypothyroidism, the immune alterations were more evident, T-lymphocytes count rose, but their functional activity declined, indicating impaired cooperation of immunocytes as a result of imperfect control under low concentrations of T3." (aberrant G protein activation). Bylgyly A, et al. (2004). The effects of fluoride on thyroid hormones in rabbits. Indian Veterinary Journal 81:986-988. Balabolkin MI, Mikhailets ND, Lobovskaia RN, Chernousova NV - "The interrelationship of the thyroid and immune statuses of workers with long-term fluorine exposure" Ter Arkh 67(1):41-2(1995)

133. 1996 - Mikhailets et al. again report on the low T3 levels in same workers exposed to fluorides. Suggests that the "low T3" syndrome could be used as a diagnostic tool in assessment of "fluorosis". Mikhailets ND, Balabolkin MI, Rakitin VA, Danilov IP - "Thyroid function during prolonged exposure to fluorides." Problemy Endokrinologii 42 (1):6-9 (1996)

134. "Thyroid function was examined in 165 workers of electrolysis shops of aluminum production with more or less expressed signs of chronic fluoride intoxication (fluorosis) by radioimmunoassay of hormones and the test of 131I absorption by the thyroid. The detected thyroid abnormalities were characterized by a moderate reduction of iodine-absorbing function of the thyroid, low T3 with normal T4 level, and a slight increase of TTH concentration. These changes augmented with longer service and fluorosis progress. Hence, the syndrome of low T3 and reduced absorption of 131I may be considered as diagnostic signs of fluorosis. In case of toxic involvement of the liver in fluorosis patients, low T3 syndrome is observed much more frequently: in 75.6% cases. Liver abnormalities evidently lead to disorders in the peripheral conversion of T4 in T3, occurring primarily in liver parenchyma. Indirect effect of fluorine on the enzymatic system of deiodination cannot be ruled out as well."

135. 1996 Mahmood investigates the effects oflow doses of sodium fluoride on the thyroid glands of guinea pigs.

136. Findings are:

1. Depletion of colloid from the follicles.
2. Shrinkage of follicles.
3. Disruption of follicular basement membrane associated with oedema and degeneration of the follicular epithelial cells.
4. Increased follicular vascularity.
5. Fatty degeneration in the inter-follicular connective tissue. Mahmood Bhat GH - "Effect of fluoride ions on the thyroid glands of guinea pigs" JK Practitioner International 3(2): 94-6 (1996)

137. Paloyan Walker R, Kazuko E, Gopalsami C, Bassali J, Lawrence AM, Paloyan E - "Hyperparathyroidism associated with a chronic hypothyroid state" Laryngoscope 1107(7):903-9 (1997)

138. 1998 - Zhao et al. conduct an extensive study on mice receiving several fluoride-iodine combinations in addition to basal diet. The authors find that iodine and fluorine have "mutually interacting" effects on both goiter and fluorosis in the experimental mice. Zhao W, et al. (1998). Long-term Effects of Various Iodine and Fluorine Doses on the Thyroid and Fluorosis in Mice. Endocrine Regulations 32(2):63-70. (See abstract I See study)

139. Zhao W, Zhu H, Yu Z, Aoki K, Misumi J, Zhang X - “Long-term Effects of Various Iodine and Fluorine Doses on the Thyroid and Fluorosis in Mice” Endocr Regul 32(2):63-70 (1998)

140. 1998 - Swarup et al., investigating fluoride-intoxicated cattle near an aluminum smelter in India, find decreased levels of triiodothyronine (T3) in the affected animals when compared to normal animals. Swarup D, Dwivedi SK, Dey S, Ray SK - “Fluoride intoxication in bovines due to industrial pollution” Indian Journal of Animal Sciences 68 (7):605-608 (1998), also in Fluoride 31(4):225(1998)

141. 1999 - Data by Jooste et al shows that goitre occurrence in iodine-sufficient areas in Africa is due to fluoride. In 5 out of 6 villages goiter prevalence directly corresponds to fluoride in water, observable at concentrations even lower than deemed “optimal” for “”caries prevention”. Jooste PL, Weight MJ, Kriek JA, Louw AJ - “Endemic goitre in the absence of iodine deficiency in schoolchildren of the Northern Cape Province of South Africa” Eur J Clin Nutr 53(1):8-12 (1999)

142. 2001 - Negoita et al. report the increase of acquired hypothyroidism in the St. Regis Akwesasne Mohawks, a population long known to be poisoned by fluoride emissions from a Reynolds aluminum smelter. Negoita S, Swamp L, Kelley B, Carpenter DO - “Chronic diseases surveillance of St. Regis Mohawk Health Service patients” J Public Health Manag Pract 7(1):84-91 (2001)

143. 2001 - Trabelsi M, et al. Effect of fluoride on thyroid function and cerebellar development in mice. Fluoride 34: 165-173. (See study) Travbesli M, Guermazi F, Zeghal N - “Effect of fluoride on thyroid function and cerebellar development in mice” Fluoride 34(3):165-173 (2001)

144. 2001 - 2002 - Gupta et al. (India) and Suketa (Japan) show that in cases of fluorosis there is hyperparathyroidism, as seen in elevated parathyroid hormone (PTH) levels. 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) http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11224578&dopt=Abstract

145. Liu G, et al. (2002). Effect of sodium fluoride upon activity of peroxidase in the thyroid gland of chickens. Chinese Journal of Veterinary Science and Technology 32:32-33.

146. 2002 - As a result of research into molecular biology there are hundreds upon hundreds of studies available documenting the actions of fluorides upon G proteins, the “On” and “Off” switches involved in cellular signal transmission.

147. Suketa Y - “Fundamental and applied studies on transport and metabolism of electrolytes and glucose—aim to contact with molecular biology” Yakugaku Zasshi 122(8):507-25 (2002) http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12187767

148. During the 1980s and 1990s fluorides become known as the universal G-protein activator. Although there have been numerous studies before showing that fluorides act like TSH, the thyroid-stimulating-hormone - as seen above -, it can now be documented in deep detail, for it is known that G proteins in thyroid physiology are normally absolutely dependent on TSH and are inactive without it. TSH is the master, sometimes also referred to as the “first violinist in the orchestra”. The TSH receptor is the only receptor known able to activate all G protein families, an activity directly imitated by fluoride. Liu G, et al. (2003). Effects of adding selenium to diets on the function of thyroid of fluorositic chicks. Journal of Shanghai Jiaotong University - Agricultural Science 21: 177-180.

149. 2004 - Shen et al. show both an antagonistic as well as synergistic relationship of iodine and fluoride on phospholipid and fatty acid composition in brain cells of rats, depending on the amount of iodine. Shen X, Zhang Z, Xu X - “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 (2004)
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15208994
(re:antagonistic relationship of iodine and fluoride on phospholipid and fatty acid composition in brain cells of rats)

150. 2004 - Wang et al. investigate the effects of fluoride and low iodine on biochemical indexes in the brain and learning/memory in offspring rats. “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.” Wang J, Yaming G, Ning H, Wang S - “Effects of high fluoride and low iodine on biochemical indexes of the brain and learning-memory of offspring rats” Fluoride 37(3):201-8 (2004)

151. 2004 - Bouaziz et al. investigate the effects of fluoride on thyroid hormones and bone in suckling mice and find a reduction of plasma free T4 and T3 levels in the offspring, as well as accelerated bone resorption activity. (Bone formation is regulated by the endocrine system.) Bouaziz H, Ammar E, Ghorbel H, Ketata S, Jamoussi K, Ayadi F, Guermazi F, Zeghal N - “Effect of fluoride ingested by lactating mice on thyroid function and bone maturation of their suckling pups” Fluoride 37(2):133-142 (2004) Bylgyly A, et al. (2004). The effects of fluoride on thyroid hormones in rabbits. Indian Veterinary Journal 81:986-988.

152. 2005 - Dr. Susheela and co-workers present not only the first reports on TSH and free TH levels in children and adolescents with DF but, in addition, show that even in children without DF - but elevated fluoride serum levels - abnormal TH metabolism is present, as previously observed in workers exposed to fluoride, as well as children and adults with various amounts of fluoride in the water supply. Susheela AK, et al. (2005). Excess fluoride ingestion and thyroid hormone derangements in children living in Delhi, India. Fluoride 38: 98-108. Susheela AK, Bhatnagar M, Vig K, Mondal NK - “Excess fluoride ingestion and thyroid hormone derangements in children living in Delhi, India” Fluoride 38(2):98-108 (2005)

153. Anon - “The specific features of the development of iodine deficiencies in children living under environmental pollution with fluorine compounds” Gig Sanit (6):53-5 (2005) MEDLINE

154. 2005 - Ruiz-Payan et al. show that even at 1 ppm (fluoride in water) T3 levels are reduced in adolescents living in Northern Mexico. Ruiz-Payan A, Duarte-Gardea M, Ortiz M, Hurtado R - “Chronic effects of fluoride on growth, blood chemistry, and thyroid hormones in adolescents residing in three communities in Northern Mexico” Abstracts, XXVIth ISFR Conference, Wiesbaden, Germany, September 26-29, 2005

155. Schuld A. (2005). Is dental fluorosis caused by thyroid hormone disturbances? Fluoride 38: 91-94

156. 2005 - Russian researchers investigate iodine deficiency in areas polluted with fluoride from air: 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."

157. Fluorin could affect hormone levels of each layer of the Hypothalamus-Hypophysis-Testis axis, and show the male reproductive endocrine disturbing effects. Ma X, 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

158. "Thus, excessive F administration induces thyroid dysfunction in rats; dietary Pr and Ca level play key roles in F-induced thyroid dysfunction." Source: Wang H, Yang Z, Zhou B, Gao H, Yan X, Wang J. Fluoride-induced thyroid dysfunction in rats: roles of dietary protein and calcium level. Toxicol Ind Health. 2009 Feb;25(1):49-57.

159. "The consumption of drinking water rich in fluoride has toxic effects on the central nervous system. . . Our results show that biologically relevant concentrations of fluoride are capable of increasing cell migration in tumour cells, suggesting that exposure to fluoride could stimulate tumour infasion." Source Mendoza-Schulz A, et al The effects of fluoride on cell migration, cell proliferation, and cell metabolism in GH4C1 pituitary tumour cells, Toxicol Lett. 2009 Oct 28;190(2):179-86.

160. F(-) is an oxidizing agent and a well-known reversible enzymatic inhibitor that interferes with the enzyme acdtivity of at least 80 proteins. . . Exp;osure to high levels of F(-) in drinking water may decrease insulin mRNA and its secretion from beta-cells, and might therefore affect the OGTT (oral glucose tolerance test). Source Garcia-Montalvo EA et al Fluoride exposure impairs glucose tolerance via decreased insulin expression and oxidative stress, Toxicology 2009 Sep 19;263(2-3):75-83.

161. "Thus, excessive F administration induces thyroid dysfunction in rats; dietary PRr and Ca level play key roles in F-induced thyroid dysfunction." Wang H, Yang Z, et al, Fluoride-induced thyroid dysfunction in rats: roles of dietary protein and calcium level, Toxicol Ind Health 2009 Feb; 25(1):49-57

162. "Otosclerosis is a common form of hearing loss characterized by abnormal bone remodeling in the otic capsule. . . Environmental factors include fluoride and viral factors, particularly measles . . . " Source Schrauwen I, Van Camp G., The etiology of otosclerosis: a combination of genes and environment. Laryngoscope 2010 Jun;120(6):1195-202. Department of Medical Genetics, University of Antwerp.

163. "Fluoride could effect hormone levels of each layer of the hypothalamus-hypophsis-testis axis, and show the reproductive endocrine disturbing effects. The reproductive endocrine disturbing effects of male maybe more severe than those of female." Hao P, MaX et al Effects of fluoride on human hypothalamus-hypophsis-testis axis hormones, Wei Sheng Yan Jiu 2010 Jan;39(1):53-5.

D. Likely and Possible Harm of Cancer: Teratogenicity, Altered Growth, Functional Deficit, and Death.

Although the EPA DRA does not include cancer, the EPA must include cancer in a dose response analysis. Five years have passed since the NRC (2006) report was published and additional studies indicate the EPA must include cancer in a dose response analysis.

According to the National Toxicology Program, "the preponderance of evidence" from laboratory 'in vitro' studies indicates that fluoride is a mutagen. Fluoride fits within EPA's Cancer Guidelines and Supplemental Guidance as a mutagen, carcinogenic,[218]

[218] Appendix 120 p. 1-3.

and carcinogenic. Fluoride in water contributes to the total exposure of fluoride. The EPA cannot assume people will not get additional fluoride from other sources. Although the DRA specifically states that it does not include a review of cancer, these studies are a wakeup call and we request the EPA reassess fluoride in water as a mutagen.

It is generally accepted that if a substance can induce genetic damage there is a heightened risk that it could cause cancer as well.

While the concentrations of fluoride causing mutagenic damage in the in vitro studies is higher than the concentrations found in human blood, there are certain "microenvironments" in the body (e.g. pineal gland) where the concentrations of fluoride can accumulate to levels comparable to, or in excess of, those causing mutagenic effects in the laboratory.

Of particular concern are a series of studies indicating that fluoride can cause osteosarcoma in both fluoride-treated male rats and boys under the age of 20 living in fluoridated areas. Of additional concern are recent studies indicating that:

- Primates (humans and great apes) are more susceptible to the mutagenic effects of fluoride than rodents (rats);

- An increased rate of mutagenic damage was detectable in humans exposed to only modestly elevated levels of fluoride; and

- Workers exposed to fluoride in industry - in the absence of other known carcinogens such as PAH - suffered an increased occurrence of bladder cancer.

1. "A number of investigators have utilized the SCE (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." Sheth FJ, et al. (1994). Sister chromatid exchanges: A study in fluorotic individuals of North Gujurat. Fluoride 27: 215-219.

2. "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 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. 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." Wu DQ, Wu Y. (1995). Micronucleus and Sister Chromatid Exchange Frequency in Endemic Fluorosis. Fluoride 28: 125-127.

3. "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... HF and SiF4 are the main air pollutants; however, dust containing fluoride, phosphate fog, ammonia (NH3), and sulfur dioxide (SO2) were also released in small amounts into the air during fertilizer production. These pollutants may also make a contribution to the induction of SCES. Hence, further study of the induction effect of HF or SiF4 alone on SCEs in human lymphocytes to understand the cytogenetic damage of fluoride pollution in the air would be needed." Meng Z, et al. (1995). Sister-chromatid exchanges in lymphocytes of workers at a phosphate fertilizer factory. Mutation Research 334(2):243-6.

4. "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 ($p < 0.01$) [13]. 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 DNA." Meng Z, Zhang B. (1997). Chromosomal aberrations and micronuclei in lymphocytes of workers at a phosphate fertilizer factory. Mutation Research 393: 283-288.

5. "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."Joseph S, Gadhia PK. (2000). Sister chromatid exchange frequency and chromosome aberrations in residents of fluoride endemic regions of South Gujarat. Fluoride 33: 154-158.

6. "The disagreements among the in vivo tests for chromosome damage in rodents can not yet be reconciled. There are a few reports of positive results for chromosome aberrations in rodent bone marrow and testes, but other studies, using similar protocols and dose ranges, have reported no induced chromosome damage... Therefore, at this time, the in vivo clastogenicity of fluoride should be considered unresolved." 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.

7. "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 treated with the high dose, a value which is twice the level of the negative control." 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 74:566-72.

8. "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." Suzuki Y, Li J, Shimizu H. (1991). Induction of micronuclei by sodium fluoride. Mutation Research 253:278.

9. "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 - 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."
SOURCE: Pati PC, Bhunya SP. (1987). Genotoxic effect of an environmental pollutant, sodium fluoride, in mammalian in vivo test system. Caryologia 40:79-87.

10. "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."
SOURCE: 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.

11. "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." Mohamed AH, Chandler ME. (1982). Cytological effects of sodium fluoride on mice. Fluoride 15: 110-18.

12. "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 ½ to 4 ½ 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." Gileva EA, et al. (1975). The mutagenic activity of inorganic fluorine compounds. Fluoride 8: 47-50.

13. "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." Voroshilin SI, et al. (1975). Mutagenic effect of hydrogen fluoride on animals. Tsitol Genet. 9: 42-44.

14. "On the grounds of the results obtained during our experiments F compounds are able to produce certain changes in chromosomes from somatic cells of animals treated in vivo by them... Most of the aberrations observed in the case of bone marrow cells were chromatid-type aberrations... [W]e entertain the opinion that the main damage to chromosomes during our experiments with F compounds also took part during the S-phase... [T]hese data enable us to consider as sufficiently established the conclusion that inorganic fluorine compounds may present a mutagenic danger to human beings." Voroshilin SI, et al. (1973). Cytogenetic effect of inorganic fluorine compounds on human and animal cells in vivo and in vitro. Genetika 9: 115-120.

15. "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." Taylor A, Taylor NC. (1965). Effect of sodium fluoride on tumor growth. Proceedings of the Society for Experimental Biology and Medicine 119:252-255.

16. "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 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." 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.

17. "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." 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.

18. "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." SOURCE: Environment Canada. (1993). Inorganic Fluorides: Priority Substances List Assessment Report. Government of Canada, Ottawa.

19. "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 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 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 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." 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.

20. "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." Marier J, Rose D. (1977). Environmental Fluoride. National Research Council of Canada. Associate Committe on Scientific Criteria for Environmental Quality. NRCC No. 16081.

21. "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, considereing previous studies, we think that fluoride can cause lipid peroxidation, DNA damage and apoptosis, and that there is a positive relationship among these changes." 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.

22. "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." Kleinsasser NH, et al. (2001). [Cytotoxicity and genotoxicity of fluorides in human mucosa and lymphocytes]. Laryngorhinootologie 80(4):187-90.

23. "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 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." 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.

24. "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." 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.

25. "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." Mihashi M, Tsutsui T. (1996). Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. Mutation Research 368:7-13.

26. "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)." Khalil AM. (1995). Chromosome aberrations in cultured rat bone marrow cells treated with inorganic fluorides. Mutation Research 343:67-74.

27. "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." Gritsan, NP. (1993). Cytogenetic effects of gaseous fluorides on grain crops. Fluoride 26: 23-32.

28. "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." 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.

29. “We show here that NaF is clastogenic not only in human cells but also in great ape cells. The mechanism of NaF clastogenicity is still unknown, but the same profile of chromosomal aberrations in man and chimpanzees suggests that its action on these cells and the response of the cells will be consistent. The different response to NaF among non-human primates might give us a clue to clarify the mechanism of NaF clastogenicity.” Kishi K, Ishida T. (1993). Clastogenic activity of sodium fluoride in great ape cells. Mutation Research 301:183-8.

30. “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.” Suzuki Y, Li J, Shimizu H. (1991). Induction of micronuclei by sodium fluoride. Mutation Research 253:278.

31. “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.” Crespi CL, et al. (1990). Sodium fluoride is a less efficient human cell mutagen at low concentrations. Environmental Molecular Mutagenesis 15:71-7.

32. “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.” 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.

33. “Inducibility of chromosome aberrations of the cells following treatment with sodium fluoride was also dependent upon the phase of cell cycle. Significant increase in the incidence of chromosome aberrations was observed only in cultures treated during early and/or middle S phases of the cell cycle. These results indicate that cytotoxicity and clastogenicity of sodium fluoride to cultured human diploid fibroblasts are cell phase dependent, and that the cells in early and middle S phases are more sensitive to these effects.” 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. 77:436-47.

34. “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 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 direct-acting carcinogens or procarcinogens. Pretreatment of the cells with noncarcinogens or weakly-acting carcinogens or administration of NaF prior to treatment with the carcinogen failed to enhance the yield of transformation. Transformation was enhanced even when the NaF treatment was delayed for several days after the carcinogen treatment. However, the continued presence of NaF was necessary for maintenance of the increased level of transformation. Removal of NaF prior to termination of the assay resulted in a reversal of the transformed clonal morphologies to a normal phenotype such that the final yield of transformants was decreased, but was still greater than that observed after carcinogen treatment alone.” Jones CA, et al. (1988). Sodium fluoride promotes morphological transformation of Syrian hamster embryo cells. Carcinogenesis 9: 2279-84.

35. “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 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.” 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

36. “Chromosomal aberrations were recorded for all the concentrations used. Maximum effect at all concentrations was observed after 24 hours of treatment. Several kinds of abnormalities were revealed with the main ones being bridges, double bridges, sidearm bridges, bridges with fragments, tripolar and multipolar anaphases with and without bridges, fragments, and laggards. “Y” and “X” configurations were also noted at metaphase... The authors conclude that sodium-fluoride may be considered to be clastogenic in these cells.” Albanese R. (1987). Sodium fluoride and chromosome damage (in vitro human lymphocyte and in vivo micronucleus assays). Mutagenesis 2:497-9.

37. “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.” Caspary WJ, et al (1987). Mutagenic activity of fluorides in mouse lymphoma cells. Mutation Research 187:165-80.

38. “The results are used to illustrate the problems associated with quantitative extrapolation from in vitro tests to human risk, as follows. (1) There appears to be a threshold response (clastogenicity vs. dose) with NaF at around 10 micrograms/ml (48 h exposure) but a more definitive conclusion must await elucidation of the mechanisms of clastogenicity. (2) NaCl is weakly clastogenic at 1000 times the threshold dose for NaF. The mechanisms are unlikely to be similar. (3) No clastogenicity was detected with NaF below about 30% mitotic inhibition but the relationship between clastogenicity and mitotic inhibition was similar for NaF and MMC. (4) There was no obvious threshold in the relationship between clastogenicity and cell killing with NaF. MMC was less clastogenic than NaF at equitotoxic doses. Observations 3 and 4 preclude the possibility of regarding the clastogenicity of NaF as a false positive by virtue of associated cytotoxicity.” Scott D, Roberts SA. (1987). Extrapolation from in vitro tests to human risk: experience with sodium fluoride clastogenicity. Mutation Research 189:47-58.

39. “These observations, and an analysis of the colony size of trifluorothymidine-resistant mutants in TK+/- cells, suggest that sodium fluoride is clastogenic to dividing cultured mammalian cells at high, toxic concentrations. Further work is desirable to investigate the mechanism by which chromosomes are damaged at high concentrations of fluoride, since without such a mechanistic understanding, extrapolation of our data to the human situation must be insecure.” Cole J, et al. (1986). The mutagenicity of sodium fluoride to L5178Y [wild-type and TK+/- (3.7.2c)] mouse lymphoma cells. Mutagenesis 1:157-67.

40. “The clastogenic effect of NaF has been tested by the use of several cytogenetic assay systems, but the findings on its genotoxicity are not

consistent. In this study, the effects of NaF on chromosomes, unscheduled DNA synthesis (UDS) and sister-chromatid exchanges (SCEs) were investigated using cultured human lymphocytes. For clastogenicity testing, cells were treated for 24 h in various concentrations of NaF. At least two donors were tested for each concentration and more than 10,000 cells were totally observed... Sodium fluoride treatment had remarkable effects on the induction of isochromatid gaps and chromosome breaks (NUpds)." Kishi K, Tonomura A. (1984). Cytogenetic effects of sodium fluoride. Mutation Research 130: 367.

41. "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." 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.

42. " 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." 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.

43. "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." Tsutsui T, Ide K, Maizumi H. (1984). Induction of unscheduled DNA synthesis in cultured human oral keratinocytes by sodium fluoride. Mutation Research 140:43-8.

44. "The study, by light and fluorescent microscopy, of sternal and femoral bone marrow taken from young Swiss mice exposed for period up to 280 days to elevated levels of sodium fluoride in drinking water, has revealed morphologic abnormalities in cell structure and mitotic figure formation in immature leukocytes. Alterations in the content and distribution of RNA and DNA also appear after several weeks of exposure... 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." Greenberg SR. (1982). Leukocyte response in young mice chronically exposed to fluoride. Fluoride 15: 119-123.

45. "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." Jachimczak D, Skotarczak B. (1978). The effect of fluorine

and lead ions on the chromosomes of human leucocytes in vitro. Genetica Polonica 19: 353-7.

46. “These findings indicate that HF in addition to being a mutagenic agent is also able to reduce crossing over in certain chromosome segments.” Mohamed AH. (1977). Cytogenetic effects of hydrogen fluoride gas on maize. Fluoride 10: 157-164.

47. “while NaF can be a potent meiotic mutagen in the particular in vitro experimental situations reported here, the variation of in vitro sensitivity between the mouse (which nevertheless showed some oocyte abnormality when tested in vivo) and the higher forms (cow and ewe) would suggest an assessment of abnormal progeny from the latter species for chromosomal abnormalities in NaF-contaminated areas, as a reasonable next step for ascertaining the probability of the mutagenicity of this compound.” Jagiello G, Lin JS. (1974). Sodium fluoride as potential mutagen in mammalian eggs. Archives of Environmental Health 29:230-5.

48. “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.” Gerdes RA, et al. (1971). The effects of atmospheric hydrogen fluoride upon Drosophila melanogaster. II. Fecundity, hatchability and fertility. Atmospheric Environment 5:117-122.

49. “Genetic differences were observed in the response of the progeny of treated flies. The maintenance of a population at sub-lethal concentrations of HF revealed an apparent accumulation of of physiological abberations resuting in sterility in the treated flies. Results indicate that treatment increased the incidence of genetic abberations as measured by at least two parameters.” 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.

50. “Maize seedlings of the genotype A1A2C1Wx were fumigated in growth chambers with hydrogen fluoride (HF) at a concentration of about 3 ug/m3. The experiment was run for 10 days, with the first group of treated plants removed from the chambers after 4 days and then at intervals of 2 days. Microsporocyte smears from the treated plants revealed chromosomal aberations that included asynaptic regions, translocations, inversions, and bridges plus fragments or fragments by themselves. It is believed that these abnormalities were due to the physiological effect of HF causing the chromosomes to become sticky and/or to the occurrence of chromatid breakage followed by reunion to form structural changes. These findings indicate that HF is a mutagenic agent.” Mohamed AH. (1970). Chromosomal changes in maize induced by hydrogen fluoride gas. Canadian Journal of Genetics and Cytology 12: 614-620.

51. “Studies on the effects of HF on meiotic chromosomes of tomatoes indicated a trend toward a higher frequency of chromosomal aberrations with an increase in the fumigation period. It was indicated that HF was capable of inducing paracentric inversions with the possibility of the induction of deficiencies, duplications or even translocations. The progeny obtained from the treated plants produced a number of abnormal phenotypes, the same as, or similar to, known mutations. Further studies in maize microsporocytes for plants treated with HF confirmed the cytological results obtained in tomatoes with clear evidence of the occurrence of inversions, translocations and deficiencies. These results suggest that HF seems to affect primarily the DNA

molecule by blocking its replication, probably through its action on the enzymatic system." Mohamed AH. (1969). Cytogenetic effects of hydrogen fluoride on plants. Fluoride 2: 76-84.

52. "From the results, it is clear that NaF, not being mutagenic by itselft, interacts with the mechanism of mutation induction by X-irradiation in fully mature spermatozoa. In fact, the enhancing effect has been observed in 21 out of 23 experiments where pre-treatment with NaF was compared to that with saline." Mukerjee RN, Sobels FH. (1968). The effect of sodium fluoride and idoacetamide on mutation induction by X-irradiation in mature spermatozoa of drosophila. Mutation Research 6: 217- 25.

53. As acknowledged by the U.S. National Toxicology Program there is a "biological plausibility" of a link between fluoride exposure and osteosarcoma. The biological plausibility centers around three facts: 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 can artificially stimulate the proliferation of bone cells (osteoblasts). In addition to its biological plausibility, there is now a substantive body of evidence indicating that fluoride can in fact induce osteosarcomas in both animals and humans.

54. Most notably, a recent national case control study conducted by scientists at Harvard University found a significant relationship between fluoride exposure and osteosarcoma among boys, particularly if exposed to fluoridated water between the ages of 6 and 8 (the mid-childhood growth spurt). The Harvard study's findings are consistent with the U.S. National Toxicology Program's congressionally-mandated fluoride/cancer study in rats; the National Cancer Institute's 1990 analysis of osteosarcoma rates among young males in fluoridated versus unfluoridated areas in the U.S., and the New Jersey Department of Health's 1992 analysis of osteosarcoma rates among young males in fluoridated versus unfluoridated areas of Central New Jersey.

55. In addition, two later independent analyses of NCI's national cancer data also found a relationship between fluoridation and osteosarcoma among young males (Yiamouyiannis 1993; Takahashi 2001). The evidence - laboratory, animal, and human - suggests that fluoride could either directly initiate, or contribute to, the development of osteosarcoma in boys under the age of 20.

56. "Osteosarcoma presents the greatest a priori plausibility as a potential cancer target site because of fluoride's deposition in bone, the NTP animal study findings of borderline increased osteosarcomas in male rats, and the known mitogenic effect of fluoride on bone cells in culture. Principles of cell biology indicate that stimuli for rapid cell division increase the risks for some of the dividing cells to become malignant, either by inducing random transforming events or by unmasking malignant cells that previously were in nondividing states." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 275.

57. " It is biologically plausible that fluoride affects the incidence rate of osteosarcoma, and that this effect would be strongest during periods of growth, particularly in males. First, approximately 99% of fluoride in the human body is contained in the skeleton with about 50% of the daily ingested fluoride being deposited directly into calcified tissue (bone or dentition). Second, fluoride acts as a mitogen, increasing the proliferation of osteoblasts and its uptake in bone increases during periods of rapid skeletal growth. In the young, the hydroxyapatite structure of bone mineral exists as many extremely small crystals each surrounded by an ion-rich hydration shell, providing a greater surface area for fluoride exchange to occur." Bassin EB, Wypij D, Davis RB, Mittleman MA. (2006). Age-specific Fluoride Exposure in Drinking Water and

Osteosarcoma (United States). Cancer Causes and Control 17: 421-8.

58. “if fluoride were to exert a neoplastic effect, it is reasonable to expect that this might be expressed in a tissue that accumulates fluoride. This would include bone, and, therefore, there is biological plausibility for an association between sodium fluoride administration and the development of bone osteosarcomas.” 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.

59. “it would appear that sodium fluoride is genotoxic in a number of genetic toxicity assays, through as yet undetermined mechanisms. So, a neoplastic effect in a tissue that accumulates fluoride would appear possible.” Bucher J. (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. 30-31.

60. “[T]he carcinogenicity of fluoride is consistent with growth stimulation of osteoblasts, unscheduled DNA synthesis by human fibroblasts, and transformation of embryonal hamster fibroblasts into transplantable sarcoma cells. Osteoblasts are differentiated fibroblasts, and fluoride is accumulated in the skeleton. Therefore, osteosarcoma would be the natural target effect to look for in a cancer bioassay of fluoride, and an excess of osteosarcoma in rats exposed to fluoride in drinking water clearly confirms an a priori hypothesis.” Freni S.C., Gaylor, D.W. (1992). International trends in the incidence of bone cancer are not related to drinking water fluoridation. Cancer 70: 611-8.

61. “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.” Gelberg KH. (1994). Case-control study of osteosarcoma. Doctoral Thesis, Yale University. p. 13.

62. “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.” Mihashi M, Tsutsui T. (1996). Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. Mutation Research 368:7-13.

63. “Osteosarcomas of the bone were observed in 3/80 (4%) high-dose and in 1/50 (2%) mid-dose male rats. An additional osteosarcoma, which was determined to be of subcutaneous origin, was observed in a fourth high-dose rat. No osteosarcomas were seen in controls or in male rats receiving 25 ppm. The neoplasms were clearly malignant (one metastasized to the lung) and there was complete agreement concerning the diagnoses at both the Quality Assessment and the Pathology Working Group stages of histopathology review...

Osteosarcomas (in bone or extraskeletal) are not commonly observed in control male rats in NTP studies. The historical incidence in control male rats from dosed feed or water studies is 10/2,106 (0.47%)...

The four osteosarcomas of bone (one in the mid-dose and three in the high-dose

groups) in the current studies occurred with a statistically significant dose-response trend by the logistic regression test (P=0.027); the pairwise comparison of the incidence in the high-dose group versus that in controls was no statistically significant (P=0.099). The statistical significance of the trend test is increased (P=0.010) when the subcutaneous osteosarcoma in the fourth high-dose rat is included in the incidence, but the pairwise comparison remains not significant (P=0.057). The incidence of bone osteosarcomas of 3/80 and the incidence of all osteosarcomas of 4/80 in the high-dose male rats are both significantly greater than the rate of 0.6% for osteosarcomas and osteomas at all sites in control male rats in the historical database...

To summarize these considerations, 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 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 findings are inconclusive, but are weakly supportive of an association between sodium fluoride administration and the occurrence of osteosarcomas in male rats." 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. 71-73.

64. "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." World Health Organization. (2002). Environmental Health Criteria 227: FLUORIDES. World Health Organization, Geneva.

65. "At the request of the Committee, we have enclosed a brief description of the time trends for bone and joint cancers and for osteosarcomas in the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI), and the relationship of these trends to fluoridation of drinking water supplies. The SEER Program, begun in 1973, is a group of population-based cancer registries that covers approximately 10% of the U.S. population... Table 1 presents the data for the entire SEER program split into 2 time periods (1973-80 and 1981-87). The incidence of all bone and joint cancers over all ages increased slightly between these two periods. When examined by age, the only increase occurred for the rates among those under age 20, where an 18% rise occurred for the sexes combined, reflecting a 23% rise in males and a 13% rise in females. When osteosarcomas are considered separately, there was essentially no change in the incidence rate over time for the sexes combined, reflecting the averaging of an 18% rise for males and an 11% decline among females. Among males, the upward trend resulted mainly from the experience of those under age 20, whose rates rose from 0.36 to 0.55 (53%).

It was possible to evaluate these same trends for groupings of counties within the SEER areas that were "non-fluoridated" as well as for those undergoing abrupt fluoridation at some time before the establishment of the SEER program... As shown in Table 2, the pattern for the entire SEER program of a rising rate of bone and joint cancers at all ages combined, due mainly to trends under age 20, was seen in the "fluoridated" counties but not in the "non-fluoridated" counties. Tables 3 and 4 are restricted to the patterns among males. Once again, the larger increase in males under age 20 seen in the aggregate data for all bone and joint cancers is seen only in the "fluoridated" counties. For osteosarcomas among males, increases were seen for those

under age 20 in both the “fluoridated” and “non-fluoridated” areas, although more prominently in the “fluoridated” counties.

Based on these data, one could conclude that summarized over all ages and both sexes, there were no meaningful time trends in incidence of these tumors. However, for bone and joint cancers, temporal increases were seen among those under age 20 in both sexes. For osteosarcomas, there were some increases, but only among young males. In addition, these patterns were associated with the fluoridation status of the counties for which these trends were assessed...In summary, analysis of incidence data from the SEER program has revealed some age- and sex-specific increases over time for bone and joint cancers, and for osteosarcomas, which are more prominent in fluoridated than in non-fluoridated areas. 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 RN, et al. (1990). Time trends for bone and joint cancers and osteosarcomas in the Surveillance, Epidemiology and End Results (SEER) Program. National Cancer Institute. In: DHHS (1991).

66. “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 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 fluoridatiuon at the municipal level with the municpal 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.” Cohn PD. (1992). A Brief Report On The Association Of Drinking Water Fluoridation And The Incidence of Osteosarcoma Among Young Males. New Jersey Department of Health: Environmental Health Service: 1- 17 Fluoride & Osteosarcoma - Analysis of National Cancer Instiute’s National Data & New Jersey Health Department’s Data (Yiamouyiannis 1993):

67. “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 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.” Yiamouyiannis JA. (1993). Fluoridation and cancer: The biology and epidemiology of bone and oral cancer related to fluoridation. Fluoride 26:83-96

68. “Age-specific and age-standardized rates (ASR) of registered cancers for nine communities in the U.S.A. (21.8 million inhabitants, mainly white) were obtained from IARC data (1978-82, 1983-87, 1988-92)... The incidence rate of bone cancer as the mean of three five-years ASRs was significantly correlated with FD (fluoridated water) only in males, with CIR-100 of 1.22, whereas in 1978-82 it showed a high CIR-100 of 2.53 Takahashi K., Akiniwa K., Narita K. (2001). Regression analysis of cancer incidence rates and water fluoride in the U.S.A. based on IACR/IARC (WHO)

data (1978-1992). International Agency for Research on Cancer. Journal of Epidemiology 11:170-9.

69. "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." Mihashi M, Tsutsui T. (1996). Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. Mutation Research 368:7-13.

70. "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, Wypij D, Davis RB, Mittleman MA. (2006). Age-specific Fluoride Exposure in Drinking Water and Osteosarcoma (United States). Cancer Causes and Control 17: 421-8.

71. Freni S.C., Gaylor, D.W. (1992). International trends in the incidence of bone cancer are not related to drinking water fluoridation. Cancer 70: 611-8.

72. Gelberg K.H., Fitzgerald E.F., Hwang S., Dubrow R. (1995). Fluoride exposure and childhood osteosarcoma: a case-control study. American Journal of Public Health 85:1678-83.

73. Hrudey S.E., Soskolne C.L., Berkel J., Fincham S. (1990). Drinking water fluoridation and osteosarcoma. Canadian Journal of Public Health 81(6):415-6.

74. Mahoney M.C., Nasca P.C., Burnett W.S., Meius J.M. (1991). Bone cancer incidence rates in New York State: time trends and fluoridated drinking water. American Journal of Public Health 81: 475-9.

75. McGuire S.M., Vanable E.D., McGuire M.H., Buckwalter J.A., Douglass C.W. (1991). Is there a link between fluoridated water and osteosarcoma? Journal of the American Dental Association 122:38-45.

76. Moss M.E., Kanarek M.S., Anderson H.A., Hanrahan L.P., Remington P.L. (1995). Osteosarcoma, seasonality, and environmental factors in Wisconsin, 1979-1989. Archives of Environmental Health 50:235-41.

77. Operskalski E.A., et al. (1987). A case-control study of osteosarcoma in young persons. American Journal of Epidemiology 126:118-26.

E. Likely and Possible Damage to Kidney: Teratogenicity, Altered Growth, Functional Deficit and Death.

1. As noted by Dr. Edward Groth, a veteran Senior Scientist at Consumers Union:

"It seems probable that some people with severe or long-term renal disease, which might not be advanced enough to require hemodialysis, can still experience reduced fluoride excretion to an extent that can lead to fluorosis, or aggravate skeletal complications associated with kidney disease... It has been estimated that one in every 25 Americans may have some form of kidney disease; it would seem imperative that the magnitude of risk to such a large sub-segment of the population be determined through extensive and careful study. To

date, however, no studies of this sort have been carried out, and none is planned" (Groth 1973; Doctoral Thesis; Stanford University).

Because the kidney accumulates more fluoride than all other soft tissues (with the exception of the pineal gland), there is concern that excess fluoride exposure may contribute to kidney disease - thus initiating a "vicious cycle" where the damaged kidneys increase the accumulation of fluoride, causing in turn further damage to the kidney, bone, and other organs.

The possibility that fluoride exposure can cause direct damage to kidney tissue is supported by a long line of animal and human studies.

In studies on fluoride-exposed animals, kidney damage has been reported at levels as low as 1 ppm if the animals consume the water for long periods of time.

In humans, elevated rates of kidney damage are frequently encountered among populations with skeletal fluorosis. In addition, several case reports suggest that some individuals with kidney disease can experience significant recovery in their clinical signs and symptoms following the provision of fluoride-free water.

2. "Epithelia in lung, skin, and kidney are often exposed to fluoride, and tissue damage in lung and kidney due to fluoride is well documented. Nevertheless, the biological effects of fluoride on epithelia are poorly investigated. In the present study, we report effects of sodium fluoride (NaF) on the differentiation of a human epithelial cell line, HaCaT. These cells may serve as a keratinocyte model, because they express a wide spectrum of keratins (Ks), and they associate into stratified tissue-like arrangements along with changes in their keratin pattern. NaF was added to the culture medium at concentrations of 0.5 and 5 mM. . . . The changes in keratin expression were not reversed by withdrawal of fluoride. Taken together, NaF at high dose blocked terminal differentiation of HaCaT cells, visible by keratin expression and failing stratification. This effect may disturb tissue formation due to altered cell interactions." Prado E, Wurtz T, Ferbus D, Shabana EH, Forest N, Berdal A. Sodium fluoride influences the expression of keratins in cultured keratinocytes. Cell Biol Toxicol. 2010 Aug 1

3. "Fluoride, of all inorganic substances, is among the least likely to be identified by a routine toxicological analysis. Acute poisonings with salts of hydrofluoric or fluorosilicic acid, however, although relatively uncommon, may occur. . . . In the first case, the results were: blood - 130mugF/ml, stomach - 1150mugF/g, small intestine content - 19.6mugF/g, kidney - 56.0mugF/g, and urine - 1940mugF/ml. In the second case, the contents of fluorine and zinc in blood and internal organs were the following: blood - 6.03mugF/ml, 23.8mugZn/ml; brain - 1.39mugF/g, 7.54mugZn/g; stomach - 152mugZn/g; stomach content - 293mugF/g, 84.4mugZn/g; small intestine - 37.5mugZn/g; small intestine content - 63.4mugF/g, 19.6mugZn/g; liver - 9.49mugF/g, 81.0mugZn/g; kidney - 29.6mugF/g, 39.2mugZn/g; and exceeded the normal levels of these elements in biological material many times." Lech T. Fatal cases of acute suicidal sodium and accidental zinc fluorosilicate poisoning. Review of acute intoxications due to fluoride compounds. Forensic Sci Int. 2010 Jul 22.

4. "Therefore it can be concluded that black berry administration could minimize the toxic effects of fluoride indicating its free radical-scavenging and potent anti-oxidant activities." Hassan HA, Abdel-Aziz AF., Food Chem Toxicol.

Evaluation of free radical-scavenging and anti-oxidant properties of black berry against fluoride toxicity in rats. 2010 Aug-Sep;48(8-9):1999-2004. Epub 2010 May 22

5. "Rats received a single intravenous injection of HFA (3.2, 6.4, or 9.6 (LD(5)) mg/kg) or saline. . . . Conclusions: We consider that acute nephrotoxicity of HFA caused renal injury, and the harmful effects of HFA were subsequently aggravated by its delayed metabolism." Mitsui G, Dote T, Yamadori E, Imanishi M, Nakayama S, Ohnishi K, Kono K. Toxicokinetics and Metabolism Deteriorated by Acute Nephrotoxicity after a Single Intravenous Injection of Hydrofluoric Acid in Rats. J Occup Health. 2010 Oct 12

6. "The results indicate that the affected regions contain moderate to high levels of fluoride." Chronic kidney diseases of uncertain etiology (CKDue) in Sri Lanka: geographic distribution and environmental implications. Chandrajith R, Nanayakkara S, Itai K, Aturaliya TN, Dissanayake CB, Abeysekera T, Harada K, Watanabe T, Koizumi A. Environ Geochem Health. 2010 Sep 18.

7. "These data suggest that oim (Osteogenesis imperfecta murine) mice have reduced bone strength due to homotrimeric type I collagen, independent of bone fluoride content." Carleton SM, Whitford GM, Phillips CL. Dietary fluoride restriction does not alter femoral biomechanical strength in col1a2-deficient (oim) mice with type I collagen glomerulopathy. J Nutr. 2010 Oct;140(10):1752-6. Epub 2010 Aug 19.

8. "Selective low (15 mg sodium fluoride (NaF)/L) and relatively high (150 mg NaF/L) doses of in vivo fluoride (F) treatment to Swiss albino mice through drinking water elicited organ-specific toxicological response. All the F-exposed groups showed severe alterations in both liver and kidney architectures, but there was no significant change in the rate of water consumption and body weight." Chattopadhyay A, Podder S, Agarwal S, Bhattacharya S. Fluoride-induced histopathology and synthesis of stress protein in liver and kidney of mice. Arch Toxicol. 2010 Sep 22. [Epub ahead of print]

9. "[A] fairly substantial body of research indicates that patients with chronic renal insufficiency are at an increased risk of chronic fluoride toxicity. Patients with reduced glomerular filtration rates have a decreased ability to excrete fluoride in the urine. These patients may develop skeletal fluorosis even at 1 ppm fluoride in the drinking water... The National Kidney Foundation in its 'Position Paper on Fluoride—1980' as well as the Kidney Health Australia express concern about fluoride retention in kidney patients. They caution physicians to monitor the fluoride intake of patients with advanced stages of kidney diseases. However, a number of reasons will account for the failure to monitor fluoride intake in patients with stages 4 and 5 of chronic kidney diseases and to detect early effects of fluoride retention on kidneys and bone. The safety margin for exposure to fluoride by renal patients is unknown, measurements of fluoride levels are not routine, the onset of skeletal fluorosis is slow and insidious, clinical symptoms of this skeletal disorder are vague, progression of renal functional decline is multifactorial and physicians are unaware of side effects of fluoride on kidneys or bone." Schiffl H. (2008). Fluoridation of drinking water and chronic kidney disease: absence of evidence is not evidence of absence. Nephrology Dialysis Transplantation 23:411.

10. "Individuals with kidney disease have decreased ability to excrete fluoride in urine and are at risk of developing fluorosis even at normal recommended limit of 0.7 to 1.2 mg/l." Bansal R, Tiwari SC. (2006). Back pain in chronic renal failure. Nephrology Dialysis Transplantation 21:2331-2332.

11. "Persons with renal failure can have a four fold increase in skeletal fluoride content, are at more risk of spontaneous bone fractures, and akin to skeletal fluorosis even at 1.0 ppm fluoride in drinking water." Ayoob S, Gupta AK. (2006).

Fluoride in Drinking Water: A Review on the Status and Stress Effects. Critical Reviews in Environmental Science and Technology 36:433–487

12. "In patients with reduced renal function, the potential for fluoride accumulation in the skeleton is increased. It has been known for many years that people with renal insufficiency have elevated plasma fluoride concentrations compared with normal healthy persons and are at a higher risk of developing skeletal fluorosis." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p140 .

13. "Skeletal fluorosis seems possible, especially in hot climates or with renal compromise, from drinking excessive quantities of instant or bottled teas. Our observations support the need for better understanding of the amounts and systemic effects of fluoride in teas." Whyte M. (2006). Fluoride levels in bottled teas. American Journal of Medicine 119:189-190.

14. "We hypothesize that elevated serum F levels might contribute to the disturbances in mineral ion homeostasis that are observed in patients with CRI [Chronic Renal Insufficiency]. This is of particular concern since the incidence of dental fluorosis has increased due to increased F– uptake from multiple fluoridated sources. The ubiquitous presence of F in food and beverage products regardless of the degree of water fluoridation suggests that the overall F exposure in individuals with CRI may need to be more closely monitored." Mathias RS, et al. (2000). Increased fluoride content in the femur growth plate and cortical bone of uremic rats. Pediatric Nephrology 14:935–939

15. "It is important to control the intake of this element [fluoride] and the prolonged use of fluoridated dental products in the subjects with chronic renal insufficiency, to avoid a risk of fluorosis." Torra M, et al. (1998). Serum and urine fluoride concentration: relationships to age, sex and renal function in a non-fluoridated population. Science of the Total Environment 220: 81-5.

16. "[A] fairly substantial body of research indicates that people with kidney dysfunction are at increased risk of developing some degree of skeletal fluorosis. ... However, there has been no systematic survey of people with impaired kidney function to determine how many actually suffer a degree of skeletal fluorosis that is clearly detrimental to their health." Hileman B. (1988). Fluoridation of water.Questions about health risks and benefits remain after more than 40 years. Chemical and Engineering News August 1, 1988, 26-42.

17. "It seems probable that some people with severe or long-term renal disease, which might not be advanced enough to require hemodialysis, can still experience reduced fluoride excretion to an extent that can lead to fluorosis, or aggravate skeletal complications associated with kidney disease... It has been estimated that one in every 25 Americans may have some form of kidney disease; it would seem imperative that the magnitude of risk to such a large sub-segment of the population be determined through extensive and careful study. To date, however, no studies of this sort have been carried out, and none is planned." Groth, E. (1973). Two Issues of Science and Public Policy: Air Pollution Control in the San Francisco Bay Area, and Fluoridation of Community Water Supplies. Ph.D. Dissertation, Department of Biological Sciences, Stanford University, May 1973.

18. "It would not be surprising if there were some undetected cases of skeletal fluorosis in the Australian population in individuals with pathological thirst disorders and/or impaired renal function. However, the matter has not been systematically examined. This matter should be the subject of careful and systematic review." National Health and Medical Research Council. (1991). The effectiveness of water fluoridation. Canberra, Australia: Australian Government Publishing Service.

19. “Though fluorosis is prevalent in certain geographic parts of the world, it is likely to occur in other parts... in people with latent kidney disease even when they consume relatively lower amounts of fluoride than in endemic regions.” Reddy DR, et al. (1993). Neuro-radiology of skeletal fluorosis. Annals of the Academy of Medicine, Singapore 22(3 Suppl):493-500.

20. “Impairment of renal function can prolong the plasma half-life and contribute to clinical toxicity at lower concentrations of fluoride intake.” Fisher RL, et al. (1989). Endemic fluorosis with spinal cord compression. A case report and review. Archives of Internal Medicine 149: 697-700.

21. “Persons with chronic renal failures constitute a possible group at-risk with respect to the occurrence of skeletal fluorosis, because of an increased fluoride retention after oral intake. Based on the results of one study, in which the difference in retention between nephritic patients and healthy persons was quantified (average retention: 65% and 20%, respectively), a total daily intake of about 1.5 mg appears to be the maximum acceptable intake for nephritic patients. In view of the limitations of this comparative study and of the individual differences in retention and sensitivity, this figure must only be regarded as an indication.” National Institute for Public Health and Environmental Protection. (1989). Integrated criteria document fluorides. Report No 758474010. The Netherlands.

22. “The skeletal complication of fluoride is more common in renal disease. Because of the impairment in renal excretion of fluoride, high circulating concentrations of fluoride may be achieved in renal disease.” Pak CY. (1989). Fluoride and osteoporosis. Proceedings of the Society for Experimental Biology and Medicine 191: 278-86.

23. “Fluoridation of drinking water up to 1.2 ppm apparently does not pose a potential risk to bone provided the renal function is normal... We should, however, recognize that it is difficult to give a strict value for a safe fluoride concentration in drinking water, because individual susceptibility to fluoride varies.” Arnala I, et al. (1985). Effects of fluoride on bone in Finland. Histomorphometry of cadaver bone from low and high fluoride areas. Acta Orthopaedica Scandinavica 56(2):161-6.

24. “Because the kidney is the main pathway of fluoride excretion, patients with chronic renal failure are especially vulnerable to osseous accumulation of ingested fluoride and to potentially deleterious effects.” Fisher JR, et al. (1981). Skeletal fluorosis from eating soil. Arizona Medicine 38: 833-5.

25. “The finding of adverse effects in (kidney) patients drinking water with 2 ppm of fluoride suggests that a few similar cases may be found in patients imbibing 1 ppm, especially if large volumes are consumed, or in heavy tea drinkers and if fluoride is indeed the cause.” Johnson W, et al. (1979). Fluoridation and bone disease in renal patients. In: E Johansen, DR Taves, TO Olsen, Eds. Continuing Evaluation of the Use of Fluorides. AAAS Selected Symposium. Westview Press, Boulder, Colorado. pp. 275-293.

26. “In the human body, the kidneys are probably the most crucial organ during the course of low-dose long-term exposure to fluoride. Healthy kidneys excrete 50 to 60% of the ingested dose (Marier and Rose 1971). Kidney malfunction can impede this excretion, thereby causing an increased deposition of fluoride into bone. Marier (1977) has reviewed data showing that, in persons with advanced bilateral pyelonephritis, the skeletal fluoride content can be 4-fold that of similarly-exposed persons with normal kidneys. Similarly, Mernagh et al. (1977) have reported a 4-fold higher skeletal fluoride content in persons with the renal failure of osteodystrophy. It has also been shown (Seidenberg et al. 1976; Hanhijarvi 1975) that plasma F- levels can be 3 ½ to 5 times higher than normal in persons with renal insufficiency. It is thus apparent

that persons afflicted with some types of kidney malfunction constitute another group that is more "at risk" than is the general population." Marier J, Rose D. (1977). Environmental Fluoride. National Research Council of Canada. Associate Committe on Scientific Criteria for Environmental Quality. NRCC No. 16081.

27. "It is generally agreed that water fluoridation is safe for persons with normal kidneys. Systemic fluorosis in patients with diminished renal function, however, seems a reasonable possibility. In such patients, fluoride may be retained with resulting higher tissue fluoride levels than in persons with normal renal function." Juncos LI, Donadio JV. (1972). Renal failure and fluorosis. Journal of the American Medical Association 222:783-5.

28. "Prolonged polydipsia (excessive thirst) may be hazardous to persons who live in areas where the levels of fluoride in drinking water are not those usually associated with significant fluorosis." Sauerbrunn BJ, et al. (1965). Chronic fluoride intoxication with fluorotic radiculomyelopathy. Annals of Internal Medicine 63: 1074-1078.

29. "The question of the effect of water containing 1 p.p.m. upon patients with severe impairment of kidney function requires special consideration in view of the fact that radiologic evidence of chronic fluorosis has been found in two persons with severe kidney disease who died at the early ages of 22 and 23 years, respectively..." Heyroth F. (1952). Hearings Before the House Select Committee to Investigate the Use of Chemicals in Foods and Cosmetics, House of Representatives, 82nd Congress, Part 3, Washington D.C., Government Printing Office, p. 28.

30. "All patients with dental fluorosis and anemia and/or signs of renal impairment should have radiographic examinations of the skeletal system to rule out the existence of fluoride osteosclerosis... It is likely that the reason our patient retained fluorine in his bones was that he had renal damage of long standing; without this the osteosclerosis might not have developed." Linsman JF, McMurray CA. (1943). Fluoride osteosclerosis from drinking water. Radiology 40: 474-484.

31. "Fluoride is bone-seeking due to its high affinity for calcium phosphate and therefore accumulates in bone. Radiological changes can be quite similar to changes of renal osteodystrophy, and therefore the diagnosis may be missed unless specifically investigated." Bansal R, Tiwari SC. (2006). Back pain in chronic renal failure. Nephrology Dialysis Transplantation 21:2331-2332.

32. "[R]enal disease and fluoride cause similar changes. This overlap makes it very difficult to assess the effect of fluoride per se in these patients." Johnson W, et al. (1979). Fluoridation and bone disease in renal patients. In: E Johansen, DR Taves, TO Olsen, Eds. Continuing Evaluation of the Use of Fluorides. AAAS Selected Symposium. Westview Press, Boulder, Colorado. pp. 275-293.

33. "The findings of osteosclerosis, osteomalacia and increased bone resorption have been confirmed in experimental fluorosis in animals. It can be seen, therefore, that fluoride bone disease could mimic renal osteodystrophy." Cordy PE, et al. (1974). Bone disease in hemodialysis patients with particular reference to the effect of fluoride. Transactions of the American Society of Artifical Internal Organs 20: 197-202.

34. "[T]he observed changes (osteomalacia, osteitis fibrosa and osteoporosis) were similar to those induced by high doses of fluoride in humans and experimental animals, in which widened osteoid seams have been observed, and where increased areas of resorption due to secondary hyperparathyroidism may be seen." Posen GA, et al. (1971). Renal osteodystrophy in patients on long-term hemodialysis with fluoridated water. Fluoride 4: 114- 128.

35. "Osteosclerosis from chronic renal disease associated with secondary hyperparathyroidism may produce similar changes (as fluorosis), and indeed

may have intensified the findings (of fluorosis) in one of our patients." SOURCE: Morris JW. (1965). Skeletal fluorosis among indians of the American Southwest. American Journal of Roentgenology, Radium Therapy & Nuclear Medicine 94: 608-615.

36. In the fluoride-treated patients, "we observed osteoclasts resorbing bone beneath osteoid seams, and fragments of osteoid isolated in the bone marrow. This type of resorption beneath unmineralized bone matrix is often observed in osteomalacia, particularly that caused by renal abnormalities and associated secondary hyperparathyroidism." Lundy MW, et al. (1995). Histomophometric analysis of iliac crest bone biopsies in placebo-treated versus fluoride-treated subjects. Osteoporosis International 5:115-129.

37. "During our field studies our attention was drawn to the high incidence of bone disease and bony leg deformities with clinical invalidism in children exposed to high intake of endemic fluoride in drinking water. Due to variable and unusual clinical features, these children (with fluorosis) had often been mistaken for rickets, renal osteodystrophy, osteosclerosis and hereditary osteopathies etc." Teotia M, Teotia SP, Singh KP. (1998). Endemic chronic fluoride toxicity and dietary calcium deficiency interaction syndromes of metabolic bone disease and deformities in India: year 2000. Indian Journal of Pediatrics 65:371-81.

38. "A 40-year-old American Indian woman with chronic pyelonephritis and renal failure complained of progressive muscular weakness, fatigue, and increasingly severe pain in her ribs, low back, and left hip. X-ray study of these areas showed evidence of osteosclerosis, compatible with either renal osteodystrophy or skeletal fluorosis... No other pathologic changes were apparent in the bones or ligaments..." Fisher JR, et al. (1981). Skeletal fluorosis from eating soil. Arizona Medicine 38: 833-5.

39. "Human kidneys... concentrate fluoride as much as 50-fold from plasma to urine. Portions of the renal system may therefore be at higher risk of fluoride toxicity than most soft tissues." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p236.

40. "Based on these studies it is known that, among soft tissues, the kidney has the highest fluoride concentrations. This is mainly attributable to high concentrations within the tubular and interstitial fluids in the medullary papillary regions." Whitford G. (1996). The Metabolism and Toxicity of Fluoride. 2nd Revised Edition. Karger: Basel. p 30. (NOTE: Since the publication of this report, it has been discovered that the soft tissue of the pineal gland contains higher fluoride levels than the kidney.)

41. "Effects in the kidneys are of the first to be seen in fluoride exposure of mammals. The reason for this is considered to be the relative high concentrations of fluoride found in the kidneys and in the urine during exposure." Hongslo CF, Hongslo JK, Holland RI. (1980). Fluoride sensitivity of cells from different organs. Acta Pharmacologica et Toxicologica 46:73-77.

42. "OBJECTIVE: To explore the dose-effect relationship of water fluoride levels and renal damage in children and observe the difference of renal function between high-loaded fluoride people and dental fluorosis people in the same water fluoride level region. METHODS: 210 children were divided into seven groups in term of drinking water fluoride levels and whether they suffered from dental fluorosis. Fluoride concentrations in urine and serum and activities of urine NAG and gamma-GT were determined. RESULTS: The urine and serum fluoride of high-loaded fluoride people and dental fluorosis people increased compared with control, moreover fluoride contents in urine and serum increased gradually with the increase of fluoride level in drinking water.

Urine NAG and gamma-GT activities significantly increased in dental fluorosis people from area of 2.58 mg/L fluoride in drinking water and in those two groups from area of 4.51 mg/L fluoride in drinking water. Moreover, there existed an obvious dose-effect relationship between the drinking water fluoride concentration and NAG and gamma-GT activity. CONCLUSION: Over 2.0 mg/L fluoride in drinking water can cause renal damage in children, and the damage degree increases with the dinking water fluoride content. Renal damage degree is not related to whether the children suffered from dental fluorosis and mainly due to water fluoride concentration." Liu JL, Xia T, Yu YY, Sun XZ, Zhu Q, He W, Zhang M, Wang A. (2005). [The dose-effect relationship of water fluoride levels and renal damage in children] Wei Sheng Yan Jiu. 34(3):287-8.

43. "In my medical practice I have encountered two cases in which fluoridated water interfered with kidney function. One of these, Miss G.L., 27 years old, had been under my care from July 1966 to September 1969 for allergic nasal and sinus disease. She had a congenital cystic kidney necessitating consultation with a urologist. As shown by its inability to excrete indigo carmine, a dye employed as an indicator of kidney function, the left kidney was not working and was slated for removal. This patient also reported having pains and numbness in arms and legs, spasticity of the bowels, ulcers in the mouth, headaches, and a progressive general disability - symptoms of possible intolerance to fluoride - for about 15 years. Her water supply (Highland Park, Michigan) had been fluoridated since September 1952. On February 1, 1967, I instructed her to avoid fluoridated water for drinking and cooking. Within a few weeks all the above-mentioned symptoms disappeared, and another kidney dye test on June 12, 1967, astonishingly revealed that the left kidney had begun to function again! A follow-up 5 years later revealed that the patient had remained in good health as long as she refrained from drinking fluoridated water.

44. The other patient, Mrs E.P., 39 years old, who visited me on August 25, 1969, had advanced pyelitis of the left kidney, beginning with osteosclerotic changes in the pubic bones, and exostosis at the sternum, accompanied by the same clinical picture as in the patient just discussed. The function of the diseased kidney and the other symptoms improved markedly within six weeks after she stopped drinking the municipal water in Midland, Michigan (fluoridated since January 1946). Twenty-four hour urinary fluoride excretions before and after the tests were 2.39 and 4.20 mg, respectively. For most of her life she had resided in Lubbock, Texas (water supply fluoride then 4.4 ppm). The development of osteosclerosis in this case was not surprising, since - as recorded in fluoridated Evanston, Illinois, and also in a fluoridated Finnish community - kidney patients retain as much as 60% more fluoride than do persons in normal health. In the Finnish work blood fluoride levels were 3 to 4 times higher than normal in the patients with renal disorders." Waldbott GL, et al. (1978). Fluoridation: The Great Dilemma. Coronado Press, Inc., Lawrence, Kansas. pp. 155-156.

45. "Evidence of chronic fluoride intoxication, associated with renal tubular dysfunction in the group of FMBD patients, brings to focus the possibility that fluoride toxicity may be responsible for both bone and kidney disease in FMBD... Evidence is available in the literature to support our observation of fluoride-induced renal damage." Harinarayan CV, et al. (2006). Fluorotoxic metabolic bone disease: an osteo-renal syndrome caused by excess fluoride ingestion in the tropics. Bone 39: 907-14.

46. "Renal function especially glomerular filtration rate was very sensitive to fluoride exposure. Inorganic phosphate concentrations in urine were significantly lower in the residents in fluorosis areas in China than in non-fluorosis area in China and Japan.... The results show that exposure to excess fluoride has caused dental/skeletal fluorosis and reduced glomerular filtration rate in the residents living in

fluorosis areas..” Ando M, et al. (2001). Health effects of fluoride pollution caused by coal burning. Science of the Total Environment 271(1-3):107-16.

47. “We report a case of fluoride intoxication related to potomania of Vichy water, a highly mineralized water containing 8.5 mg/L of fluoride. Features of fluoride osteosclerosis were prominent and end-stage renal failure was present. The young age of the patient, the long duration of high fluoride intake, and the absence of other cause of renal insufficiency suggest a causal relationship between fluoride intoxication and renal failure.” Lantz O, et al. (1987). Fluoride-induced chronic renal failure. American Journal of Kidney Disorders 10(2):136-9.

48. “Kidney damage (1) in distal and proximal tubular function, (2) in glomerular filtration, occurred in 40 to 60 year olds residing in El Quel an endemic fluorosis area in Southern Algeria compared to normals from Algiers. Functional renal disturbances are proportional to the degree of fluoride accumulation which incrases in relation to: a) the level of fluoride in drinking water, b) the fluoride level in nails and c) the radiological grade (O I II III) of fluorosis.” Reggabi M, et al. (1984). Renal function in residents of an endemic fluorosis area in southern Algeria. Fluoride 17: 35-41.

49. “Complete urine examinations including urea, creatinine and fluoride clearances were carried out on 25 cases of endemic fluorosis... In 10 healthy nonfluorotic subjects urea, creatinine and fluoride clearances were measured simultaneously as a control. The following results were obtained: The mean values for maximum urea clearance and standard urea clearance were low compared to mean control values. The decline in creatinine and fluoride clearances compared to the controls was statistically significant, an indication that chronic fluoride intoxication leads to a distinct impairment of glomerular function in human beings.” Jolly SS, et al. (1980). Kidney changes and kidney stones in endemic fluorosis. Fluoride 13: 10-16.

50. “The kidney function of 25 radiologically proven cases of endemic fluorosis was studied at the Medical College of Patiala. Evidence of statistically significant decrease in creatinine clearance is presented. Some structural abnormalities in kidneys have been described. No significant tubular abnormalities could be demonstrated by water loading and water deprivation tests.” Singla VP, et al. (1976). The kidneys. Fluoride 9: 33-35.

51. “The question is whether the chronic excessive fluoride intake caused the renal damage (either directly or indirectly) or whether the systemic fluorosis was due to impaired renal function.” Juncos LI, Donadio JV Jr. (1972). Renal failure and fluorosis. Journal of the American Medical Association 222(7):783-5.

52. “The distribution of findings suggestive of not-normal genitourinary conditions was approximately the same for the fluoride-exposed group and the control group except for the incidence of albuminuria which was found to be higher in the exposed group. This finding and its distribution in the subgroups suggest the possibility of a relationship between fluoride exposure and increased excretion of albumin in the urine.” Derryberry OM, et al. (1963). Fluoride exposure and worker health. Archives of Environmental Health 6: 503-511.

53. “There is evidence from animal experiments that fluoride in large amounts causes gross alterations of renal structure and decreased tubular function. Injury with necrosis of the columnar cells lining the proximal convoluted tubules is the primary lesion... Kidney function tests were done in 28 of our cases. Blood urea ranged from 15 to 20 mg/100 ml with an average of 33. Urea clearance was done in only six cases and showed impaired function in five. The ratio of the concentration of inorganic phosphorous excreted in the urine to that in the serum is approximately 50 in normal subjects. This value increases with renal insufficiency. It averaged 67 in our cases. We found significant aminoaciduria in 4 cases. The concentration and dilution tests were

essentially normal. Other kidney function tests were not done, but the existence of aminoaciduria, slightly increased blood urea, impairment of urea clearance, and a high phosphorus ratio as described all suggest a subtle disturbance of kidney function which needs further elaboration." Singh A, et al. (1963). Endemic fluorosis. Epidemiological, clinical and biochemical study of chronic fluoride intoxication in Punjab. Medicine 42: 229-246.

54. "Of the 19 patients in the series, 12 were examined for the presence of albuminuria, and this was found to be present in 11. The urinary excretion of fluorine damages the kidney, which results in the common finding of albuminuria... Renal damage does appear to be a frequent occurrence and is probably due to the excretion of fluorine, analagous to renal damage caused by heavy metals." Kumar SP, Harper RA. (1963). Fluorosis in Aden. British Journal of Radiology 36: 497-502.

55. "Urea Clearance Test: This test (Van Slyke method) was performed in fourteen cases... The results showed marked impairment of renal function. The mean figures for the maximum and standard clearance were 26.24 and 39.67% of the normal respectively." Siddiqui AH. (1955). Fluorosis in Nalgonda district, Hyderabad-Deccan. British Medical Journal ii (Dec 10): 1408-1413.

56. "Osteosclerosis may be a dangerous sequel to the chronic ingestion of fluorine-containing water supplies, since it may give rise to a secondary anemia due to encroachment upon the blood-forming marrow. There is also the possibility of kidney damage due to chronic fluoremia." Linsman JF, McMurray CA. (1943). Fluoride osteosclerosis from drinking water. Radiology 40: 474-484.

57. "Renal function was tested by determination of the filtration rate, blood urea clearance, uric acid clearance, and chloride clearance. (a) Filtration rate - ... In six cases, the filtration rate was below the normal lower limit and in three cases was within normal limits or above. (b) Blood urea clearance - This was estimated by van Slyke's method. In all the cases the figures were below the normal lower limit and in some very much below the limit. The filtration rate and blood urea clearance values show that, in the majority of the cases, kidney function is impaired, in some markedly so." Shortt HE, et al. (1937). Endemic fluorosis in the Madras presidency. Indian Journal of Medical Research 25: 553-568.

58. "In the 1960s, the widespread use of the inhalational anaesthetic methoxyflurane was associated with a significant occurrence of postoperative renal dysfunction. This was attributed to hepatic biotransformation of methoxyflurane and subsequent release of inorganic fluoride ions into the circulation. Based upon the clinical experience with methoxyflurane, serum fluoride concentrations exceeding 50 mumol/l were considered to be nephrotoxic." Nuscheler M, et al. (1996). [Fluoride-induced nephrotoxicity: fact or fiction?]. Anaesthesist 45 Suppl 1:S32-40.

59. "Evidence for fluoride nephrotoxicity has accumulated largely from the adverse effects of halogenated anesthetics on renal function." Partanen S. (2002). Inhibition of human renal acid phosphatases by nephrotoxic micromolar concentrations of fluoride. Experimental and Toxicologic Pathology 54(3):231-7.

60. "The predominant factors in the production of methoxyflurane nephrotoxicity appear to be high methoxyflurane dosage and serum inorganic fluoride concentration." Mazze RI. (1976). Methoxyflurane nephropathy. Environmental Health Perspectives 15:111-9.

61. "Kidney damage can appear within a few days following methoxyflurane anesthesia. This phenomenon was studied by Cousins and Mazze (1973), who reported that peak (i.e. transient) post-anesthesia plasma F- levels in afflicted humans exceeded 90 umol/l. The nephrotoxicity was accompanied by an increased urine volume of low osmolarity, and increased thirst, with the syndrome

tending to obey a short-term dose-response pattern in man. Mazze et al. (1972) and Cousins et al. (1974) have shown that kidney damage in rats exposed to methoxyflurane was caused by high inorganic fluoride concentrations and not by oxalic acid, which is also a metabolic breakdown product of methoxyflurane. Taves et al. (1972) also related the nephrotoxicity and polyuria to the metabolically released inorganic fluoride." Marier J, Rose D. (1977). Environmental Fluoride. National Research Council of Canada. Associate Committe on Scientific Criteria for Environmental Quality. NRCC No. 16081.

62. "In the kidney, glomerular hypercellularity and mesangial proliferation was apparent in animals from both the NaF and AlF3 treatment groups. Congruent with the glomerular changes was deposition of protein in the tubules. There was a significant increase in the extent of monocyte infiltration in the animals treated with with AlF3 compared to controls... Histological evidence of glomerular distortions and other signs of kidney disorders were found in animals in both the AlF3 and NaF groups, although expressed differently. It is possible that physiological alterations in kidney function, not related to histological evidence of injury, were greater in the AlF3 group than the NaF group. The overall Al content of the kidneys in the AlF3 group was nearly double that found in the NaF and control groups. Since the kidney is critical to the elimination of both Na and Al, such alterations may have influenced the body burden of these elements, detoxification in general, as well as homeostasis of a variety of important ions, such as calcium." Varner JA, et al. (1998). Chronic administration of aluminum-fluoride and sodium-fluoride to rats in drinking water: Alterations in neuronal and cerebrovascular integrity. Brain Research 784: 284-298.

63. "The mean kidney enzyme activity rate was measured at 0.3863 for the control animals. In studies on experimental animals a marked reduction in kidney enzyme activity was noted in the 1 ppm group; it was measured at 0.2016 showing 47.8% decrease over the normal. Animals in the 5, 10, and 100 ppm groups showed no further ostensible inhibition in activity rate." Sullivan WD. (1969). The in vitro and in vivo effects of fluoride on succinic dehydrogenase activity. Fluoride 2:168-175.

64. "No gross lesions were found in the kidneys. Microscopic examinations were made on the kidneys from 6 animals which had not received fluoride in the drinking water, on 3 receiving 1 ppm, on 1 receiving 5 ppm, and on 6 receiving 10 ppm. Interstitial nephritis was observed in all the animals examined histologically, and the severity increased in proportion to the level of the sodium fluoride in the drinking water. Renal tubule hypertrophy and hyperplasia were found in those animals receiving sodium fluoride in the water but not in the 6 rats which had not been given sodium fluoride supplementation." Ramseyer WF, et al. (1957). Effect of sodium fluoride administration on body changes in old rats. Journal of Gerontology 12: 14-19.

65. "[K]idneys of animals drinking water with containing 5 ppm fluoride showed certain cytochemical characteristics which may be interpreted in terms of deleterious metabolic effects in the kidneys, which excrete most of the fluorides from the organism. This is in agreement with some earlier reported observations that kidneys, more than other organs of the body, begin to show microscopic changes after prolonged daily ingestion levels of fluoride which may produce few gross changes other than fluoride storage in bones and teeth. Ogilvie (1948) showed that a dose of 7.5 mg of sodium fluoride given intraperitoneally each day for 100 days to rats produced morphological changes in the kidneys which included oedema in the interstitial connective tissue and increased vascularity of the glomeruli and medulla. These observations suggest that fluoride compounds cannot be treated as totally harmless when administered over long periods of time in relatively small concentrations... It is believed that the increased thirst and polyyuria observed in fluoridated animals is a result of functional changes in the kidneys... Our studies show a significant change in the

activity of succinate dehydrogenase in the kidneys of the animals maintained on higher levels of fluoride in the drinking water." Manocha SL, et al. (1975). Cytochemical response of kidney, liver and nervous system to fluoride ions in drinking water. Histochemical Journal 7: 343-355.

66. "Our study provides the first evidence that one of the effects of long-term F exposure is a change in expression of the plasma membrane and endoplasmic reticulum Ca++ pumps in the kidney. In summary, we provided rats with fluoride in their drinking water, which produced graded, plasma fluoride concentrations that occur in humans. Our studies showed that chronic high fluoride ingestion decreases the rate of Ca++ transport across renal tubule endoplasmic reticulum and plasma membranes, and reduced the amount of ER and PM Ca++ pump protein present in the kidney membranes. We conclude that chronic high fluoride ingestion may decrease the expression, increase the breakdown, or increase the rate of turnover of plasma membrane and endoplasmic reticulum Ca++ pump proteins and possibly other enzymes as well. The observed decreases in the rate of Ca++ transport and associated decreases in plasma membrane and endoplasmic reticulum Ca++ pump expression could affect in vivo Ca++ homeostasis." Borke JL, Whitford GM. (1999). Chronic fluoride ingestion decreases 45Ca uptake by rat kidney membranes. Journal of Nutrition 129:1209-13.

67. "These results demonstrate that NaF induces the process of apoptosis in renal tubules via activation of the Bax expression and Bcl-2 suppression and this action is dose dependent; thus, apoptosis plays some role in the kidney injury induced by fluoride. Our data also suggest that OPN probably acts in a protective role against apoptosis in fluoride-treated renal cells." Xu H, et al. (2006). Effect of sodium fluoride on the expression of bcl-2 family and osteopontin in rat renal tubular cells. Biological Trace Element Research 109:55-60.

68. "An experiment was carried out on Sprague-Dawley rats (adult males) that for 50 days were administered, in the drinking water, NaF and NaF with caffeine (doses, respectively: 4.9 mg of NaF/kg body mass/24 h and 3 mg of caffeine/kg body mass/24 h). Disturbances were noted in the functioning of kidneys, which were particularly noticeable after the administration of NaF with caffeine. Changes in the functioning of kidneys were also confirmed by such parameters as the level of creatinine, urea, protein, and calcium. Modifications of the enzymatic antioxidative system (superoxide dismutase, catalase, and glutathione peroxidase) and lipid peroxidation (malondialdehyde) were also observed. Changes in the contents of the above parameters as well as pathomorphological examinations suggest increased diuresis, resulting in dehydration of the rats examined." Birkner E, et al. (2006). Influence of Sodium Fluoride and Caffeine on the Kidney Function and Free-Radical Processes in that Organ in Adult Rats. Biological Trace Element Research 109:35-48.

69. "This experiment was designed to investigate the lipid peroxidation and histological effects of chronic fluorosis on first- and second-generation rat kidney tissues... Hydropic epithelial cell degenerations and moderate tubular dilatation were observed in some proximal and distal tubules. There were markedly focal mononuclear cell infiltrations and hemorrhage at some areas of the interstitium, especially at the corticomedullar junction. Mononuclear cell infiltrations were also evident in some peritubular and perivascular areas. Most of the vascular structures were congestive. Many Bowman capsules were narrowed. The severe degenerative changes in most of the shrunken glomerules and vascular congestion were also observed." Karaoz E, et al. (2004). Effect of chronic fluorosis on lipid peroxidation and histology of kidney tissues in first- and second-generation rats. Biological Trace Element Research 102:199-208.

70. “Some halogenated agents, especially methoxyflurane, because of a higher level of fluoride production, induce a renal concentrating defect that could be related to an ascending limb impairment. We investigated the mechanisms of fluoride toxicity on an immortalized cell line... The results suggest that the Na-K-ATPase pump is a major target for fluoride toxicity in Henle’s loop.” Cittanova ML, et al. (2002). Fluoride ion toxicity in rabbit kidney thick ascending limb cells. European Journal of Anaesthesiology 19(5):341-9.

71. “The purpose of this study was to assess renal damage in experimental fluorosis. Young albino rabbits were injected with 5, 10, 20, and 50 mg NaF/kg body weight/day for fifteen weeks and then sacrificed. No significant clinical signs of toxicity were found in animals exposed to the lowest dose. At the higher doses, however, the cytoachitecture of the kidneys exhibited increasing amounts of cloudy swellings, degeneration of tubular epithelia, tissue necrosis, extensive vacuolization in renal tubules, hypertrophy and atrophy of glomeruli, exudation, interstitial oedema, and interstitial nephritis. These changes in the kidneys result in impaired renal function in chronic fluoride intoxication.” Shashi A, et al. (2002). Toxic effects of fluoride on rabbit kidney. Fluoride 35: 38-50.

72. “Fluoride nephropathy was exhibited as decreased fluoride excretion and appearance of urinary B2 microglobulin.” Cao J, et al. (2001). Prevention of brick teas fluorosis in rats with low-fluoride brick tea on laboratory observation. Food & Chemical Toxicology 39: 615-619.

73. “The toxicokinetics of F were studied by analyzing plasma concentration of F after intravenous injection of 2.86, 5.71 and 8.57 mg/kg into male Wistar rats. A dose-response relationship was recognized between these F doses and renal tissue injury.” Dote T, et al. (2000). Toxicokinetics of intravenous fluoride in rats with renal damage caused by high-dose fluoride exposure. International Archives of Occupational and Environmental Health 73 Suppl:S90-2.

74. “Results showed that the total phospholipid content significantly decreased in the kidney of the rats treated with high doses of fluoride and the main species influenced were phosphatidylethanolamine (PE) and phosphatidylcholine (PC). Decreased proportions of polyunsaturated fatty acids were observed in PE and PC in kidney of fluoride-treated animals compared to controls. No changes could be detected in the amounts of cholesterol and dolichol in kidneys between the rats treated with fluoride and controls. A significant decrease of ubiquinone in rat kidney was observed in the groups treated with excessive fluoride. High levels of lipid peroxidation were detected in kidney of the rats with fluorosis. It is plausible that the specific modification of lipid composition results from lipid peroxidation. The oxidative stress and modification of cellular membrane lipids may be involved in the pathogenesis of chronic fluorosis and provide a possible explanation for the gross system damage observed in the body, especially in soft tissues and organs.” Guan ZZ, et al. (2000). Changed cellular membrane lipid composition and lipid peroxidation of kidney in rats with chronic fluorosis. Archives of Toxicology 74:602-8.

75. “Wistar rats were provided with distilled water containing NaF(100 mg/L), and were administered through gavage with Na2SeO3[0.1 mg/(kgBW.d)] and/or ZnSO4[14.8 mg/(kg BW.d)]. The results of biochemical, pathological and ultrastructural examinations showed that fluoride could cause serious renal impairments. The major damage induced by fluoride was epithelia of proximal renal tubules. The lipid peroxidation might be one of the mechanisms of fluoride toxicity. Na2SeO3 and ZnSO4 could antagonize the renal impairments induced by fluoride through their antioxidation. The cooperative effect of Na2SeO3 and ZnSO4 was more powerful than either Na2SeO3 or ZnSO4 alone.” Xue C, et al. (2000). [Study on antagonistic effects of

selenium and zinc on the renal impairments induced by fluoride in rats] Wei Sheng Yan Jiu 29(1):21-3.

76. “In kidney, focal intertubular mononuclear cell infiltration was observed even at the 79 ppm level. Besides, at 132 ppm, atrophied glomeruli with more periglomerula space were noticed. More pronounced changes like periglomerular fibrosis and tubular nephrosis were observed at 191 ppm F level.” Kapoor V, et al. (1993). Effect of dietary fluorine on histopathological changes in calves. Fluoride 26: 105-100.

77. “At the higher dose (84 ppm in water), fluoride produced polyuria, polydipsia, and weight loss. Previous studies showed that fluoride is nephrotoxic and produces polyuria and polydipsia in the rat.” Turner RT, et al. (1989). The effects of fluoride on bone and implant histomorphometry in growing rats. Journal of Bone and Mineral Research 4: 477-484.

78. “The effects of chronic fluoride excess in the mouse were studied by means of polarizing microscopy in combination with a special staining technique employing Sirius red F3B, a dye which renders collagen fibrils sharply visible. It was observed that changes occur in three renal areas: the interstitium, the intrinsic vasculature and Bowman’s capsule. The collagen content of each area increases after about 100 days of the total fluoride exposure... Although Bowman’s capsule was thickened, the glomerular tufts and the nephrons showed edematous swelling and degeneration. A concept is developed to illustrate how early inflammatory response to the chemical effects of fluoride excess leads to vascular injury, parenchymal ischemia and fibrosis.” Greenberg SR. (1986). Response of the renal supporting tissues to chronic fluoride exposure as revealed by a special technique. Urologia Internationalis 41(2):91-4.

79. “marked renal toxicity was observed in postweaning rats treated on Day 29. The NaF exposure resulted in increased kidney weight and kidney/body weight ratio, profound diuresis, decreased urinary osmolality, and decreased ability to concentrate urine during water deprivation. Urinary chloride excretion was decreased for the first 2 days after NaF exposure, then increased in water-deprived rats 120 hr after treatment. Glucosuria and hematuria were present for 2 days after treatment with 48 mg/kg. Histological lesions were apparent in the proximal tubules of the treated Day 29 rats. Thus, the kidney of the suckling rat is largely unresponsive to NaF toxicity. Renal sensitivity increases abruptly after weaning in the Day 29 rat.” Daston GP, et al. (1985). Toxicity of sodium fluoride to the postnatally developing rat kidney. Environmental Research 37:461-74.

80. “Dose related congestion of the duodenum, liver, kidney, and lung was observed in all animals. For the two higher doses, kidney degeneration and tubular necrosis were associated with glomerular inflammation. Serum fluoride had a dose related increase, while serum calcium and glucose concentrations showed initial dose dependent decreases. Diuresis was increased for the two higher doses on day 3 or 4 following treatment.. The authors conclude that acute fluoride poisoning in sheep induces severe disturbances of kidney and liver function as reflected by the altered activity of many enzymes.” Kessabi M, et al. (1985). Experimental acute sodium fluoride poisoning in sheep: Renal, hepatic, and metabolic effects. Fundamentals of Applied Toxicology 7: 93-105

81. “Activities of various enzymes were determined biochemically and histochemically in the liver and kidney of rats subjected for 10 mo. to fluoride (F-) concentrations of 0 (control), 10 (group 1) and 25 ppm (group 2) in drinking water. The activity of alkaline phosphatase, acid phosphatase and succinic dehydrogenase decreased. ATPase activity increased in liver and kidney of group 2 (25 ppm) animals. Lactic dehydrogenase activity also decreased but only in the kidney histochemically.

Alterations in enzyme activities were pronounced in proximal and distal convoluted tubules of the kidney... F- interfered with intracellular metabolism in liver and kidney." Singh M, Kanwar KS. (1981). Effect of fluoride on tissue enzyme activities in rat: Biochemical and histochemical studies. Fluoride 14: 132-141.

82. "Effects in the kidneys are of the first to be seen in fluoride exposure of mammals. The reason for this is considered to be the relative high concentrations of fluoride found in the kidneys and in the urine during exposure." SOURCE: Hongslo CF, Hongslo JK, Holland RI. (1980). Fluoride sensitivity of cells from different organs. Acta Pharmacologica et Toxicologica 46:73-77..

83. "The present study assesses the effect of sodium fluoride administration on kidneys of mice. One hundred adult male Albino mice were fed 10 ppm (Group A), 500 ppm (Group B), and 1000 ppm (Group C) of sodium fluoride for 3 months... The most consistent changes in the kidneys were cloudy swelling of the tubular cells. In the highest dosage groups (B and C), sacrificed at the end of three months, we found marked necrosis of tubular cells, atrophy of the glomeruli, and areas of interstitial infiltration of round cells. It is concluded that kidneys are adversely affected by prolonged use of sodium fluoride." Kour K, Singh J. (1980). Histological findings in kidneys of mice following sodium fluoride administration. Fluoride 13: 163-167.

84. "In summary, Fischer 344 rats pretreated with NaF or anesthetized with methoxyflurane showed more diuresis and natriuresis than did control animals. Urinary osmolarity was lower in the fluoride-treated group. Free water reabsorption was markedly reduced, while free water excretion was not significantly altered by pretreatment with fluoride. The results suggest that NaF and methoxyflurane alter renal function primarily by inhibiting active chloride transport in the ascending limb of Henle's loop." Roman RJ, et al. (1977). Renal tubular site of action of fluoride in Fischer-344 rats. Anesthesiology 46: 260-264.

85. "In the present study, evidence was obtained which indicated a close relationship between polyuria and changes in certain urinary ion excretion in fluorosis. The maximum increase in urine volume occurred during the first day following treatment. Polyuria was accompanied by significant increases in urinary K+, Na+, Mg2+, Ca2+, and inorganic phosphate... In our experiments, mitochondrial ATPase in the kidney was found to be decreased by the dose of fluoride tested. To our knowledge, this is the first report on the in vivo effects of fluoride on renal (Na+ K+)-ATPase activity. The decrease in activity is apparently responsible for urinary Na+ loss and a decrease in serum Na+. In addition fluoride treatment also resulted in a significant decrease in (Ca2+ Mg2+)-ATPase activity which can be held responsible for the increase in urinary Ca2+." Suketa Y, Mikami E. (1977). Changes in urinary ion excretion and related renal enzyme activities in fluoride-treated rats. Toxicology and Applied Pharmacology 40: 551-9.

86. "In the Sprague-Dawley rats, during moderate fluoride administration (120 umol/kg per day), urine osmolality and cyclic AMP excretion decreased and urine volume increased... During larger daily doses of fluoride (240 umol/kg per day) urinary osmolality and cyclic AMP decreased and volume increased, which was similar to the changes seen during lower fluoride dosages, but these parameters did not change after exogenous vasopressin." Wallin JD, Kaplan RA. (1977). Effect of sodium fluoride on concentrating and diluting ability in the rat. American Journal of Physiology 232: F335-40.

87. "Frascino et al (1970, 1972) studied the effects of inorganic fluoride on the renal concentration mechanisms in dogs. The high blood fluoride levels interfere with both the generation of maximally concentrated urine and tubular free water reabsorption." Gottlieb LS, Trey C. (1974). The effects of fluorinated anesthetics on the liver and kidneys. Annual Review of Medicine 25: 411-429.

88. “Supplemental fluoride lowered both the urinary calcium and phosphorus concentrations. The lowering of urinary calcium concentration was due to a dilution of excreted calcium by a fluoride-induced polyuria, since dietary sodium fluoride did not reduce the urinary calcium excretion (% of intake)... The polyuria induced by fluoride was accompanied by an enhanced sodium excretion and a decrease in osmolality. These results were consistent with previous findings that the administration of fluoride caused polyuria in laboratory animals. Further, the renal sodium gradient was markedly reduced in the fluoride-induced diuretic rat.” Hamuro Y. (1972). Relationship between prevention of renal calcification by fluoride and fluoride-induced diuresis and reduction of urinary phosphorus excretion in magnesium-deficient KK mice. Journal of Nutrition 102: 893-900.

89. “The present findings indicate that 50 uM plasma fluoride results in a definite increase in rate of urine flow and are consistent with the estimate made from the experience of Goldemberg in humans. The present findings also agree with the data from 3 patients who had received methoxyflurane anesthesia. Two of these patients had inorganic serum fluoride concentrations of 20 to 30 uM and no obvious diuresis; whereas the patient with a concentration of 275 uM had marked polyuria. The agreement lends further weight to the suggestion that metabolism of methoxyflurane to inorganic fluoride is a major factor in the nephrotoxicity noted after anesthesia with methoxyflurane.” SOURCE: Whitford GM, Taves DR. (1971). Fluoride-induced diuresis: Plasma concentrations in the rat. Proceedings of the Society for Experimental Biology and Medicine 137:458-460.

90. “the kidneys were abnormal in most of the animals given fluorides, with the most severe changes associated with the highest doses and longest survival periods. In addition to the previously well-known dilatation of the renal loops and ducts, PAS-positive casts were seen in pronounced cases in many dilated ducts and also typical granlulomas in the medullo-cortical zone and occasionally in the outer part of the cortex.”
SOURCE: Poulson H, Ericcson Y. (1965). Chronic toxicity of dietary sodium monofluorophosphate in growing rats, with special reference to kidney changes. Acta pathologica et microbiologica Scandinavica 65: 493-504.

91. “The renal lesions seen in rats ingesting 200-500 ppm fluoride in the water for 5 days were: (1) necrosis of the tubular cells, and (2) a dilatation of the tubules especially in the corticomedullary region. Neither lesion occurred in all the rats examined; necrosis was seen more often than tubular dilatation. The tubular dilatation was similar to the lesion seen in a few rats after single, large doses of sodium fluoride (Taylor et al., 1961) and to the lesion described by Pindborg (1957) after feeding 0.05% sodium fluoride in the diet for 21-28 days... The ingestion of fluoride levels of 1-50 ppm for 6 months did not produce renal lesions in the rat. A level of 100 ppm fluoride for this period of time caused dilatation of the renal tubules in two of 12 rats.” Taylor JM, et al. (1961). Toxic effects of fluoride on the rat kidney. II. Chronic effects. Toxicology and Applied Pharmacology 3:290-314.

92. “All animals in group 2, which received the fluoride throughout the entire experimental period, revealed kidney changes histologically typical of chronic fluoride intoxication... The sequence of the changes in the “fluorosed kidney” is dilation of the Henle loops, followed by dilation of the convoluted tubules and later by inflammation. During the recovery process the dilation disappeared first, followed by a slower reduction of inflammation. As would be expected the amount of fibrosis was unchanged. Finally, it should be mentioned that a year after the cessation of excessive fluoride diet a minority of rats still had dilated Henle loops and convoluted tubules. In these cases the interstitial inflammation and fibrosis were most pronounced. It remains

for future research to establish how much fluoride it is possible to give rats without creating irreversible kidney changes." Lindemann G, et al. (1959). Recovery of the rat kidney in fluorosis. Archives of Pathology 67: 30-33.

93. "Two hundred and twenty-six white rats were given a diet containing 0.05 per cent sodium fluoride (226 ppm) for periods ranging from 3 to 56 days. It was established that changes in the kidneys occured regularly after 21-28 days on the diet... The kidney changes consisted primarily in dilatation of the Henle loops in the juxtacortical area of the medulla, soon followed by a flattening of the epithelium in the convoluted tubules in the cortex and a distention of the tubules, possibly due to some kind of 'stop' in the Henle loops." Pindborg JJ. (1957). The effect of 0.05 per cent dietary sodium fluoride on the rat kidney. Acta pharmacolgica et toxicologica 13: 36-45.

94. 'In previous papers, the author reported impairment of renal function due to fluorosis. The current study presents morphological renal changes of rabbits and young albino rats due to fluorosis... On gross examination, no marked changes were observed. However, in both groups which had been given 30 and 50 mg of NaF per kg of body weight, inflammatory changes in the glomeruli with increased cellularity, capillary hyperemia, exudation, hypertrophy or atrophy, tubular degeneration with cloudy swelling, vascular degeneration and protein casts or blood in the tubular lumens were seen microscopically... The above-mentioned morphological changes, combined with impairment of renal function described in the previous reports, indicate that fluoride causes serious damage to kidneys." Kawahara H. (1956). Experimental studies on the changes of the kidney due to fluorosis. Part III. Morphological studies on the changes of the kidney of rabbits and growing albino rats due to sodium fluoride. Shikoku Acta Medica 8:283-28. (Abstracted in: Fluoride 1972; 5:50-53.)

95. "In previous papers the author reported disturbances of renal function, especially changes in the urine, serum NPN, serum creatinine and serum chlornatrium of rabbits due to ingestion of fluoride. The current investigation deals with the effect of sodium fluoride on renal clearance, particularly on plasma urea clearance, on renal plasma flow (RPF) and glomerular filtration rate (GFR) in rabbits... The authors concluded from the experimental data presented here that the administration of fluoride in the above doses impairs the kidney function." Kawahara H. (1956). Experimental studies on the changes of the kidney due to fluorosis. Part II. Influence of sodium fluoride on renal clearance in rabbits. Shikoku Acta Medica 8:273-282. (Abstracted in: Fluoride 1972; 5:48-50.)

96. "The following experiments were conducted in order to determine possible renal changes by fluoride. Mature male rabbits weighing over 1.5 kg were given orally 1%, 3%, 5% sodium fluoride solutions which provided 10, 30 and 50 mg respectively of sodium fluoride per kg body weight... The above results or urine and blood suggest that renal damage occurs in fluorosis." Kawahara H. (1956). Experimental studies on the changes of the kidney due to fluorosis. Part I: Influence of sodium fluoride on the urine changes and non-protein nitrogen, creatinine and sodium chloride in serum of rabbits. Shikoku Acta Medica 8:266-272. (Abstracted in: Fluoride 1972; 5:46-48.)

97. "Rats given small amounts of NaF in the diet exhibited, in addition to the well-known skeletal and dental fluorosis, marked polydipsia and polyuria... The histological examination indicated that in the kidneys there was a vascular, glomerular and more obviously tubular degeneration leading finally to interstitial fibrosis." Bond AM, Murray MM. (1952). Kidney function and structure in chronic fluorosis. British Journal of Experimental Pathology 33: 168-176.

98. "The only organ found to be changed macroscopically was the kidney... The kidneys all had the same appearance, being contracted and paler in colour than normally; the surface was irregular, in most cases granulated. Only some of the rats

displayed macroscopic kidney changes of this kind... Under the microscope the kidneys of Rats 4,5,6,10,11,21,22,25 all showed signs of a chronic, mostly interstitial nephritis of uniform character; the changes were slight in Rats 5 and 6, which had not shown macroscopic changes, pronounced in the others... The changes in the kidney of Rat 21 are described below as being typical: The kidney is contracted, the surface very uneven. The changes are diffusely spread. Many glomeruli show serous or hyaline degeneration. The lumina of tubuli in most cases are irregularly dilated; this often forms cystic areas with an abundant serous content. Epithelium in the tubuli is low but well preserved. Universally there is proliferous development of connective tissue; the tissue is hyperaemic and contains scattered round-cell infiltration. A slight calcification in the tissue is observed in one place. Vessels normal." Roholm, K. (1937). Fluorine Intoxication. London: Lewis p 219.

F. Likely and Possible Damage to GI Tract: Teratogenicity, Altered Growth, and Functional Deficit.

Gastrointestinal symptoms (e.g. nausea, abdominal pain, vomiting) are the most common early symptoms of acute fluoride poisoning.

Among people hypersensitive to fluoride, gastrointestinal ailments have been produced by 1 mg tablets of fluoride or by consumption of water fluoridated at 1 ppm. (A 1 mg fluoride tablet is more damaging than 1 ppm fluoride in water because a tablet produces a higher fluoride concentration in the stomach.)

A review of reports to Poison Control Centers in Utah found that vomiting was induced in children after ingestion of 5 to 9 mg of fluoride. In double-blind experiments, single doses of 6.8 mg of fluoride have induced vomiting, and other gastric symptoms, within 30 minutes.

A single ingestion of as little as 3 mg of fluoride, in carefully controlled clinical trials, has been found to produce damage to the gastric mucosa in healthy adult volunteers. No research has yet been conducted to determine the effect of lower doses with repeated exposure.

In studies where fluoride has been used (at doses of 18-34 mg/day) as an experimental drug for the treatment of osteoporosis, gastrointestinal disturbances are one of the two main side effects consistently encountered.

Among humans suffering from skeletal fluorosis, there is an increased occurence of gastrointestinal disorders. When fluoride intake is reduced among these patients, the gastrointestinal problems are among the first symptoms to disappear.

1. "A program emphasizing a greatly reduced intake of fluoride and the inclusion of essential nutrients in the daily diet during pregnancy led to a striking increase in hemoglobin, an improved body mass index, fewer low birth weight babies, and reduced numbers of pre-term deliveries." Anemia in pregnancy: an easily rectifiable problem, Susheela Guest editorial Fluoride 43(2)104–107 April-June 2010
2. "It is concluded: 1) Ingested fluoride damages gastroduodenal mucosa. 2) Gastrointestinal discomfort can be an early warning sign of fluorosis. 3) Fluoride toxicity should be considered a possible reason for non-ulcer dyspepsia, especially in fluorosis endemic areas. 4) Gastrointestinal discomfort during sodium fluoride therapy calls for extreme caution and close monitoring. 5) Gastrointestinal discomfort in the form of dyspeptic symptoms should be an important iagnostic feature when identifying fluorosis patients and should not be dismissed as non-specific." Susheela AK, et al. (1992). Fluoride ingestion and its correlation with gastrointestinal discomfort. Fluoride 25: 5-22.
3. "The numerous fluoridation studies in the past failed to rigorously

test for changes in GI symptoms and there are no studies on drinking water containing fluoride at 4 mg/L in which GI symptoms were carefully documented." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 230.

4. "GI effects appear to have been rarely evaluated in the fluoride supplement studies that followed the early ones in the 1950s and 1960s." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 231.

5. "Studies are needed to evaluate gastric responses to fluoride from natural sources at concentrations up to 4 mg/L and from artificial sources." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 258.

6. "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.

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." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 229-230.

7. "Fluoride has several mechanisms of toxicity. Ingested fluoride initially acts locally on the intestinal mucosa. It can form hydrofluoric acid in the stomach, which leads to GI irritation or corrosive effects. Following ingestion, the GI tract is the earliest and most commonly affected organ system." eMedicine.com "Ingested fluoride is transformed in the stomach to hydrofluoric acid, which has a corrosive effect on the epithelial lining of the gastrointestinal tract. Thirst, abdominal pain, vomiting, and diarrhea are usual symptoms. Hemorrhage in the gastric mucosa, ulceration, erosions, and edema are common signs." Environmental Protection Agency. (1999). Recognition and Management of Pesticide Poisonings. 5th Edition. (Available online)

8. "Estimating the incidence of toxic fluoride exposures nationwide also is complicated by the existence of biases. Parents or caregivers may not notice the

symptoms associated with mild fluoride toxicity or may attribute them to colic or gastroenteritis, particularly if they did not see the child ingest fluoride. Similarly, because of the nonspecific nature of mild to moderate symptoms, a physician's differential diagnosis is unlikely to include fluoride toxicity without a history of fluoride ingestion." Shulman JD, Wells LM. (1997). Acute fluoride toxicity from ingesting home-use dental products in children, birth to 6 years of age. Journal of Public Health Dentistry 57: 150-8.

9. "There are a few case reports of GI upset in subjects exposed to drinking water fluoridated at 1 mg/L. Those effects were observed in only a small number of cases, which suggest hypersensitivity. However, the available data are not robust enough to determine whether that is the case." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p250.

10. "The patient was a seven-year old white child with an itchy skin rash, headache, epigastric distress, generalized weakness, and listlessness. Her discomfort was such that most of her time in school was spent in the nurse's room. When the tablets (1 mg/day) were withdrawn, symptoms disappeared but returned again when therapy was reinstituted. Again withdrawal resulted in disappearance of symptoms. The patient has been symptom free since. The parents of this child refused to allow further experimentation." Feltman R. (1956). Prenatal and postnatal ingestion of fluoride salts: A progress report. Dental Digest 62: 353-357.

11. "The patient's face cleared up in three days on discontinuing the fluoride. Upon resuming the tablets (1 mg/day) the rash recurred in two days, this time accompanied by nausea. Tablets were again withdrawn and symptoms disappeared. Two weeks later the patient returned to the clinic and was directed to take the tablets again. The patient took the tablets for three days, the rash reappeared and she developed serious symptoms including vomiting with blood showing in the vomitus. The fluoride prescription was discontinued. The patient then continued an uneventful pregnancy and delivered a healthy baby." Feltman R. (1956). Prenatal and postnatal ingestion of fluoride salts: A progress report. Dental Digest 62: 353-357.

12. "On 6/10/57 the patient while being kept on a low calcium diet was given a placebo test of 300 cc. of distilled water. It caused no ill effect. On June 12th 2 mg. NaF (0.9 mg. F) in 300 cc. of distilled water was administered. The patient was not aware that the water contained fluoride. She had previously had similar tests (glucose tolerance and urea clearance). Within 20 minutes she developed a generalized urticaria associated with cough and pain in the gastric region followed by marked flatulence in the abdomen. This test was repeated on June 18th, after placing the patient on a high calcium (2 gms.) diet to which 1.3 gms. of calcium lactate had been added. The patient experienced the same symptoms as had occurred subsequent to the above-described test. Urticaria dominated the picture. Since eliminating fluoridated water for drinking and cooking foods all symptoms have subsided." Waldbott GL. (1958). Allergic Reactions from Fluorides. International Archives of Allergy 12: 347-355.

13. "One percent of our cases reacted adversely to the fluoride (1 mg/day tablets). By the use of placebos, it was definitely established that the fluoride and not the binder was the causative agent. These reactions, occurring in gravid women and in children of all ages in the study group affected the dermatologic, gastro-intestinal and neurological systems. Eczema, atopic dermatitis, urticaria, epigastric distress, emesis, and headache have all occurred with the use of fluoride and disappeared upon the use of placebo tablets, only to recur when the fluoride tablet was, unknowingly to the patient, given again. When adverse reactions occur, the therapy can be readily discontinued and the patient or parent advised of the fact that sensitivity exists and the element is to be avoided as much as possible." Feltman R, Kosel G. (1961). Prenatal

and postnatal ingestion of fluorides - Fourteen years of investigation - Final report. Journal of Dental Medicine 16: 190-99.

14. “L.W., a 6-year-old girl, consulted one of us (GLW) on December 26, 1963, for an allergic survey because of what appeared to be gastro-intestinal allergy. She had been taking Poly-Vi-Flor, three to four drops daily, since early infancy. Her complaints were frequent nausea, vomiting, pains in the hypogastrium and episodes of abdominal cramps, diarrhea, headaches, and occasional bloody stools followed by fever, up to 104 degrees. These attacks occurred on an average of every ten days. The child failed to gain weight. At first the diagnosis of food allergy and/or chronic appendictis was considered but neither diagnosis was corroborated by x-rays and an allergic work-up. Since the gastro-intestinal episodes usually occurred within one-half hour of the ingestion of the fluoride drops, the medication was discontinued. Improvement began immediately and was followed by complete recovery.” Shea JJ, et al. (1967). Allergy to fluoride. Annals of Allergy 25:388-91.

15. “Patch tests were done for chewing gum, Lifesavers, a fluoride toothpaste which she had been using since the onset of the lesions and a non-fluoride toothpaste. The fluoride toothpaste gave a two plus reaction. During the development of the positive patch test reaction the patient experienced a flareup of the oral lesions associated with severe abdominal pain. The smear from the ulcer revealed a normal flora. After changing to a non-fluoride toothpaste the oral lesions, as well as an accompanying submaxillary lymphadenitis and the abdominal pains, subsided completely. On December 3, 1986, this child had a recurrence of the stomatitis. It began within 15 minutes after brushing her teeth and was again followed by severe abdominal pain. She had inadvertently used a fluoridated toothpaste.” Shea JJ, et al. (1967). Allergy to fluoride. Annals of Allergy 25:388-91.

16. “C.P., female age 14 months, had been taking Tri-Vi-Flor drops regularly since 3 weeks of age. Shortly thereafter she started having a persistent diarrhea. At 8 weeks of age she developed what appeared to be pylorospasm, but a pylorotomy failed to relieve the gastric symptoms. At the age of 10 months she suffered from rhinorrhea, dyspnea, intermittent swelling of the salivary glands and submaxillary lymphadenopathy. These symptoms failed to respond to antihistamines and antibiotics. On December 5, 1965, the mother discontinued the drops. Within three days there was a marked improvement. The child has remained symptom free since eliminating the drops.” Shea JJ, et al. (1967). Allergy to fluoride. Annals of Allergy 25:388-91.

17. “An 8-year-old girl gave a history since infancy, of abdominal pains associated with anorexia, frequent pyelitis and pruritus vulvae. Since early 1956 she had intermittently spastic pains and paresthesias in legs and arms. She consulted me because of seasonal upper respiratory allergy... On 6/18/57 the patient was given as a placebo 300 cc. of distilled water without ill effect. The following day a test dose of 6.8 mg. of fluoride (as NaF) elicited within 20 minutes moderately severe vomiting.” Waldbott GL. (1958). Allergic Reactions from Fluorides. International Archives of Allergy 12: 347-355.

18. “After having avoided fluoride water for 2 weeks, the patient was given, 2 days before the test, 6.8 mg. of F as NaF and another 6.8 mg. on the day of the test. The first dose caused no ill effect. However, within 30 minutes after she had taken the second dose she developed a severe outbreak of urticaria, cephalgia, paresthesias in legs and hands. She became lethargic and developed pain in the epigastric region followed by spastic pain in the lower abdomen. These symptoms began to clear in about one hour... Only 3.6 percent of the total test dose of 6.8 mg. of F was recovered in the urine within 24 hours.” Waldbott GL. (1958). Allergic Reactions from Fluorides. International Archives of Allergy 12: 347-355.

19. “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.” Spak CJ, et al. (1990). Studies of human gastric mucosa after application of 0.42% fluoride gel. Journal of Dental Research 69:426-9.

20. “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.” Das TK, et al. (1994). Toxic effects of chronic fluoride ingestion on the upper gastrointestinal tract. Journal of Clinical Gastroenterology 18(3):194-9.

21. “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.” Muller P, et al. (1992). Sodium fluoride-induced gastric mucosal lesions: comparison with sodium monofluorophosphate. Z Gastroenterol. 30(4):252-4.

22. “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." Spak CJ, et al. (1989). Tissue response of gastric mucosa after ingestion of fluoride. British Medical Journal 298:1686-7.

23. "The use of fluoride in the prophylaxis or treatment of osteoporosis seems highly questionable for the following reasons: ... © there are frequent gastrointestinal disturbances and arthralgias..." Inkovaara JA. (1991). Is fluoride treatment justified today? Calcified Tissue International 49 Suppl:S68-9.

24. "the fluoride-treated women (dose = 34 mg/day F) had about 3.0 times as many side effects as the women given placebo. The side effects fell into one of two major categories - those due to gastric irritation and those due to pain the lower extremities. The gastric symptoms consisted mainly of nausea or, less commonly, epigastric pain and vomiting, or both. The fluoride-treated women had these symptoms 2.9 times more frequently than the women given placebo." Riggs BL, et al. (1990). Effect of Fluoride treatment on the Fracture Rates in Postmenopausal Women with Osteoporosis. New England Journal of Medicine 322:802-809.

25. "Of 48 patients who began sodium fluoride therapy (dose = 9.0 - 27 mg/day F), 25 developed significant side-effects (10 with nausea and dyspepsia, 1 with gastrointestinal hemorrhage)." Hodsman AB, Drost DJ. (1989). The response of vertebral bone mineral density during the treatment of osteoporosis with sodium fluoride. Journal of Clinical Endocrinology and Metabolism 69:932-8.

26. "Results from several large trials indicate that significant side effects attributable to treatment occur in about one-third to one-half of patients. Symptoms have been of two types—periarticular and gastrointestinal... Gastrointestinal symptoms consist of epigastric pain, nausea, vomiting, and occasionally, blood-loss anemia; these presumably result from the irritant effect of fluoride ion on gastric mucosa. The frequency of gastric side effects can be reduced by giving the calcium supplement concomitantly in the form of calcium carbonate, an effective antacid. Diarrhea occurs occasionally." Riggs BL. (1983). Treatment of osteoporosis with sodium fluoride: An appraisal. Bone and Mineral Research 2: 366-393.

27. Twenty-three of the fluoride-treated patients (dose = 18-27mg/day) had adverse reactions (38 per cent), which caused five of them to discontinue therapy; 13 had rheumatic symptoms (joint pain and swelling or painful plantar fascial syndrome), nine had gastrointestinal symptoms (severe nausea and vomiting, peoptic ulcer, or blood-loss anemia), and one had both rheumatic and gastrointestinal symptoms." Riggs BL, et al. (1982). Effect of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal osteoporosis. Comparison with conventional therapy. New England Journal of Medicine 306:446-50.

28. "Major gastrointestinal side effects also occurred (dose = 18-30

mg/day). Two patients had recurrent vomiting that could be controlled only when the dosage of sodium fluoride was reduced to 15 and 7.5 mg daily, respectively." Riggs BL, et al. (1980). Treatment of primary osteoporosis with fluoride and calcium: Clinical tolerance and fracture occurrence. Journal of the American Medical Association 243: 446-449.

29. "Treatment was ended in the fluoride group more frequently than in the controls ($P < 0.001$), usually because of abdominal discomfort." Inkovaara J, et al. (1975). Prophylactic fluoride treatment and aged bones. British Medical Journal 3(5975):73-4.

30. "Six (of 11) patients complained of occcasional epigastric dyspepsia." Jowsey J, et al. (1972). Effect of combined therapy with sodium fluoride, vitamin D and calcium in osteoporosis. The American Journal of Medicine 53: 43-49.

31. "Sodium fluoride in the dose used (dose = 23-68 mg/day F) often causes anorexia or epigastric pain." Rich C. (1966). Osteoporosis and fluoride therapy. Journal of the American Medical Association 196: 149.

32. "Non-ulcer dyspeptic complaints or gastrointestinal complaints were observed in all of the (fluorosis) patients before treatment. During the first impact assessment reduction in health complaints, especially in gastrointestinal discomfort, was most striking. Most of the patients ~ 70% showed relief in gastrointestinal complaints during first impact assessment. During the second impact assessment all of the patients showed relief from gastrointestinal complaints." Susheela AK, Bhatnagar M. (2002). Reversal of fluoride induced cell injury through elimination of fluoride and consumption of diet rich in essential nutrients and antioxidants. Molecular and Cellular Biochemistry 234-235:335-40.

33. "A prospective case-controlled study was performed to evaluate the gastrointestinal symptoms and mucosal abnormalities occurring in patients with osteofluorosis. Ten patients with documented osteofluorosis and ten age- and sex-matched healthy volunteers were included in the study... All patients with osteofluorosis had gastrointestinal symptoms, the most common being abdominal pain. Endoscopic abnormalities were found in seven patients with osteofluorosis. In all 7 of these patients, chronic atrophic gastritis was seen on histology. Electron microscopic abnormalities were observed in all 10 patients with osteofluorosis. These included loss of microvilli, cracked-clay appearance, and the presence of surface abrasions on the mucosal cells. None of the control subjects had any clinical symptoms or mucosal abnormalities. It was concluded that gastrointestinal symptoms as well as mucosal abnormalities are common in patients with osteofluorosis." Dasarathy S, et al. (1996). Gastroduodenal manifestations in patients with skeletal fluorosis. Journal of Gastroenterology 31:333-7.

34. "The present study was conducted to assess the prevalence and severity of non-skeletal manifestations, especially gastrointestinal disturbances, in an area of skeletal and dental fluorosis... The subjects, numbering 1958 inhabitants belonging to 489 families residing in four endemic villages of Faridabad District of Haryana State, were interviewed on health complaints... It is concluded that in an endemic (fluorosis) zone, where the inhabitants are consuming water of high fluoride content, the occurrence of gastrointestinal complaints - viz., loss of appetite, nausea, abdominal pain, flatulence, constipation and intermittent diarrhoea - is one of the early warning signs of fluoride toxicity and fluorosis. When water with negligible amounts of fluoride (safe water) is provided, the complaints disappear within a fortnight." Susheela AK, et al. (1993). Prevalence of endemic fluorosis with gastro-intestinal manifestations in people living in some North-Indian villages. Fluoride 26: 97-104

35. "A prospective case controlled study was conducted to evaluate the role of fluoride as a possible aetiological factor for non-ulcer dyspepsia (NUD).

Twenty patients with NUD and 10 age and sex matched healthy controls were subjected to clinical evaluation, upper gastrointestinal endoscopy and biopsies from the gastric antrum and duodenum... Fluoride levels in the drinking water, serum and urine were estimated using a ION 85 ion-analyser. These levels were significantly higher in patients with NUD than in controls (P less than 0.05).. The fluoride levels in serum and urine correlated with the symptoms, histological and electron microscopic abnormalities (P less than 0.05). It was concluded that chronic exposure to fluoride may result in NUD and should be considered in patients where other known cause of dyspepsia have been excluded." Gupta IP, et al. (1992). Fluoride as a possible etiological factor in non-ulcer dyspepsia. Journal of Gastroenterology and Hepatology 7:355-9.

G. Likely and Possible Risk of Immune System Damage: Teratogenicity, Altered Growth, and Functional Deficit.

1. "When bone turnover occurs, the potential exists for immune system cells and stem cells to be exposed to concentrations of fluoride in the interstitial fluids of bone that are higher than would be found in serum." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 258.

2. "[P]atients who live in either an artificially fluoridated community or a community where the drinking water naturally contains fluoride at 4 mg/L have all accumulated fluoride in their skeletal systems and potentially have very high fluoride concentrations in their bones. The bone marrow is where immune cells develop and that could affect humoral immunity and the production of antibodies to foreign chemicals." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 249.

3. "There is no question that fluoride can affect the cells involved in providing immune responses. The question is what proportion, if any, of the population consuming drinking water containing fluoride at 4.0 mg/L on a regular basis will have their immune systems compromised? Not a single epidemiologic study has investigated whether fluoride in the drinking water at 4 mg/L is associated with changes in immune function. Nor has any study examined whether a person with an immunodeficiency disease can tolerate fluoride ingestion from drinking water." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 250.

4. "From an immunologic standpoint, individuals who are immunocompromised (e.g., AIDS, transplant, and bone-marrow-replacement patients) could be at greater risk of the immunologic effects of fluoride." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 258.

5. "It is paramount that careful biochemical studies be conducted to determine what fluoride concentrations occur in the bone and surrounding interstitial fluids from exposure to fluoride in drinking water at up to 4 mg/L, because bone marrow is the source of the progenitors that produce the immune system cells." National

Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 259.

H. Likely and Possible Harm to the Reproductive System: Teratogenicity, Altered Growth, and Functional Deficit.

1. "It can be concluded that oxidative endometrial damage plays an important role in F-induced endometrial toxicity, and the modulation of oxidative stress with vitamins reduces F-induced endometrial damage both at the biochemical and histological levels. Guney M, Oral B, Deminirin H, Karahahan N, Mungan T, Delibas N, Protective effects of vitamins C and E against endometrial damage and oxidative stress in fluoride intoxication. Clin Exp Pharmacol Physiol. 2007 May-Jun;34(5-6):467-74
2. High doses of fluoride have repeatedly been found to interfere with the reproductive system of animals. Commonly observed effects in fluoride-exposed animals include: oxidative stress, damaged sperm, reduced sperm count, and reduced fertility.
3. According to the authors of a recent study in the journal Reproductive Toxicology: "We conclude that fluoride treatment is associated with testicular disorders, which may be due to induction of oxidative stress in reproductive organs along with possible adverse effects of fluoride on pituitary testicular axis.The detailed mechanism of fluoride treatment on the male reproductive system has not been elucidated and will be the subject of future experiments " (Ghosh et al 2002).
4. Research on possible reproductive effects in humans is limited. Some recent research, however, indicates that fluoride exposure (at lower doses than given to animals) can cause toxic effects to human Sertoli cells and gonadotrophs, reduction in circulating testosterone, and reductions in total fertility rate. The dose at which fluoride can begin to cause these effects is not yet known.
5. "the relationship between fertility and fluoride requires additional study." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p161.
6. "The effects of fluoride on the reproductive system merit further investigation in animal and human studies." Department of Health & Human Services. (U.S. DHHS) (1991). Review of Fluoride: Benefits and Risks. Department of Health and Human Services, USA. p. 88-89.
7. "A few human studies suggested that high concentrations of fluoride exposure might be associated with alterations in reproductive hormones, effects on fertility, and developmental outcomes, but design limitations make those studies insufficient for risk evaluation." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 6.
8. "Fluoride-induced reproductive effects have been reported in experimental models and in humans. However, these effects were found in heavily exposed scenarios. Therefore, in this work our objective was to study reproductive parameters in a population exposed to fluoride at doses of 3-27 mg/day (high-fluoride-exposed group-HFEG). Urinary fluoride levels, semen parameters, and reproductive hormones in serum (LH, FSH, estradiol, prolactin, inhibin-B, free and total testosterone) were measured. Results were compared with a group of individuals exposed to fluoride at lower doses: 2-13 mg/day (low-fluoride-exposed group-LFEG). A significant increase in FSH ($P<0.05$) and a reduction of inhibin-B, free testosterone, and prolactin in serum ($P<0.05$) were noticed in the HFEG. When HFEG was compared to LFEG, a decreased

sensitivity was found in the FSH response to inhibin-B ($P<0.05$). A significant negative partial correlation was observed between urinary fluoride and serum levels of inhibin-B ($r=-0.333$, $P=0.028$) in LFEG. Furthermore, a significant partial correlation was observed between a chronic exposure index for fluoride and the serum concentrations of inhibin-B ($r=-0.163$, $P=0.037$) in HFEG. No abnormalities were found in the semen parameters studied in the present work, neither in the HFEG, nor in the LFEG. The results obtained indicate that a fluoride exposure of 3-27 mg/day induces a subclinical reproductive effect that can be explained by a fluoride-induced toxic effect in both Sertoli cells and gonadotrophs." Ortiz-Perez D, et al. (2003). Fluoride-induced disruption of reproductive hormones in men. Environmental Research 93:20-30.

9. "The first step in assessing a health risk by a substance to humans is the identification of its harmful effects on animals. A health risk to humans is assessed using results from human epidemiological studies in conjunction with results from animal studies. The Newburgh-Kingston Study (Schlesinger et al, 1956) showed an earlier age of first menarche in girls living in the fluoridated Newburgh than in unfluoridated Kingston. The current animal study indicates that fluoride is associated with an earlier onset of puberty in female gerbils. Furthermore, more research was recommended on the effects of fluoride on animal and human reproduction (USPHS, 1991). This project has contributed new knowledge in this area." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 177.

10. "OBJECTIVE: The present study focuses on serum testosterone concentrations in patients with skeletal fluorosis, in order to assess the hormonal status in fluoride toxicity... 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." Susheela AK, Jethanandani P. (1996). Circulating testosterone levels in skeletal fluorosis patients. Journal of Toxicology and Clinical Toxicology 34(2):183-9.

11. "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... Most regions showed an association of decreasing TFR [Total Fertility Rate] with increasing fluoride levels. Meta-analysis 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." Freni SC. (1994). Exposure to high fluoride concentrations in drinking water is associated with decreased birth rates. Journal of Toxicology and Environmental Health 42:109-121.

12. "There are no published reports in the literature on reproductive toxicity of fluoride in men. However, two Russian studies showed that chronic occupational exposure to fluoride-contaminated compounds might affect reproductive

function. Men who had worked in the cryolite industry for 10-25 years and who demonstrated clinical skeletal fluorosis showed decreases in circulating testosterone and compensatory increases in follicle-stimulating hormone when compared with controls (Tokar and Savchenko, 1977). Of the exposed men, those exposed to cryolite for 16-25 years had increased luteinizing-hormone levels as compared with men exposed for 10-15 years. Women exposed occupationally to air heavily laden with superphosphates demonstrated increases in menstrual irregularities and genital irritations when compared with unexposed controls (Kuznetzova, 1969). However, occupational exposure to many other compounds in the cryolite and superphosphate industries makes it difficult to implicate any one substance, such as fluoride, in inducing these health effects. A recent study of women employed in silicon water manufacturing (fabrication room workers) showed a relative risk of spontaneous abortion of 1.45 times that of women (of the same ages) who worked in nonfabrication rooms (Schenker et al., 1992). The overall increase in risk ranged from about 20 to 40%. There was a dose-response relationship and a consistency of findings for persons exposed to on specific class of solvents. Spontaneous abortions were also associated with fluoride exposure but only in one work group, and a strong dose-response was not present. The authors characterized the fluoride-associated increase in relative risk of spontaneous abortions as 'less consistent' than the results of exposure to some solvents in this study and 'less consistent' with other research."National Research Council. (1993). Health effects of ingested fluoride. Report of the Subcommittee on Health Effects of Ingested Fluoride. National Academy Press, Washington, DC. p. 73-74.

13. "Semen analysis including sperm morphology assessment has been suggested to be a useful indication of the factors in man's macro-environment, which can modulate or damage spermatogenesis (Mac Leod & Gold 1953). The present study was aimed to determine the reproductive toxic effects of male rat after ingestion of NaF [4.5-9 ppm] through drinking water. The route chosen in this study for exposure was via drinking water to mimic human exposure and to reflect the impact on fertility, after chronic ingestion. The decreased sperm number and motility observed in experimental rats might be responsible for decreasing male fertility. Decrease in male reproductive potential was observed in rats and rabbits after exposure to fluoride (Kumar & Susheela 1994, 1995; Narayana & Chinoy 1994; Zhang et al. 2000; Collins et al. 2001). Besides decreased sperm count, sperm motility, the sperm viability and HOS sperm coiling percentages were also adversely affected in NaF-exposed rats. These changes were greater in rats exposed to higher dose of NaF. The decreased testicular steroidogenic enzyme activity levels may lead to decreased steroidogenesis in experimental rats, which in turn may suppress the reproductive activities in the male rats." Pushpalatha T, Srinivas M, Sreenivasula Reddy P. (2005). Exposure to high fluoride concentration in drinking water will affect spermatogenesis and steroidogenesis in male albino rats. Biometals 18:207-12.

14. "The content of NaF in testis and the ratio of apoptotic spermatogenic cell in fluoride treatment groups significantly increased with increased experimental dosage and prolonged experimental period ($P < 0.05$). Meanwhile, the serum estradiol level significantly decreased ($P < 0.05$), which was negatively correlated with the content of NaF in testis as well as the ratio of apoptotic spermatogenic cell ($P < 0.05$). CONCLUSION: Excessive fluoride could lead disturbance to serum estradiol level during some range of dose and time, which is an important factor to spermatogenic cell apoptosis." Jiang CX, et al. (2005). [Relationship between spermatogenic cell apoptosis and serum estradiol level in rats exposed to fluoride]. Wei Sheng Yan Jiu. 34:32-4.

15. "These data suggest that a zinc-enriched diet protects seminiferous tubules against fluoride toxicity by preventing the fluoride-induced testicular

zinc deprivation." Krasowska A, et al. (2004). Zinc protection from fluoride-induced testicular injury in the bank vole (Clethrionomys glareolus). Toxicology Letters 147: 229-235.

16. "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." Ghosh D, et al. (2002). Testicular toxicity in sodium fluoride treated rats: association with oxidative stress. Reproductive Toxicolology 16(4):385.

17. "To study the mechanisms of the antagonistic action of selenite on fluoride-induced male reproductive damages, and find out the optimal level of selenite in drinking water against fluoride toxicity... Results: Fluoride could cause the elevation of fluorine concentrations in blood and urine, the abnormalities of trace elements in serum and testis, as well as the significant increase of lipid peroxide (LPO) levels, and the obvious decreases of activities of glutathione peroxidase (GSH-Px) and ATPase in testis and epididymis of rats exposed to fluoride in drinking water (68 mg/L)." Yang KD, et al. (2002). [Study on antagonistic effects of selenite on fluoride-induced impairments of testis and epididymis in rats]. Chung-Kuo Kung Kung Wei Sheng 18: 427-9.

18. "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." Zakrzewska H, et al. (2002). In vitro influence of sodium fluoride on ram semen quality and enzyme activities. Fluoride 35: 153-160.

19. "From the foregoing data, it is evident that the administration of sodium fluoride or aluminium chloride alone induced (reproductive) toxicity in female mice. This toxicity was enhanced by their combined treatment (Group IV) in affecting steroidogenesis in ovary, carbohydrate metabolism in uterus, and causing a hypercholesterolemic effect in mice."

20. Chinoy NJ, Patel TN. (2001). Efects of sodium fluoride and aluminium chloride on ovary and uterus of mice and their reversal by some antidotes. Fluoride 34: 9-20.

21. "The effects of sodium fluoride (NaF) ingestion (10 mg NaF/kg body weight) and the possible therapeutic effects of ascorbic acid (AA, 15 mg/animal/day) and/or calcium phosphate (Ca, 25 mg/animal/day) on the reproductive

functions and fertility of male mice were investigated. NaF-ingestion brought about a significant decline in sperm acrosomal acrosin and hyaluronidase. Cauda epididymal sperm stained with alcoholic acidic silver nitrate reagent revealed acrosomal damage and deflagellation. However, sperm nuclear integrity was not affected by the treatment. The reduced activity of the enzymes as well as the structural and metabolic alterations in the sperm led to a significant decrease in sperm count, and motility and live:dead ratios but an increase in abnormal sperm which ultimately lead to a poor fertility rate. The cessation of NaF-treatment was not conducive to bringing about a complete recovery. However, the administration of AA or Ca to NaF-treated mice revealed significant recovery from fluoride toxicity in all the above parameters." Chinoy NJ, Sharma A. (2000). Reversal of fluoride-induced alteration in cauda epididymal spermatozoa and fertility impairment in male mice. Environmental Sciences 7: 29-38.

22. "Sexually mature male Swiss mice were exposed at 60 days of age to 100, 200 and 300 ppm sodium fluoride (NaF) in their drinking water for 4 weeks or 10 weeks. The effect of NaF exposure on fertility was assessed by breeding these males with untreated female mice after the exposure periods. Fertility was significantly reduced at all three concentrations by exposure for 10 weeks but not for 4 weeks. The number of implantation sites and viable fetuses was significantly reduced in females mated with males that had ingested NaF at a concentration of 200 ppm for 10 weeks. Relative weights of seminal vesicles and preputial glands were significantly increased in mice exposed to 200 and 300 ppm NaF for 4 weeks but not in mice exposed for 10 weeks. These results indicate that long-term ingestion of NaF adversely affects fertility in male mice." Elbetieha A, et al. (2000). Fertility effects of sodium fluoride in male mice. Fluoride 33: 128-134.

23. "In summary, we found that sodium fluoride administered in drinking water to rats for 30 days at doses averaging 22.6 mg/kg/day caused definite fetotoxic effects. There was a reduction in the number of viable fetuses and an increase in the number of pregnant rats with resorptions as well as an increase in the total number of resorptions." Hiyasat AS. (2000). Reproductive Toxic effects of ingestion of sodium fluoride in female rats. Fluoride 33(2): 79-84.

24. "These results clearly indicate that protein supplementation is beneficial to overcome the toxic effects of fluoride on testicular steroidogenesis, protein, carbohydrate, and energy and oxidation metabolisms in the reporductive organs of male mice. Protein deficiency, on the other hand, aggravates fluoride toxicity. A protein-supplemented diet might therefore substantially mitigate certain fluoride-induced health hazards in humans living in endemic areas." Chinoy NJ, Mehta D. (1999). Effects of protein supplementation and deficiency on fluoride-induced toxicity in reproductive organs of male mice. Fluoride 32: 204-214.

25. "Studies on the beneficial effects of vitamins E and D supplementation on functions of caput and cauda epididymides, their spermatozoa, vas deferens and seminal vesicle of sodium fluoride (NaF) treated male mice were carried out. The NaF treatment resulted in significant decrease in the body and epididymis weight but those of vas deferens and seminal vesicle were not affected. NaF treatment brought about alterations in epididymal milieu as elucidated by the significant decrease in levels of sialic acid and protein as well as activity of ATPase in epididymides. As a result, the sperm maturation process was affected leading to a significant decline in cauda epididymal sperm motility and viability. This caused a significant reduction in fertility rate. The cauda epididymal sperm count was also significantly reduced. The data obtained suggest that fluoride treatment induced significant metabolic alterations in the epididymides, vas deferens and seminal vesicles of mice." Chinoy NJ, Sharma A.

(1998). Amelioration of fluoride toxicity by vitamin E and D in reproductive functions of male mice. Fluoride 31: 203-216.

26. “Conclusions: The modification of some parameters related to fertility by the repeated oral NaF intake, in rodents, suggest that NaF has potential to disturb male fertility.” Pinto R, et al. (1998). NaF may disturb male fertility in rodents. Toxicology Letters 95(Suppl 1): 214.

27. “Effects of sodium fluoride (NaF) (30 mg kg-1 body weight) and ascorbic acid ingestion along with sodium fluoride for 30 days each were studied to evaluate its possible role as an ameliorative agent on functions of reproductive organs and spermatozoa of the fluorotic guinea pig. The cauda epididymal spermatozoa were highly sensitive to the effects of sodium fluoride as their structural and metabolic alterations led to marked decreases in their motility, live:dead ratio and sperm mitochondrial activity index but increases in sperm abnormalities and alterations in sperm membrane phospholipids, particularly phosphatidylinositol and phosphatidyl serine. The activities of ATPase and succinate dehydrogenase as well as glutathione levels were decreased in testis by sodium fluoride treatment, revealing disturbances in its metabolism.” Chinoy NJ, et al. (1997). Fluoride toxicity in the testis and cauda epididymis of guinea pig and reversal by ascorbate. Medical Science Research 25: 97-100.

28. “The toxic effects were evaluated of sodium fluoride (NaF) ingestion on the physiology of tissue components of testis and epididymis of adult, male albino rats, and the possible reversal of the effects by use of some antidotes. The results revealed that the testis and cauda epididymal proteins were altered, with disappearance of some proteins and induction of some new ones. This is the first report of such changes... On comparing the alterations in protein profile, phospholipds and glutathione in both tissues, it was evident that the protein profile was disturbed more in testis than in cauda epididymis, whereas phospholipids and gluthathione levels were affected more in cauda than in testis... As the proteins of testis and cauda epididymis are known to be involved as androgen carrier proteins, in testicular functions and in sperm motility, it follows that NaF treatment might affect the levels of these proteins as well as alter sperm motility and viability.” Chinoy NJ, et al. (1997). Fluoride toxicity on rat testis and cauda epididymal tissue components and its reversal. Fluoride 30: 41-50.

29. “The section on the effects of fluoride on the physiological signs of sexual maturity in the gerbil was a preliminary, pilot study. There were not enough subjects to make any firm conclusions so an interpretation of the data is conjectural. However, the results do suggest that the HF (High-Fluoride) females had an accelerated onset of puberty as judged by several indices of pubertal development in rodents. At 7 weeks, the HF females were significantly heavier than the LF females ($p < 0.004$); as heavy as the HF males and LF males. The ventral gland in the HF female developed significantly earlier than in the LF female ($p < 0.004$). Vaginal opening occurred earlier in the HF female than in the LF female ($p < 0.03$).” Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 173-174.

30. “At 16 weeks, the HF [High-Fluoride] males had a significantly lower mean testes weight than the LF [Low-Fluoride] males: 1.10 ± 0.11 vs. 1.32 ± 0.18 g, respectively ($p < 0.002$). The reason for this is not clear.” Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 177.

31. “The present communication addresses the effect of chronic fluoride toxicity on the structure of rabbit Leydig cells using light, scanning and transmission electron microscopy... [T]he extensive degenerative changes (which are

progressive) seen in the Leydig cells due to fluoride toxicity may lead to a decrease in testosterone production resulting initially in regression of seminiferous tubules and structural damage of the epididymis and finally cessation of spermatogenesis." Susheela AK, Kumar A. (1997). Ultrastructural studies on the leydig cells of rabbits exposed to chronic fluoride toxicity. Environmental Sciences 5:79-94.

32. "Sodium fluoride (NaF) at a dose of 10 mg/kg body weight was administered orally to male rats (Rettus norvegicus) daily for 30 and 50 days to evaluate the effect of the physiology of some sex accessory glands and sperm functions. The effects of withdrawal upon cessation of NaF ingestion, and of administering ascorbic acid (AA) and/or calcium (Ca++) along with NaF, were also investigated. The results revealed that the NaF treatment caused a significant elevation in serum fluoride levels with a simultaneous rise in Ca++ levels. This could be attributed to the formation of a calcium fluoride complex leading to calcium accumulation. The treatment resulted in structural and metabolic alterations in sperm, leading to low sperm motility, a low sperm mitochondrial activity index (SMAI), reduced viability (live:dead ratio), and changes in sperm membrane phospholipids (particularly phosphatidylinositol, phosphatidylserine and phosphatidylethanolamine, which would affect hormone receptor interaction and their functions). A significant reduction in electrolyte levels of sperm also occurred which would also affect their viability. The protein levels in cauda epididymal sperm suspension, vas deferens, seminal vesicle and prostate were significantly decreased after NaF administration, which may be due to altered protein metabolism by interference of fluoride ions. The changes in epididymal protein profile, with absence of some proteins and induction of some new ones, were probably a result of the "stress proteins" in NaF-treated rats affecting the structural and functional integrity of sperm. Glycogen accumulation in vas deferens and a decrease in fructose in seminal vesicles and vas deferens indicated disturbances in carbohydrate metabolism in these organs. However, withdrawl of treatment resulted in partial recovery. A significant recovery from NaF-induced toxic effects occurred following administation of ascorbic acid and/or calcium, while combined treatment (AA + Ca++) for 70 days manifested a synergistic effect. The transient fluoride-induced effects were reversible. The results, corroborated by earlier data from our laboratory, show that fluoride has a definite effect on male reproduction and fertility. Ascorbic acid and calcium are proposed as therapeutic agents in endemic populations for ameiloration of effects of fluoride." Chinoy NF, et al. (1995). Amelioration of fluoride toxicity in some accessory reproductive glands and spermatozoa of rat. Fluoride 28: 75-86.

33. "Fifty four Wistar male rats were randomly divided into three groups, drinking water containing 0.6 mg/L (control group), 100 mg/L, and 200 mg/L sodium fluoride, respectively. Rats were killed at the second, fourth and sixth weeks after experiment initiation, respectively. The levels of serum testosterone, testis cholesterol, and hepatic tissue cholesterol were determined. Results showed that the serum testosterone level had decreased with time in rats drinking water containing 100 and 200 mg/L fluoride. While testis cholesterol level did not change, it was significantly decreased in the liver at the fourth and sixth week when compared with the control group. Results suggest that fluoride may have some harmful effects on the reproductive system in male rats." Zhao ZL, et al. (1995). The influence of fluoride on the content of testosterone and cholesterol in rat. Fluoride 28: 128-130.

34. "The therapeutic effects of ascorbic acid and calcium (Ca2+) supplementation on reproductive functions of fluoride-treated (10 mg/kg body weight) male rats were investigated. Sodium fluoride treatment resulted in a decrease in almost all parameters studied except concentration of testicular cholesterol, which implies that androgen synthesis might not be affected by NaF treatment. Succinate dehydrogenase

activity decreased in testis suggesting that its oxidative metabolism was altered by NaF treatment. Adenosine triposphatase activity, protein, and sialic acid levels in caput and cauda epididymides also showed a decrease. All these changes resulted in a significant decrease in sperm motility and thereby fertility rate." Chinoy NF, et al. (1994). Beneficial effects of ascorbic acid and calcium on reproductive functions of sodium fluoride-treated prepubertal male rats. Fluoride 27: 67-75.

35. "OBJECTIVE—To address the role of fluoride in causing defects to spermatids and epididymal spermatozoa. METHODS—Male rabbits were treated with 10 mg NaF/kg body weight daily for 18 months and maintained under identical laboratory conditions along with the control rabbits not given NaF. Testis and epididymis (caput) were investigated for ultrastructural details of spermatids and spermatozoa. RESULTS—A wide variety of structural defects were observed in the flagellum, the acrosome, and the nucleus of the spermatids and epididymal spermatozoa of fluoride-treated rabbits. Abnormalities included absence of outer microtubules, complete absence of axonemes, structural and numeric aberrations of outer dense fibers, breakdown of the fibrous sheath, and structural defects in the mitochondria of the middle piece of the flagellum. Detachment and peeling off of the acrosome from the flat surfaces of the nucleus were also observed. CONCLUSION—The abnormalities observed render the sperm nonfunctional and ineffective, and thus there is a possible role of fluoride in causing infertility." Kumar A, Susheela AK. (1994). Ultrastructural studies of spermiogenesis in rabbit exposed to chronic fluoride toxicity. International Journal of Fertility and Menopausal Studies 39(3):164-71.

36. "The effects of ingestion of sodium fluoride (NaF), 10 mg/kg body weight for 50 days, on the structure and metabolism of sperm of albino rats (Rattus norvegicus), were investigated. In different groups of rats, the reversible effects upon withdrawal of NaF treatment and by administering some therapeutic agents, viz., ascorbic acid and calcium alone and in combination with NaF (50 and 70 days), on sperm structure and metabolism were also studied. The results revealed that the sperm acrosomal hyaluronidase and acrosin were reduced after 50 days of NaF treatment. Sperm stained with acidic alcoholic silver nitrate revealed acrosomal damage and deflagellation, which might be causative factors for the reduced activity of the enzymes. These alterations also resulted in a decline in sperm motility. The cauda epididymal sperm count was decreased, perhaps because of spermatogenic arrest. Thus, the low sperm motility and count ultimately contributed toward reduction in fertility by NaF treatment. However, withdrawal of NaF treatment for 70 days produced incomplete recovery, while administration of ascorbic acid and calcium, individually and in combination, brought about significant recovery of fluoride-induced effects. Thus, the effects of fluoride on sperm structure and metabolism of rats are transient and reversible." Narayana MV, Chinoy NJ. (1994). Reversible effects of sodium fluoride ingestion on spermatozoa of the rat. International Journal of Fertility and Menopausal Studies 39(6):337-46.

37. "In view of reports of infertility among human populations in fluorosis prevailing regions, we investigated the effect of fluoride ingestion on testicular steroidogenesis in rats. Sodium fluoride (NaF) was administered to the rats orally at a daily dose of 10mg/kg bodyweight for 50 days. The treatment did not cause significant change in testicular cholesterol levels, indicating that metabolism was not altered and that there was no hypo/hypercholesterolemic effect. In addition, activities of the intermediary enzymes in androgenesis, viz., 3ß- and 17ß-hydroxysteroid dehydrogenase were only modestly decreased by NaF ingestion. Subsequently, the determination of circulating androgen levels in NaF-treated rats showed a downward trend compared to those of the control group, suggesting alteration in testosterone concentration. The

histomorphometric studies revealed significant change in the Leydig cell diameter m correlation with the androgen levels. These results indicate that fluoride does interfere with steroidogenesis in short-term lowdose exposures in rats." Narayana MV, Chinoy NJ. (1994). Effect of fluoride on rat testicular steroidogenesis. Fluoride 27: 7-12.

38. "In fluorotic rats, testicular cholesterol and serum testosterone levels were not affected. However, succinate dehydrogenase activity in testis was inhibited. Similarly, adenosine triphosphatase activity and sialic acid levels in epididymides were also suppressed with more pronounced effect on cauda epididymis. Consequently, sperm motility and count were decreased leading to a significant decline in fertility by fluoride treatment. Hence, rat is also sensitive to fluoride toxicity." Chinoy NJ, et al. (1992). Effects of fluoride ingestion on the physiology of reproductive organs of male rats. Journal of Environmental Biology 13: 55-61.

39. "Summary: Sodium fluoride (NaF) fed to adult male albino mice at a dose of 10 mg and 20 mg/kg body weight, caused a significant decrease in sperm county and motility. Scanning electron microscopy and silver nitrte staining showed large numbers of deflagellated spermatozoa, with acrosomal, midpiece and tail abnormalities. The treatment caused loss of fertility rate when normal cycling female mice were mated with treated males." Chinoy NJ , Sequeira E. (1992). Reversible fluoride induced fertility impairment in male mice. Fluoride 25 71-76.

40. "Male Wistar rats were exposed to fluoride (F) at concentrations of 100- and 200 ppm in their drinking water for 6- and 16 weeks. The high F intake caused several-fold increase in the F concentrations in the testes and bone as compared with control rats, both after the 6- and 16 wk exposure; the bone F, but not testicular F, appeared to increase with dose and time. F exposure (100- and 200 ppm) decreased significantly the concentrations of zinc (Zn) in the testes, plasma, liver and kidneys particularly in the 16 wk groups; in the bone Zn tended to increase, however... Fifty percent of the 100- and 200 ppm F rats after 16 weeks exhibited histopathologic changes in the germinal epithelium of the testes, which resembled those in Zn-deficient rats. The data suggest that a deprivation of testicular Zn due to a high F intake may be directly responsible for the injury of testicular tubules." Krasowska A, Wlostowski T. (1992). The effect of high fluoride intake on tissue trace elements and histology of testicular tubules in the rat. Comparative Biochemistry and Physiology: Part C 103(1):31-4.

41. "A single microdose (50 micrograms/50 microL) injection of sodium fluoride (NaF) into the vasa deferentia of adult male albino rats (Rattus norvegicus) caused arrest of spermatogenesis and absence of spermatozoa in the lumina of the seminiferous tubules of the testes, which consequently led to a decline in the sperm count in the caudae epididymides. Scanning electron microscopy of cauda and vas deferens sperm revealed deflagellation and tail abnormalities. This is probably related to the alterations in the internal milieu of these organs which rendered the spermatozoa immotile and consequently caused fertility impairment in the experimental animals. Thus microdoses of sodium fluoride were found to affect reproductive function and fertility rate." Chinoy NJ, et al. (1991). Microdose vasal injection of sodium fluoride in the rat. Reproductive Toxicolology 5(6):505-12.

42. "Fluoride was orally administered to rabbits at 10 mg NaF/kg body weight for 18 or 29 months. The animals were then killed and the structure of the testis, epididymis and vas deferens studied under light and scanning electron microscopes. In animals treated for 29 months, the spermatogenic cells in the seminiferous tubules were disrupted, degenerated and devoid of spermatozoa. In animals treated for 18 or 29 months, loss of cilia on the epithelial cells lining the lumen of the ductuli efferentes of the caput epididymidis and of stereocilia on the epithelial cells lining the lumen of the vas

deferens was observed. In some regions of the epithelial lining of the lumen of the ductuli efferentes and vas deferens, the boundaries of the cells were not clear and appeared to be peeled off. Mucus droplets were abundant in the vas deferens of control animals, but absent in both the treated groups. Spermatogenesis ceased only in animals treated for 29 months. The difference in the structural changes observed in the testes of the 2 treated groups may have been due to the blood-testis barrier. It is concluded that ingestion of high concentrations of fluoride has harmful effects on the male reproductive system." Susheela AK, Kumar A. (1991). A study of the effect of high concentrations of fluoride on the reproductive organs of male rabbits, using light and scanning electron microscopy. Journal of Reproductive Fertility 92(2):353-60.

43. "The aim of the study was to evaluate relationship between infertility and the histological structure of the testes following the subcutaneous administration of different doses of sodium fluoride (5, 10, 20 and 50 mg/kg/day), for 100 days, to groups of six male albino rabbits; the six control animals were given 1 cc distilled water/kg b.w./day for the same length of time. Deficient maturation and differentiation of the spermatocytes and an increase in the amount of interstitial tissue were found in the experimental animals. In the higher dosage groups, spermatogenesis stopped and the seminiferous tubules became necrotic. The study thus established the existence of a definite relationship between fluorosis and testicular damage." Shashi A. (1990). Histopathological changes in rabbit testes during experimental fluorosis. Folia Morphol (Praha) 38(1):63-5.

44. "Albino rabbits were injected sodium fluoride solutions in the concentration of 5, 10, 20 and 50 mg/kg body weight/day subcutaneously for 100 days. The control rabbits were given 1 cc of distilled water for the same period and sacrificed. The ovary was examined for histopathological changes. Animals in control and 5 mg fluoride treated groups displayed normal follicles with oocytes and interstitial tissue in ovaries. In animals treated with 10 and 20 mg fluoride, ovary exhibited congested oocytes in the follicles, necrosis of follicle cells and interstitial oedema. The degenerative changes were most pronounced in animals treated with 50 mg fluoride, in which complete atrophy of follicles along with oocyte disintegration and marked necrosis of cells accompanied by infiltration of monocytes, lymphocytes and histiocytes in interstitial tissue occurred. The data indicate that the structural alterations in the ovary were more pronounced with the concomitant increase in the dose of fluoride." Shashi A. (1990). Histopathological changes in rabbit ovary during experimental fluorosis. Indian Journal of Pathology and Microbiology 33(2):113-7.

45. "The effect of high fluoride intake (100 and 200 ppm) in the ration was studied in male rats. After sixty days of treatment, rats showed a decrease in the mean diameter of the seminiferous tubules and the percentage of the tubules containing spermatozia and increase in the in the thickness of the peritubular membranes. The effect was more prominent with the higher dose of fluoride. Serum testosterone level in rats [which] received 200 ppm fluoride showed a sharp decrease, whereas in those treated with 100 ppm did not differ significantly from the control. The fertility performance of treated rats was reduced and the results revealed a reduction in the number of pregnant females and newborns of both treated groups. Lowest dose of fluoride had a similar but less marked effect on the fertility performance than the higher dose. It is concluded that the high fluoride intake causes a decline in the reproductive performance of the adult male rats, although the clinical signs in the teeth are absent." Araibi AA, et al. (1989). Effect of high fluoride on the reproductive performance of the male rat. Journal of Biological Sciences Research 20: 19-30.

46. "The effects of sodium fluoride (NaF) ingestion in two doses (10 and 20 mg/kg body weight) for 30 days on histology and histocytometry of reproductive

organs of the adult male mouse were investigated. In order to study reversibility, treatment was withdrawn for one and two months... NaF treatment caused severe disorganization and denudation of germinal epithelial cells of seminiferous tubules with absence of sperm in the lumina. The Leydig cell and nucleus diameters were not affected. The caput epididymis showed fewer changes than the cauda. However, epithelial cell nuclear pyknosis and absence of luminal sperm were observed. A reduction in epithelial cell height, nuclear pyknosis, denudation of cells, and absence of sperm occurred in the cauda epididymis. The vas deferens epithelium showed nuclear pyknosis, clumped stereocilia, and cell debris but no sperm in the lumen and an increase in the lamina propria. The prostate and seminal vesicles were not affected by treatment. Withdrawal of treatment caused marked recovery in the histoarchitecture of these organs. The effects of NaF treatment are therefore transient and reversible." Chinoy NJ , Sequeira E. (1989). Effects of fluoride on the histoarchitecture of reproductive organs of the male mouse. Reproductive Toxicolology 3(4):261-7.

47. "Reduction of ingested fluoride in a skulk of silver foxes resulted in the reduction of fluoride burden, decreased neonatal mortality and increased kit production during a two breeding and whelping season period." Eckerlin RH, et al. (1988). Ameliorative effects of reduced food-borne fluoride on reproduction in silver foxes. Cornell Veterinarian 78(4):385-91.

48. "Sixty-six eastern screech-owls (Otus asio) were paired and randomly assigned to dietary treatment groups of 0, 40, or 200 ppm (mg/kg) fluoride (as sodium fluoride) in November 1981. Hatching success was adversely affected at the 200 ppm (mg/kg) level, suggesting potential detrimental impacts to wild populations exposed to fluoride pollution." Pattee OH, et al. (1988). Effects of dietary fluoride on reproduction in Eastern Screech-Owls. Archives of Environmental Contamination and Toxicology 17: 213-218.

49. "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 - 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." Pati PC, Bhunya SP. (1987). Genotoxic effect of an environmental pollutant, sodium fluoride, in mammalian in vivo test system. Caryologia 40:79-87.

50. "The results provide unequivocal evidence that 250 uM fluoride inhibits testosterone secretion by rat testes perfused in vitro. Previous investigators have reported that 5-10 mM fluoride stimulates adenylate cyclase, inhibits metabolic reactions, and inhbits testosterone biosynthesis. The present observation of deleterious effects by 250 uM fluoride (5 ppm) emphasizes the sensitivity of steroidogenesis to fluoride." Chubb C. (1985). Reproductive toxicity of fluoride. Journal of Andrology 6: 59.

51. "The effects on reproduction in screech owls (Otus asio) of chronic dietary sodium fluoride administration at 0, 40, and 200 ppm were examined. Fluoride at 40 ppm resulted in a significantly smaller egg volume, while 200 ppm also resulted in lower egg weights and lengths. Day-one hatchlings in the 200 ppm group weighed almost 10% less than controls and had shorter crown-rump lengths... These results, in combination with the findings of Pattee et al., revealed significant impairment of overall reproduction, suggesting that sodium fluoride could cause slight to moderate reproduction disorders in owls in fluoride-polluted areas." Hoffman DJ, et al. (1985). Effects of fluoride on screech owl reproduction: teratological evaluation, growth, and blood chemistry in hatchlings. Toxicology Letters 26(1):19-24.

52. “A marked fall ($p < 0.01$) in the testosterone production was recorded at a fluoride concentration of 100 ppm and testosterone synthesis was maximally inhibited ($p < 0.01$) at 200 ppm. There was a noticeable, though marginal, inhibition in testosterone synthesis even at 10 ppm fluoride concentration. From 1 ppm to 200 ppm, the degree of inhibition of testosterone synthesis seems to be dependent on fluoride concentration.” Kanwar KC, Vig PS, Kalla NR (1983). In vitro inhibition of testosterone synthesis in the presence of fluoride ions. IRCS Medical Science 11: 813-814.

53. “The study was designed in order to assess the relationship between infertility and histological structure of testes following administration of varying doses of sodium fluoride. One hundred adult male albino mice were fed 10 ppm (Group A), 500 ppm (Group B) and 1000 ppm (Group C) of sodium fluoride in drinking water. The Group A animals were sacrificed at the end of one month, Group B after two and Group C after three months. The testes were removed and, after being processed in the usual manner, they were stained with hematoxylin and eosin. In Groups B and C, the higher dosage groups, there was a lack of maturation and differentiation of spermatocytes. In animals sacrificed at the end of three months, spermatogenesis had stopped and the seminiferous tubules had become necrotic. A definite relationship between fluorosis and damage to the testes has, therefore, been established by this study.” Kour K, Singh J. (1980). Histological finding of mice testes following fluoride ingestion. Fluoride 13: 160-162.

54. “Observations were made over four breeding seasons to determine the effect of excessive intake of fluorine in the drinking water on the breeding efficiency of cattle. Fifty Afrikaner heifers, maintained under ordinary ranching conditions, were divided into five groups which received 5, 8 and 12 ppm fluorine respectively in the drinking water... In the first season reproduction was normal in every respect in all groups, but in the next season there was a noteworthy increase in post-calving anoestrus in the groups receiving 8 and 12 ppm fluorine. The third season revealed an appreciable decline in fertility, notably in the animals receiving over 5 ppm fluorine. The fourth season was characterized by a marked drop in breeding efficiency as judged by calving rate and services per conception in all groups. This was most pronounced in the groups receiving 8 and 12 ppm... The adverse influence of excessive fluorine on reproduction was manifested before the animals revealed any evidence of impairment of general health, such as loss of condition and inappetence. It is concluded that for normal reproduction the fluorine content of drinking water should be under 5 ppm.” van Rensburg SWJ, de Vos WH. (1966). The influence of excess fluorine intake in the drinking water on reproductive efficiency in bovines. The Onderstepoort Journal of Veterinary Research 33: 185-194.

I. Likely and Possible Harm of Fluoride on the Pineal Gland: Teratogenicity, Altered Growth, and Functional Deficit.

1. “In terms of mineralized tissue, the mean fluoride concentration in the pineal calcification was equivalent to that in severely fluorosed bone and more than four times higher than in corresponding bone ash, i.e., 8,900 ± 7,700 vs. 2,040 ± 1,100 mg/kg, respectively. The calcification in two of the 11 pineals analysed in this study contained extremely high levels of fluoride: 21,800 and 20,500 mg/kg.” Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 167.

2. The pineal gland contains hyroxyapatite crystals, and this hard tissue accumulates more fluoride (up to 21,000 ppm) than any other hard tissue in the body (e.g. teeth and bone). The soft tissue of the adult pineal gland contains more fluoride than any other soft tissue in the body - a level of fluoride (~300 ppm) capable of inhibiting enzymes, protein synthesis and cell function. Up until the 1990s, no research had ever been conducted to determine the impact of fluoride on the pineal gland - a small gland located between the two hemispheres of the brain that regulates the production of the hormone melatonin. Melatonin is a hormone that helps regulate the onset of puberty and helps protect the body from cell damage caused by free radicals.

3. After finding that the pineal gland is a major target for fluoride accumulation in humans, Dr. Luke conducted animal experiments to determine if the accumulated fluoride could impact the functioning of the gland - particulalry the gland's regulation of melatonin. Luke found that animals treated with fluoride had lower levels of circulating melatonin, as reflected by reduced levels of melatonin metabolites in the animals' urine. This reduced level of circulating melatonin was accompanied - as might be expected - by an earlier onset of puberty in the fluoride-treated female animals.

4. Luke summarized her human and animal findings as follows: "In conclusion, the human pineal gland contains the highest concentration of fluoride in the body. Fluoride is associated with depressed pineal melatonin synthesis by prepubertal gerbils and an accelerated onset of sexual maturation in the female gerbil. The results strengthen the hypothesis that the pineal has a role in the timing of the onset of puberty. Whether or not fluoride interferes with pineal function in humans requires further investigation." FULL TEXT - html: Luke J. (2001). Fluoride deposition in the aged human pineal gland. Caries Research 35:125-128. FULL TEXT- pdf: • Luke J. (1997). PhD Thesis: The Effect of Fluoride on the Physiology of the Pineal Gland (298 pages)

5. "The single animal study of pineal function indicates that fluoride exposure results in altered melatonin production and altered timing of sexual maturity. Whether fluoride affects pineal function in humans remains to be demonstrated. The two studies of menarcheal age in humans show the possibility of earlier menarche in some individuals exposed to fluoride, but no definitive statement can be made. Recent information on the role of the pineal organ in humans suggests that any agent that affects pineal function could affect human health in a variety of ways, including effects on sexual maturation, calcium metabolism, parathyroid function, postmenopausal osteoporosis, cancer, and psychiatric disease." National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p221-22.

6. "It is remarkable that the pineal gland has never been analysed separately for F because it has several features which suggest that it could accumulate F. It has the highest calcium concentration of any normal soft tissue in the body because it calcifies physiologically in the form of hydroxyapatite (HA). It has a high metabolic activity coupled with a very profuse blood supply: two factors favouring the deposition of

F in mineralizing tissues. The fact that the pineal is outside the blood-brain barrier suggests that pineal HA could sequester F from the bloodstream if it has the same strong affinity for F as HA in the other mineralizing tissues. The intensity of the toxic effects of most drugs depends upon their concentration at the site of action. The mineralizing tissues (bone and teeth) accumulate high concentrations of F and are the first to show toxic reactions to F. Hence, their reactions to F have been especially well studied. If F accumulates in the pineal gland, then this points to a gap in our knowledge about whether or not F affects pineal physiology. It was the lack of knowledge in this area that prompted my study." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 1-2.

7. "After half a century of the prophylactic use of fluorides in dentistry, we now know that fluoride readily accumulates in the human pineal gland. In fact, the aged pineal contains more fluoride than any other normal soft tissue. The concentration of fluoride in the pineal was significantly higher ($p < 0.001$) than in corresponding muscle, i.e., 296 ± 257 vs. 0.5± 0.4 mg/kg (wet weight) respectively." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 167.

8. "Fluoride is now introduced at a much earlier stage of human development than ever before and consequently alters the normal fluoride-pharmacokinetics in infants. But can one dramatically increase the normal fluoride-intake to infants and get away with it? The safety of the use of fluorides ultimately rests on the assumption that the developing enamel organ is most sensitive to the toxic effects of fluoride. The results from this study suggest that the pinealocytes may be as susceptible to fluoride as the developing enamel organ." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 176.

9. "Alongside the calcification in the developing enamel organ, calcification is also occurring in the child's pineal. It is a normal physiological process. A complex series of enzymatic reactions within the pinealocytes converts the essential amino acid, tryptophan, to a whole family of indoles. The main pineal hormone is melatonin (MT)... If F accumulates in the pineal gland during early childhood, it could affect pineal indole metabolism in much the same way that high local concentrations of F in enamel organ and bone affect the metabolism of ameloblasts and osteoblasts." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 5.

10. "Any adverse physiological effects of fluoride depend upon the concentration at various tissue sites. Can pinealocytes function normally in close proximity to high concentrations of fluoride? One would predict that a high local fluoride concentration would affect pinealocyte function in an analogous way that a high local fluoride concentration affects: i) bone cells, since histological changes have been observed in bone with 2,000 mg F/kg (Baud et al, 1978); ii) ameloblasts, since dental fluorosis develops following fluoride concentrations of 0.2 mg F/kg in the developing

enamel organ (Bawden et al, 1992). The consequences are disturbances in the functions of bone and enamel, i.e., changes in structure (poorly mineralized bone and enamel). If the pineal accumulates fluoride at an earlier age than in previous decades, one would anticipate that a high local concentration of fluoride within the pineal would affect the functions of the pineal, i.e., the synthesis of hormonal products, specifically melatonin... The controlled animal study carried out in this study produce compelling evidence that fluoride inhibits pineal melatonin output during pubertal development in the gerbil." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 168-169.

11. "The section on the effects of fluoride on the physiological signs of sexual maturity in the gerbil was a preliminary, pilot study. There were not enough subjects to make any firm conclusions so an interpretation of the data is conjectural. However, the results do suggest that the HF (High-Fluoride) females had an accelerated onset of puberty as judged by several indices of pubertal development in rodents. At 7 weeks, the HF females were significantly heavier than the LF females ($p < 0.004$); as heavy as the HF males and LF males. The ventral gland in the HF female developed significantly earlier than in the LF female ($p < 0.004$). Vaginal opening occurred earlier in the HF female than in the LF female ($p < 0.03$)." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 173-174.

12. "The first step in assessing a health risk by a substance to humans is the identification of its harmful effects on animals. A health risk to humans is assessed using results from human epidemiological studies in conjunction with results from animal studies. The Newburgh-Kingston Study (Schlesinger et al, 1956) showed an earlier age of first menarche in girls living in the fluoridated Newburgh than in unfluoridated Kingston. The current animal study indicates that fluoride is associated with an earlier onset of puberty in female gerbils. Furthermore, more research was recommended on the effects of fluoride on animal and human reproduction (USPHS, 1991). This project has contributed new knowledge in this area." Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 177.

13. "The most plausible hypothesis for the observed significant decrease in the rate of urinary aMT6s excretion by the HF (High-Fluoride) group is that fluoride affects the pineal's ability to synthesize melatonin during pubertal development in the gerbil. Fluoride may affect the enzymatic conversion of tryptophan to melatonin. Although melatonin was the hormone investigated in this project, fluoride may also affect the synthesis of melatonin precursors, (e.g., serotonin), or other pineal products, (e.g., 5-methoxytryptamine). This would depend on the position(s) of the susceptible enzyme(s). For some unknown reason, pineal calcification starts intracellularly. Calcium has been demonstrated in pinealocyte mitochondria. Therefore, it may be a mitochondrial enzyme that is sensitive to the effects of fluoride, e.g., tryptophan-5-hydroxylase. Alternatively, fluoride may affect pinealocyte enzymes which require a divalent co-enzyme because such enzymes are particularly sensitive to fluoride." Luke J. (1997). The Effect of

Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. p. 172-173.

J. Likely and Possible Harm from Fluoride with Arthritis: Teratogenicity, Altered Growth, and Functional Deficit.

1. "The word arthritis literally means joint inflammation, but it is often used to refer to a group of more than 100 rheumatic diseases that can cause pain, stiffness, and swelling in the joints." National Institutes of Health

2. "Arthritis and chronic joint symptoms affect nearly 70 million Americans, or about one of every three adults, making it one of the most prevalent diseases in the United States. As the population ages, this number will increase dramatically." Centers for Disease Control and Prevention

3. "This patient presented with chronic symmetrical arthralgia with accompanying gastrointestinal disturbance, raising the possibility of enteropathic arthritis. The diagnosis of skeletal fluorosis was surprising, with fluoride levels being high in body fluids and drinking water." Gupta R, Kumar AN, Bandhu S, Gupta S. (2007) Skeletal fluorosis mimicking seronegative arthritis. Scandanavian Journal of Rheumatology 36(2):154-5.

4. "'Skeletal fluorosis' is a condition associated with prolonged accumulation of fluoride resulting in fragile bones having low tensile strength. It affects the joints as well as the bones. It is not easily recognizable till advanced stage. In its early stages, its symptoms may resemble those of arthritis. In its most severe stages it becomes a crippling disability that has a major public health and socio-economic impact, affecting millions of people in various regions of Africa, China and India." Ayoob S, Gupta AK. (2006). Fluoride in Drinking Water: A Review on the Status and Stress Effects. Critical Reviews in Environmental Science and Technology 36:433–487.

5. "The authors describe a 50-year-old man with previously treated cancer who was using tray-applied topical fluoride gel. He complained of gastric symptoms, difficulty in swallowing, leg muscle soreness and knee joint soreness... The patient's fluoride regimen was altered, and within a short period his urinary fluoride levels returned to normal and his symptoms resolved." Eichmiller FC, Eidelman N, Carey CM. (2005). Controlling the fluoride dosage in a patient with compromised salivary function. Journal of the American Dental Association 136:67-70.

6. "[A]rthopathy and arthritis affected a significant number of the (fluorosis) patients, resulting in functional disability... The physical signs of brick tea-type skeletal fluorosis were elbow, shoulder and knee articular dysfunction, which was the most common pathology. X-ray examination revealed that the interosseous membrane ossification, tendon attachment calcification and articular degeneration were the causes of these functional disorders." Cao J, et al. (2003). Brick tea fluoride as a main source of adult fluorosis. Food and Chemical Toxicology 41:535-42.

7. “The radiological severity of knee osteoarthritis was greater in the endemic fluorosis group than in controls... [E]ndemic fluorosis may increase the severity of osteoarthritis in the knees.” Savas S, et al. (2001). Endemic fluorosis in Turkish patients: relationship with knee osteoarthritis. Rheumatology International 21: 30-5.

8. “Early signs [of skeletal fluorosis] are vague pains and arthralgia. This generally progresses to backache, pain in the spine, and signs of stiffness and rigidity...” Littleton J. (1999). Paleopathology of skeletal fluorosis. American Journal of Physical Anthropology 109: 465-483.

9. “The initial symptoms usually were headache and weakness. These were followed by multiple joint pains, mostly in the feet, knees, and back. Spinal stiffness and kyphosis developed in a few patients.” Wang Y, et al. (1994). Endemic fluorosis of the skeleton: radiographic features in 127 patients. American Journal of Roentgenology 162: 93-8.

10. “Symptoms of pain, stiffness and diffuse aches may be dismissed as functional, but may in fact be early signs of fluoride damage to tendinous insertions and ligaments as well as joint capsules.” Anand JK, Roberts JT. (1990). Chronic fluorine poisoning in man: a review of literature in English (1946-1989) and indications for research. Biomedicine & Pharmacotherapy 44: 417-420.

11. “Clinical Phase 1 Fluorosis: Sporadic pain; stiffness of joints; osteosclerosis of pelvis & vertebral column. Clinical Phase 2 Fluorosis: Chronic joint pain; arthritic symptoms; slight calcification of ligaments...” Department of Health and Human Services. (1991). Review of fluoride: benefits and risks. Report of the Ad Hoc Subcommittee on Fluoride. Washington, DC.

12. “Vague, diffuse aches and stiffness of joints with decreased range of motion are common initial symptoms. With disease progression, kyphosis with limited spinal mobility, flexion contracture of lower extremities, and restricted chest wall expansion occur.” Fisher RL, et al. (1989). Endemic fluorosis with spinal cord compression. A case report and review. Archives of Internal Medicine 149: 697-700.

13. “Although skeletal fluorosis has been studied intensely in other countries for more than 40 years, virtually no research has been done in the U.S. to determine how many people are afflicted with the earlier stages of the disease, particularly the preclinical stages. Because some of the clinical symptoms mimic arthritis, the first two clinical phases of skeletal fluorosis could be easily misdiagnosed... Even if a doctor is aware of the disease, the early stages are difficult to diagnose. “ Hileman B. (1988). Fluoridation of water.Questions about health risks and benefits remain after more than 40 years. Chemical and Engineering News August 1, 1988, 26-42.

14. “The most frequent symptoms in those exposed >6 yr were low back pain, painful knee, elbow, and hip... Analysis of workers’ complaints showed no specific pain or other symptom that we could refer only to fluorosis...The only

characteristic feature would be multiple-joint involvement in the case of fluorosis. This would differentitate fluorosis from monoarticular osteoarthritis (OA), but unfortunately not from multiple-joint osteoarthritis or rheumatoid arthritis (RA)." Czerwinski E, et al. (1988). Bone and joint pathology in fluoride-exposed workers. Archives of Environmental Health 43: 340-343.

15. "According to our survey, clinical manifestations of fluoride injury were systemic. A wide variety of vague, subtle symptoms (i.e. backache, restricted joint movement, abdominal pain) occurred either prior to or simultaneously with the development of bone changes similar to those reported previously. Nonskeletal symptoms, therefore, are important for early diagnosis." Zhiliang Y, et al. (1987). Industrial fluoride pollution in the metallurgical industry in China. Fluoride 20: 118-125.

16. "The clinical picture was characterized by new bone formation, musculo-skeletal dysfunction leading to arthralgia, arthritis, fixed flexion deformities, peripheral neuropathy and incapacitation." Krishnamachari KA. (1986). Skeletal fluorosis in humans: a review of recent progress in the understanding of the disease. Progress in Food and Nutrition Sciences 10:279-314.

17. "[I]t is postulated that fluoride activates the calcification of cartilage... Thus it would be interesting to investigate the effect of fluoride on the evolution of joint alterations in rheumatoid arthritis and osteoarthrosis." Bang S, et al. (1985). Distribution of fluoride in calcified cartilage of a fluoride-treated osteoporotic patient. Bone 6: 207-210.

18. "Arthritis of spine and small joints of hands and fingers develops early in the course of the disease with or without demonstrable radiological changes." Bhavsar BS, Desai VK, Mehta NR, Vashi RT, Krishnamachari KAVR. (1985). Neighborhood Fluorosis in Western India Part II: Population Study. Fluoride 18: 86-92.

19. "Early bone fluorosis is not clinically obvious; often the only complaints of young adults are vague pains in the small joints of the hands, feet, and lower back. Such cases may be misdiagnosed as rheumatoid arthritis or ankylosing spondylitis." Smith GE. (1985). Repetitive Strain Injury, or Incipient Skeletal Fluorosis? (Letter.) New Zealand Medical Journal 98:328.

20. "Our findings demonstrate a highly significant relationship between the frequency of back and neck surgery, fractures, symptoms of musculoskeletal disease and a past history of diseases of the bones and joints. In the absence of so-called classic fluorosis, a disease complex was established which involves much more than merely the radiologic appearance of dense bone." Carnow BW, Conibear SA. (1981). Industrial fluorosis. Fluoride 14: 172-181.

21. "Although a few subjects had no symptoms, the fluoride exposed workers had a higher frequency of joint pain and stiffness than the control group. This joint pain resulted in disability in some cases." Boillat MA, et al. (1980). Radiological

criteria of industrial fluorosis. Skeletal Radiology 5: 161-165.

22. "[E]xtensive research from India has revealed severe arthritic changes and crippling neurological complications even where the fluoride concentration in water naturally is as low as 1.5 ppm...Even though extensive bone deformities may not be found on a large scale from fluoride in water at the 1 ppm concentration, some of the early signs of the disease, such as calcifications of ligaments, joint capsules, and muscle attachments, are likely to occur. Indeed these conditions are characteristic of osteoarthritis, in which the formation of microcrystals of apatite (known to be promoted by fluoride) has now been clearly demonstrated... For example, Pinet and Pinet described in detail X-ray changes encountered in skeletal fluorosis in North Africa that are in every respect identical with those present in the arthritic spine of the elderly elsewhere." Waldbott GL, Burgstahler AW, and McKinney HL. (1978). Fluoridation: The Great Dilemma. Coronado Press, Inc., Lawrence, Kansas.

23. "Understandably, it is not uncommon to find reference to arthritic changes, if for no other reason than the difficulty of distinguishing them from certain fluoride effects on bone." Hodge HC, Smith FA. (1977). Occupational fluoride exposure. Journal of Occupational Medicine 19: 12-39.

24. "In our material we noted degenerative changes in the lumbar spine in 95% of cases, which suggests that fluoride accelerates these changes. In addition to pain in the lower spine which is associated with radiological changes, patients with negative x-ray findings also complain of pain in the lumbar-sacral area, an indication that symptoms precede changes demonstrable by x-ray." Czerwinski E, Lankosz W. (1977). Fluoride-induced changes in 60 retired aluminum workers. Fluoride 10: 125-136.

25. "Most often the patients complained of back pain. Pains in the shoulders, elbows, forearms and lower legs were common. These pains differed in intensity and occurred constantly or periodically with no clear relationship to effort." Czerwinski E, Lankosz W. (1977). Fluoride-induced changes in 60retired aluminum workers. Fluoride 10: 125-136.

26. "The investigation of a high incidence of arthritis in 21 dairy herds disclosed elevated fluorine levels in bone samples... There was a statistical correlation between a high incidence of damage to peri-articular structures, resulting in debility and loss of production, and elevated bone fluorine." Griffith-Jones W. (1977). Fluorosis in dairy cattle. The Veterinary Record 100: 84-89.

27. "In early stages, fluorosis is usually associated only with stiffness, backache, and joint pains which may suggest the diagnosis of rheumatism, rheumatoid arthritis, ankylosing spondylitis and osteomalacia. At this stage the radiological findings of skeletal fluorosis may not be evident and therefore most of these cases are either misdiagnosed for other kinds of arthritis or the patients are treated symptomatically for pains of undetermined diagnosis (PUD). The majority of our patients had received treatment for rheumatoid arthritis and ankylosing spondylitis before they came under our

observation." Teotia SPS, et al. (1976). Symposium on the Non-Skeletal Phase of Chronic Fluorosis: The Joints. Fluoride 9: 19-24.

28. "In the initial stages, the complaints of the patients are not remarkable. At first they experience vague rheumatic pains, then the pains become localized in the spine, especially in the lumbosacral region. Later, a sensation of stiffness in the lumbar and cervical spine develop. However, we also found patients with slight radiological changes who complained of intense pains in the spine and in the large joints. On the other hand, some patients whose fluorosis was radiologically distinct were almost without complaints." Franke J, et al. (1975). Industrial fluorosis. Fluoride 8: 61-83.

29. "Many workers complained of pains at night and while resting, but movement caused them to disappear." Franke J, et al. (1975). Industrial fluorosis. Fluoride 8: 61-83.

30. "All the patients had typical diagnostic features: skeletal pains, backache, stiffness, rigidity and restricted movements of the spine and other joints." Faccini JM, Teotia SPS. (1974). Histopathological assessment of endemic skeletal fluorosis. Calcified Tissue Research 16: 45-57.

31. "Schlegel presented data on 61 cases of skeletal fluorosis among workers of a Swiss aluminum factory... Their major symptoms were arthritic changes in the joints, especially in the spine... In contrast to non-industrial fluorosis, the author noted excessive involvement of the elbow joint which is presumably due to habitual use of the arms... The author also emphasizes the difficulty in differentiating spontaneous arthrosis from fluorotic arthritis." Schlegel HH. (1974). Industrial skeletal fluoroses: preliminary report on 61 cases from aluminum smeleter. Sozial und Praventivmed. 19:269-74. (Abstracted in: Fluoride 1975; 8:177)

32. "Arthritis of the spinal column develops early in the disease with or without demonstrable radiological changes." Waldbott GL. (1974). The pre-skeletal phase of chronic fluorine intoxication. Fluoride 7:118-122.

33. "In spite of this distinctive clinical picture of advanced fluorosis, the earlier stages of the disease are more difficult to recognize. The initial symptoms are quite non-specific and not obviously linked to fluoride. The onset of fluorosis leads to tingling sensations in the hands and feet, pain similar to arthritic pain in the joints and the lower back, stiffness, and motor weakness. The first reliable diagnostic sign is increased bone density in X-ray examination, but in some early cases early bone changes are not radiologically detectable." Groth, E. (1973). Two Issues of Science and Public Policy: Air Pollution Control in the San Francisco Bay Area, and Fluoridation of Community Water Supplies. Ph.D. Dissertation, Department of Biological Sciences, Stanford University, May 1973.

34. "This case supports the premise that some forms of arthritis are related to sub-clinical fluorosis, i.e. fluorosis which is not sufficiently advanced to show

the characteristic skeletal changes radiologically." Cook HA. (1972). Crippling fluorosis related to fluoride intake (case report). Fluoride 5: 209-213.

35. "Possibly some cases of pain diagnosed as rheumatism or arthritis may be due to subclinical fluorosis which is not radiologically demonstrable." Cook HA. (1971). Fluoride studies in a patient with arthritis. The Lancet 1: 817.

36. "The onset of chronic fluorosis is insidious and may be confused with chronic debilitating diseases such as osteoarthritis, trace-element toxicosis, and trace-element deficiencies." Shupe JL. (1970). Fluorine toxicosis and industry. American Industrial Hygiene Association Journal 31: 240-247.

37. "Whereas dental fluorosis is easily recognized, the skeletal involvement is not clinically obvious until the advanced stage of crippling fluorosis... Such early cases are usually in young adults whose only complaints are vague pains noted most frequently in the small joints of the hands and feet, in the knee joints and in the joints of the spine. These cases are frequent in the endemic area and may be misdiagnosed as rheumatoid or osteo arthritis." Singh A, Jolly SS. (1970). Chronic toxic effects on the skeletal system. In: Fluorides and Human Health. World Health Organization. pp. 238-249.

38. "Most authors agree that chronic fluorosis can cause musculoskeletal discomfort and pain, despite the fact that well documented cases of fluorosis in patients without any clinical symptoms have been published... All but one of the 17 patients complained of vague pains and stiffness in the lower and upper extremities, shoulders, neck and lower back. In none of the cases could another disease of the bone or of the joints be found, except arthrotic lesions... If signs of fluorosis are present, they may lead to symptoms of the osteoarticular system." Vischer TL, et al. (1970). Industrial fluorosis. In: TL Vischer, ed. (1970). Fluoride in Medicine. Hans Huber, Bern. pp. 96-105.

39. "Joint changes or fluoric arthrosis may be very severe especially in the hip, knee and elbow joints." Soriano, M. (1968). Periostitis deformans due to wine fluorosis. Fluoride 1: 56-64.

40. "Fluoric Arthropathies: Around joints, thick marginal osteophytes develop. In some instances, they grow to such an extent as to block joint movement ('blocking arthrosis'). The joint block can also be induced by calcification of the periarticular ligament. The most common sites of articular involvement are the hips, the sacroiliac, elbow and knee joints. In older persons, the vetebral column is commonly affected. Advanced stages of the disease show atrophy and ulceration of joint cartilage." Soriano, M. (1968). Periostitis deformans due to wine fluorosis. Fluoride 1: 56-64.

41. "Another frequent finding was the calcification of ligaments and muscle attachments ...Approximately three quarters of those later found to have radiological evidence of skeletal involvement did complain of pains mainly in the back,

chest, and legs." Latham MC, Grech P. (1967). The effects of excessive fluoride intake. American Journal of Public Health 57: 651-660.

42. "In general, the metabolic patterns of osteoblasts, ameloblasts, odontoblasts, and chrondoblasts are sufficiently similar so that disturbances of cartilage might be expected... To date, any osteoarthritis observed in fluoride-treated cattle has been regarded as an unrelated process. However, excessive remodeling of the subchondral plate and cancellous end of the bone, such as occurs in osteofluorosis, will eventually lead to remodeling of the articular cartilage. Excessive cartilage remodeling leads to osteoarthritis of normal joints. Therefore, both the mechanical effects of fluoride induced remodeling and the direct action of fluoride on cartilage cells might alter cartilage. The fluoride levels and remodeling circumstances necessary to produce cartilage alteration in cattle - if it occurs - remain to be established." Johnson LC. (1965). Histogenesis and mechanisms in the development of osteofluorosis. In: H.C.Hodge and F.A.Smith, eds : Fluorine chemistry, Vol. 4. New York, N.Y., Academic press (1965) 424-441.

43. "The ligamentous calcification [of skeletal fluorosis] is often periarticular and shows as osteoarthritis of the spine and hip joints as well as of the sacro-iliac joints." Kumar SP, Harper RA. (1963). Fluorosis in Aden. British Journal of Radiology 36: 497-502.

44. In the early stages of skeletal fluorosis, the "only complaints are vague pains noted most frequently in the small joints of hands and feet, the knee joints and those of the spine. Such cases are frequent in the endemic area and may be misdiagnosed as rheumatoid or osteoarthritis. Such symptoms may be present prior to the development of definite radiological signs. A study of the incidence of rheumatic disorders in areas where fluoridation has been in progress for a number of years would be of interest." Singh A, et al. (1963). Endemic fluorosis. Epidemiological, clinical and biochemical study of chronic fluoride intoxication in Punjab. Medicine 42: 229-246.

45. "The onset was insidious, and stiffness of the back and legs was a universal complaint. Almost all the patients complained of vague fleeting pains all over the body, particularly in the spine and in the knee-joints." Singh A, et al. (1961). Skeletal fluorosis and its neurological complications. Lancet 1: 197-200.

46. "It is quite possible that endemic centres [of skeletal fluorosis] exist but that the cause of the disabling spondylitis or other joint affections has not been determined, and a diagnosis of chronic arthritis has resulted. Few cases in Canada or the United States will be found to be as dramatic as that recorded here from Southwest China, but by calling attention to the advanced stage of this condition help may be afforded to the diagnosis of early cases." Kilborn LG, et al. (1950). Fluorosis with report of an advanced case. Canadian Medical Association Journal 62: 135-141.

K. Likely and Possible Harm to Bones from Fluoride: Teratogenicity, Altered Growth, and Functional Deficit.

1. “Fracture risk and bone strength have been studied in animal models. The weight of evidence indicates that, although fluoride might increase bone volume, there is less strength per unit volume.” National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA’s Standards. National Academies Press, Washington D.C. p5.

2. “[O]ne cannot help but be alarmed by the negative effects of fluoride on bone strength consistently demonstrated in animal models.” Turner CH. (1996). Fluoride and the FDA: a curious case. (letter) Journal of Bone and Mineral Research 11(9):1369-71.

3. “Several animal studies on fluoride’s effect on bone biomechanical competence have been performed... [A]n overwhelming majority of the investigations mentioned found no effect or a negative effect of fluoride on bone strength...” Sogaard CH, et al. (1995). Effects of fluoride on rat vertebral body biomechanical competence and bone mass. Bone 16: 163-9.

4. “In A/J strain, we found significant decreases in stiffness with increasing fluoride dose treatment. There was a significant difference between the treatment group 0 ppm and 100 ppm... In the A/J strain, there was a decrease in ultimate load with increasing fluoride dose treatment, with significant differences between the treatment group 0 ppm and the treatment group 100 ppm ($p=0.017$).”
SOURCE: Mousny M, et al. (2006). The genetic influence on bone susceptibility to fluoride. Bone Aug 18; [Epub ahead of print]

5. “In group treated with NaF both the strength and stiffness were significantly decreased when compared with those in ovariectomized control.” Czerny B, et al. (2004). The Effect of Tamoxifen and Fluoride on Bone Mineral Density, Biomechanical Properties and Blood Lipids in Ovariectomized Rats. Basic & Clinical Pharmacology & Toxicology 92:162–165.

6. “The highest fluoride intake (50 mg/L) significantly diminished vertebral strength... This impairment of mineralization by fluoride appeared to be the primary cause of the diminished vertebral strength.” Turner CH, et al. (2001). Combined effects of diets with reduced calcium and phosphate and increased fluoride intake on vertebral bone strength and histology in rats. Calcified Tissue International 69: 51-57.

7. “Bending strength of the femoral shaft decreased significantly after fluoride therapy. We conclude that high fluoride intake decreases bone quality of the femoral shaft and neck in young growing rats.” Bohatyrewicz A. (1999). Effects of fluoride on mechanical properties of femoral bone in growing rats. Fluoride 32: 47-54.

8. “In this study, despite the observed increased in hardness of both cancellous and cortical bone, the fracture stress and elastic modulus of vertebrae tested in compression and femora tested in three-point bending were decreased by fluoride treatment.” Chachra D, et al. (1999). The effect of fluoride treatment on bone mineral in rabbits. Calcified Tissue International 64:345-351.

9. “It is likely that the bone changes induced by fluoride will lead to an impaired biomechanical competence of antlers from deer inhabitating regions with higher levels of environmental fluoride. We, therefore, would expect to find an increased incidence of antler breakage in such populations.” Kierdorf U, et al. (1997). Fluoride content and mineralization of red deer (Cervus elaphus) antlers and pedicles from fluoride polluted and uncontaminated regions. Archives of Environmental Contamination and Toxicology 32: 222-227.

10. “Fluoride treatment reduced all biomechanical measurements. The reductions ranged from 5% to 25%. Several of these reductions were statistically significant: the fracture force of the femoral neck was reduced by 25%, the fracture stress of the L-5 vertebra was reduced by 19%, and the bending modulus of the femur

was reduced by 21%." Turner CH, et al. (1997). Fluoride treatment increased serum IGF-1, bone turnover, and bone mass, but not bone strength, in rabbits. Calcified Tissue International 61:77-83.

11. "Fluoride concentrations of 15 and 50 ppm reduced femoral bone strength in renal-deficient animals. Femoral bone strength also was reduced in control animals given 50 ppm fluoride." Turner CH, et al. (1996). High fluoride intakes cause osteomalacia and diminished bone strength in rats with renal deficiency. Bone 19:595-601.

12. "NaF reduced the strength of cancellous bone from the L4 vertebrae, relative to the control animals, and the stiffness (resistance to deformation) of the femora." Bone strength "did not increase with bone volume, suggesting that for bones with higher volume, there was less strength per unit volume, that is, a deterioration in bone 'quality.'" Lafage MH, et al. (1995). Comparison of alendronate and sodium fluoride effects on cancellous and cortical bone in minipigs. A one-year study. Journal of Clinical Investigations 95(5):2127-33.

13. "Load corrected for ash content, which is a measure of bone quality, decreased significantly after fluoride therapy. It is concluded that the increase in bone mass during fluoride treatment does not translate into an improved bone strength and that the bone quality declines. This investigation thereby supports the hypothesis of a possible negative effect of fluoride on bone quality." Sogaard CH, et al. (1995). Effects of fluoride on rat vertebral body biomechanical competence and bone mass. Bone 16(1): 163-9.

14. "To date, animal studies of fluoride effects on bone have used young and healthy experimental animals exclusively. The effects of fluoride on old animals, that more closely represent people most likely to fracture, have not been studied.... In older rats receiving 50 ppm fluoride, failure stress was decreased by as much as 29%. Such dramatic losses in bone strength only have been shown previously in studies where fluoride intake was accompanied by calcium deficiency, yet, in this study, calcium intake in the older rats was no different from that in the younger rats... [I]t is possible that aging effects and fluoride incorporation in the bone act synergistically to decrease bone strength." Turner CH, et al. (1995). Fluoride reduces bone strength in older rats. Journal of Dental Research 74:1475-81.

15. "[S]everal investigators - including ourselves - have shown that bone strength decreases as bone fluoride levels in the mineral phase increase to beyond about 4500 ppm." Turner CH, Dunipace AJ. (1993). On fluoride and bone strength (letter). Calcified Tissue International 53: 289-290.

16. "Interfacial bonding interactions between the mineral and organic constituents of bone play an important role in the mechanical properties of cortical bone... Under a uniaxial tensile force, modification of interfacial bonding by phosphate and fluoride ions results in a reduction in the ultimate and yield stress and elastic modulus. In tension, phosphate ions effect is reversible upon removal of phosphate ions, while the fluoride ion effect is irreversible. Interestingly, when tested in compression, phosphate ion treatment results in a stiffening effect, while fluoride ions continue to lower the ultimate stress and elastic modulus." Walsh WR, Guzelsu N. (1993). The role of ions and mineral-organic interfacial bonding on the compressive properties of cortical bone. Bio-medical materials and engineering 3: 75-8

17. "The results demonstrate that water fluoride levels of 1 ppm may lead to increased bone strength, while water fluoride levels of 4 ppm would be expected to cause a decrease in bone strength." Turner CH, et al. (1992). The effects of fluoridated water on bone strength. Journal of Orthopedic Research 10:581-7. (NOTE: In subsequent studies, Turner was unable to duplicate the beneficial effects on bone

strength which he found at low doses in this study. As Turner noted in a more extensive, follow-up study: “the present results showed no evidence of increased bone strength resulting from fluoride levels below 16 ppm.” - Ref:: J Dent Res; 1995; Vol 74: 1475-81.)

18. “Bone quality seemed to be affected since significant decreases in bone-breaking strength and significant increases in bone mineralization were observed in fluoride-treated kestrels. When the breaking strength (LOAD) was expressed as the maximum load the bone can carry, no significant differences were detected among groups. However, when these figures are used to calculate the maximum stress the bone can resist, bone quality clearly decreased as more fluoride was added to the diet of the growing kestrels.” Bird DM, Carriere D, Lacombe D. (1992). The effect of dietary sodium fluoride on internal organs, breast muscle, and bones in captive American kestrels (Falco sparverius). Archives of Environmental Contamination and Toxicology 22:242-6.

19. “The reduction in interfacial bonding due to fluoride action lowers the mechanical properties of bone tissue.” Walsh WR, Guzelsu N. (1991). Fluoride ion effect on interfacial bonding and mechanical properties of bone. Journal of Biomechanics 24: 237.

20. “[T]he mechanical parameters for the fluorotic animals were unchanged...or decreased...It is concluded that the increased bone mass during the initial stages of fluoride treatment does not necessarily indicate an improved bone quality.” Mosekilde L, et al. (1987). Compressive strength, ash weight, and volume of vertebral trabecular bone in experimental fluorosis in pigs. Calcified Tissue Research 40: 318-322.

21. “The data reported herein suggested that levels of dietary F greater than 7 ppm are detrimental to bone integrity. Breaking stress and modulus of elasticity were reduced significantly at each level of added dietary F in both experiments. Similar observations have been made with nearly all species that have been subjected to F ingestion.” Burnell TW, et al. (1986). Effect of dietary fluorine on growth, blood and bone characteristics of growing-finishing pigs. Journal of Animal Science 63(6):2053-67.

22. “Thirty-six young rats were used to determine the effect of the fluoride on collagen synthesis in healing of fracture... Collagen synthesis of the callus was examined histochemically and histologically. In the fluoride-treated group, collagen synthesis was found to be defective, while it was normal in the controls.” Uslu B. (1983). Effect of fluoride on collagen synthesis in the rat. Research and Experimental Medicine 182:7-12.

23. “In the present study high levels of fluoride in the drinking water did not prevent osteoporosis, but in some experiments, by certain criteria, tended to increase it.” Robin JC, et al. (1980). Studies on osteoporosis III. Effect of estrogens and fluoride. Journal of Medicine 11(1):1-14.

24. “F at high levels, tended to decrease bone ash, cortical thickness, and mechanical strength parameters.” Guggenheim K, et al. (1976). The effect of fluoride on bone of rats fed diets deficient in calcium or phosphorus. Calcified Tissue Research 22: 9-17.

25. “The strength of osteopenic bone from calcium deprived rats, quail and roosters was significantly reduced after fluoride supplementation...This detrimental effect on bone strength must be considered in any therapeutic attempt to use fluoride ion to stimulate bone formation in osteopenic bone disorders.” Riggins RS, et al. (1976). The effect of fluoride supplementation on the strength of osteopenic bone. Clinical Orthopedics (114):352-7.

26. “The administration of sodium fluoride increased bone diameter, indicating stimulation of periosteal bone formation, but bone strength was reduced or not

affected by fluoride ingestion." Riggins RS, et al. (1974). The Effects of Sodium Fluoride on Bone Breaking Strength. Calcified Tissue Research 14: 283-289.

27. "Our observations corroborate the findings that, in general, elevated dietary fluoride results in an acceleration of bone mineralization. Uniquely, however, the increase in mineralization was accompanied by a decrease in bone strength... the changes in bone that occur with prolonged and excessive fluoride ingestion may result in a reduction of bone strength." Chan MM, et al. (1973). Effect of Fluoride on Bone Formation and Strength in Japanese Quail. Journal of Nutrition 103: 1431-1440.

28. "Femurs of fluoride-treated rats exhibited a decrease in mechanical strength as manifested by a decrease in ultimate stress to breaking as well as decrease in limit and modulus of elasticity." Wolinsky I, et al. (1972). Effects of fluoride on metabolism and mechanical properties of rat bone. American Journal of Physiology 223: 46-50.

29. "In the low calcium group a similar significant increase in flexibility appeared at the 10.0 ppm dosage level as well as the 45.0 ppm, but a significant decrease in strength at the two dosage levels were observed. These were in direct relation to the amount of fluoride given." Beary DF. (1969). The effects of fluoride and low calcium on the physical properties of the rat femur. Anatatomical Record 164: 305-316.

30. "[T]he heavily fluorinated bone tended to break under less stress than did bone from any other group. These findings suggest that the heavily fluorinated bone was not as strong as the bone from normal rats or from rats fed low-calcium diets without fluoride." Daley R, et al. (1967). The Effects of Sodium Fluoride on Osteoporotic Rats. The Journal of Bone and Joint Surgery (Abstract). 49A:796.

31. "[T]he decrease in the mean breaking strength was significant statistically" among the fluoride-treated rats, and "is in agreement with the known fact that the breaking strength of bone decreases with increased fluoride intake." Gedalia I, et al. (1964). Effects of Estrogen on Bone Composition in Rats at Low and High Fluoride Intake. Endocrinology 75: 201-205.

32. "Cristiani working with guinea pigs found that the fragility of the bones was increased about 20 per cent in the fluorized animals." Dean HT. (1936). Chronic endemic dental fluorosis. Journal of the American Medical Association 107: 1269-1273.

33. "The bones are subject to easy fracture." Blood DC, Henderson JA, Radostits OM, eds. (1979). Veterinary Medicine: A Textbook of the Diseases of Cattle, Sheep, Pgs and Horses. 5th Edition. Lea & Febiger, Philadelphia.

34. "The bone was brittle and shattered easily when cut on a bandsaw." Krook L, Maylin GA. (1979). Industrial fluoride pollution. Chronic fluoride poisoning in Cornwall Island cattle. Cornell Veterinarian 69(Suppl 8): 1-70.

35. "fluorotic specimens had a lower tensile strength and strain but a higher compressive strength and strain than the nonfluorotic ones." Gaynor F, et al. (1976). Mechanical properties and density of bone in a case of severe endemic fluorosis. Acta Orthopaedica Scandinavica 47: 489-495.

36. "Lameness, pain, exostoses, emaciation, and bone fractures were symptoms associated with horses exposed to F ingestion." Lillie RJ. (1970). Air Pollutants Affecting the Performance of Domestic Animals: A Literature Review. U.S. Dept. of Agriculture. Agricultural Handbook No. 380. Washington D.C.

37. "The first sign of fluorosis in cattle (and probably also in deer) is mottling, pitting, and black discoloration of the teeth. Affected teeth are soft and show abnormal wear. Later the leg and foot bones may become deformed or fractured,

resulting in lameness." Karstad L. (1967). Fluorosis in deer (Odoceileus virginianus). Bulletin of the Wildlife Disease Association 3:42-46.

38. "In advanced skeletal fluorosis the bones are brittle." Adams PH, Jowsey J. (1965). Sodium fluoride in the treatment of osteoporosis and other bone diseases. Annals of Internal Medicine 63: 1151-1155.

39. "In the macerated cattle specimens the bone was brittle and crumbled readily. The new bone was as fragile as chalk..." Johnson LC. (1965). Histogenesis and mechanisms in the development of osteofluorosis. In: H.C.Hodge and F.A.Smith, eds : Fluorine chemistry, Vol. 4. New York, N.Y., Academic press (1965) 424-441.

40. "One of the most prominent features of fluorosis in cattle in England, however, was the frequency of actue severe lameness, especially in the early summer. It resembled that described by Towers (1954) who associated it with fracture of the pedal bone (3rd phalanx)....This suggests that traumatic factors played a part in producing the lameness by causing damage to bones which were relatively fragile as a result of skeletal accumulation of fluorine..." Burns KN, Allcroft R. (1964). Fluorosis in Cattle. 1 - Occurrence and Effects in Industrial Areas of England and Wales 1954-57. Ministry of Agriculture, Fisheries and Food. Animal Disease Surveys Report No 2, Part I. Her Majesty's Stationery Office, London.

41. "Increased fragility of the bones may be present, and they can be friable and crumbly." Kumar SP, Harper RA. (1963). Fluorosis in Aden. British Journal of Radiology 36: 497-502.

42. "During the examination of the Achintee sheep, an unusally large number of fractures were detected; these involved ribs, mandible, and pelvis." Agate JN, et al. (1949). Industrial fluorosis: A study of the hazard to man and animals near Fort William, Scotland. Medical Research Council Memorandum No. 22. His Majesty's Stationery Office, London.

43. "High fluorine levels interfere with mineral metabolism and cause abnormal growth of bone that may be structurally weak." Huffman WT. (1949). Effects on livestock of air contamination caused by fluoride fumes. In: Air Pollution. Proceedings of the United States Technical Conference on Air Pollution. McGraw-Hill Book Co, New York. pp. 59-63.

44. "The bone is abnormally brittle." Lyth O. (1946). Endemic fluorosis in Kweichow, China. The Lancet 1: 233-235

45. "The osteomalacic condition (of fluorosis) to some extent varies with the species and age of the animal. Certain features are common, however... Common features are the reduced strength of the bones, the tendency to form exostoses, bone atrophy, and a deficient calcification." Roholm K. (1937). Fluoride intoxication: a clinical-hygienic study with a review of the literature and some experimental investigations. H.K. Lewis Ltd, London.

Published Data - Daily Fluoride Dose in Clinical Trials Reporting Increased Bone Fractures:

Trial	Age of	Length of	Average Daily	Average	Average Daily

	Patients	Treatment	Dose (mg/day)	Weight of Patients* (kg)	Dose (mg/kg)
Inkovaara 1975	78.4	8 months	25	60	0.41
Gerster 1983**	69	11 months	20.7	60	0.35
Gerster 1983**	78	21 months	22.7	60	0.37
Dambacher 1986	63.5	3 years	32	61.7	0.52
Hedlund 1989	67.7	2.1 years	22.7	60	0.37
Bayley 1990	65.3	4 years	20.9	57.7	0.36
Gutteridge 1990	68.2	3.4 years	27.8	60	0.46
Orcel 1990	69	17.1 months	23.7	60	0.40
Riggs 1990	68.2	4 years	34.1	61	0.56
Schnitzler 1990	63.6	2 years, 7 months	27***	60	0.45
Gutteridge 2002	70.9	18 of 27 months	24.5	60.2	0.41
AVERAGE	68.8	2 years, 6 months	26.2	--	0.43

* In trials where the average weight of the patients is not given, the weight is assumed to be 60 kg, which appears to the the rough average for osteoporosis patients (comprised mostly of females).
** The data from Gerster's two case studies are listed separately but are averaged together and treated as one trial for the overall average (bottom row).
*** Schnitzler provides the fluoride dose in terms of mg/kg/day, but does not provide the average weight of the patients. The 27 mg/day figure used here is based on the assumption that the average weight of Schnitzler's patients is 60 kg.

46. "Vertebral fracture rates and peripheral bone density changes were surprising - and demonstrate that NaF administration is capable of increasing vertebral fracture rates and of increasing peripheral (nonspinal) bone loss. Thus our study demonstrates the potential for an anti-osteoporosis agent, under certain circumstances, to worsen a patient's clinical state." Gutteridge DH, et al. (2002). A randomized trial of sodium fluoride (60 mg) +/- estrogen in postmenopausal osteoporotic vertebral fractures: increased vertebral fractures and peripheral bone loss with sodium fluoride; concurrent estrogen prevents peripheral loss, but not vertebral fractures. Osteoporosis International 13:158-70.

47. "We conducted an effectiveness meta-analysis to determine the efficacy of fluoride therapy on bone loss, vertebral and nonvertebral fractures and side effects in postmenopausal women...[A]lthough fluoride has an ability to increase bone mineral density at the lumbar spine, it does not result in a reduction in vertebral fractures. Increasing the dose of fluoride increases the risk of nonvertebral fractures and gastrointestinal side effects without any effect on the vertebral fracture rate." Haguenauer D, et al. (2000). Fluoride for the treatment of postmenopausal osteoporotic fractures: a meta-analysis. Osteoporosis International 11:727-38.

48. "In this investigation, we found that after 5 years of fluoride treatment of osteoporotic patients, iliac crest trabecular bone strength was reduced by

46-56% compared with pretreatment biopsies. Also, 1 year of fluoride administration seemed to reduce bone strength by 17-30%, though this was not a significant finding... [T]he results of this study support the investigations that have found an increased rate of nonvertebral fractures, and a reduction in strength could well be a direct effect of fluoride on trabecular bone." Sogaard CH, et al. (1994). Marked decrease in trabecular bone quality after five years of sodium fluoride therapy—assessed by biomechanical testing of iliac crest bone biopsies in osteoporotic patients. Bone 15: 393-99.

49. "Bone fragility during fluoride therapy for osteoporosis was observed in 24 (37.5%) of 64 patients treated with sodium fluoride, calcium, and vitamin D for 2.5 years who developed episodes of lower-limb pain during treatment. Eighteen (28%) of these patients had clinical and roentgenographic features of 41 stress fractures and 12 new spinal fractures. There were 26 periarticular, six femoral neck, three pubic rami, three tibia and fibula, one greater trochanter, and two subtrochanteric fractures. Vertebral fractures appeared first, then periarticular, then femoral neck, and lastly long-bone shaft fractures. All fractures were spontaneous in onset. The peripheral fracture rate during treatment was three times that in untreated osteoporosis." Schnitzler CM, et al. (1990). Bone fragility of the peripheral skeleton during fluoride therapy for osteoporosis. Clinical Orthopedics (261):268-75.

50. Fluoride treatment was "associated with a significant three-fold increase in the incidence of nonvertebral fractures, both incomplete and complete...This increased rate of fracturing suggests that bone formed during fluoride therapy has increased fragility." Riggs BL, et al. (1990). Effect of Fluoride treatment on the Fracture Rates in Postmenopausal Women with Osteoporosis. New England Journal of Medicine 322:802-809.

51. "Using all 61 fluoride-treated patients, femur fractures/patient were significantly correlated to bone fluoride (p less than 0.05) and to age (p less than 0.05)... These results suggest that fluoride therapy may be implicated in the pathogenesis of hip fractures which may occur in treated patients despite a rapid, marked increase in bone mass." Bayley TA, et al. (1990). Fluoride-induced fractures: relation to osteogenic effect. Journal of Bone and Mineral Research 5(Suppl 1):S217-22.

52. "We report clinical and bone morphometric findings in 18 osteoporotic patients who experienced stress fractures during fluoride therapy... Fluoride appears to be a key factor in the pathogenesis of stress fractures, and may be associated with increased trabecular resorption in some treated patients." Orcel P, et al. (1990). Stress fractures of the lower limbs in osteoporotic patients treated with fluoride. Journal of Bone and Mineral Research 5(Suppl 1): S191-4.

53. "[T]he six hip fractures occurring in patients receiving fluoride during 72.3 patient years of treatment is 10 times higher than would be expected in normal women of the same age. The probability of observing six fractures in 2 years is extremely small (0.0003). In four of the hip fracture cases, the history suggested a spontaneous fracture. These findings suggest that fluoride treatment can increase the risk of hip fracture in osteoporotic women." Hedlund LR, Gallagher JC. (1989). Increased incidence of hip fracture in osteoporotic women treated with sodium fluoride. Journal of Bone and Mineral Research 2:223-5.

54. "Thirteen cases of spontaneous fissure or fracture of the lower limbs observed in 8 patients under treatment with sodium fluoride are reported... Fluor seems to be responsible for the fissures which cannot be avoided by calcium and/or vitamin D intake... When such fissures occur, fluoride therapy must be discontinued and the limb put at rest..." Orcel P, et al. (1987). [Spontaneous fissures and fractures of the legs in patients with osteoporosis treated with sodium fluoride]. Presse Med 16:571-5

55. "How fluoride can produce stress microfractures is unclear. That

they are complications of fluoride therapy is clear, as there were no microfractures in the 101 patients in the calcium-treated group." O'Duffy JD, et al. (1986). Mechanism of acute lower extremity pain syndrome in fluoride-treated osteoporotic patients. American Journal of Medicine 80: 561-566.

56. "[T]he increased number of new crush fractures of the spine during the first year of treatment raise the possibility of fluoride-induced microfractures." Dambacher MA, et al. (1986). Long-term fluoride therapy of postmenopausal osteoporosis. Bone 7: 199-205.

57. "Two patients with moderate renal failure sustained spontaneous bilateral hip fractures during treatment with fluoride, calcium, and vitamin D for osteoporosis....As bilateral femoral neck fractures are very rare these data suggest a causal link between fractures and fluoride in patients with renal failure. Thus fluoride should be given at a lower dosage, if at all, to patients with even mild renal failure." Gerster JC, et al. (1983). Bilateral fractures of femoral neck in patients with moderate renal failure receiving fluoride for spinal osteoporosis. British Medical Journal (Clin Res Ed). 287(6394):723-5.

58. "During treatment bone pain increased and three further vertebral compression fractures occurred." Compston JE, et al. (1980). Osteomalacia developing during treatment of osteoporosis with sodium fluoride and vitamin D. British Medical Journal 281: 910-911.

59. "Fractures and exacerbation of arthrosis were more frequent in the fluoride group...The many fractures in the fluoride group, 14 during treatment and the following month as against 6 among the controls, were surprising. Three or four of the fractures in the fluoride group appeared to be spontaneous hip fractures. In the past fractures have not been regarded as being caused by fluoride but as resulting from prolonged osteoporosis before treatment. We believe that the fluoride treatment here was probably partly responsible for the fractures in our cases." Inkovaara J, et al. (1975). Phophylactic fluoride treatment and aged bones. British Medical Journal 3: 73-74.

XI. NO FEDERAL LAW IS KNOWN TO BE UNFAVORABLE TO HHS, FDA CDER, and EPA ENFORCEMENT ACTION AND OVERSIGHT.

A. Most Western Europe Governments, China, Japan, Most of British Columbia, and Thousands of US Cities have Banned, Prohibited, Stopped, or Never Started Fluoridation, in Striking Contrast, the Percentage of the US Population Drinking Fluoridated Water has Increased to Almost 75%.

B. Although Most European Dental Associations No Longer Recommend Ingesting Fluoride, Most English Speaking Dental Associations Disagree.

C. Although No National Drug Regulatory Agency World-Wide is Known to have Approved Fluoridation, US Public Health Agencies Promote Fluoridation Disregarding the Importance of Drug Regulatory Approval.

1. Artificial fluoridation chemicals are designated as hazardous waste by the Basel Convention, the most comprehensive global environmental agreement on hazardous and other wastes, signed by 170 countries. Annex III Class 6.1 Code H6.1 and Annex I Y32. Japan disposes their fluoride toxic waste in the USA public water systems.

2. Toxic substances in artificial fluoridation products, such as arsenic, lead, beryllium, vanadium, cadmium, mercury, radium, radionuclides are toxic, persistent, bioaccumulative, and anthropogenic. They are listed under the 1989 First Priority Substances lists in Canada and proposed for virtual elimination under the Canadian Environmental Protection Act (CEPA 1999, 2006 update), the 1997 Binational Toxic Strategy and the 1978 Great Lakes Water Quality Agreement.

3. The Australian Therapeutic Goods Act of 1989 is consistent with other governments (US FD&C Act) and scientific definitions of drugs or substances used for therapeutic purposes. The ATG Act defines therapeutic use as, "'therapeutic use' means use in or in connection with: preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons or animals; or influencing, inhibiting or modifying a physiological process in persons or animals."

D. Although No High Quality Studies are Provided to Support the Claim of Either Safety[219] or Efficacy, the American Dental Association (ADA),[220] Centers for Disease Control,[221] and Others Promote the Fluoridated Water Drug Claiming it is Both Safe and Effective.

The most important reason for the FDA CDER no longer to defer drug regulatory oversight of the unapproved fluoridated water drug is the lack of any human randomized controlled trials provided by manufacturers and proponents of fluoridation. Therefore, judgment is based on many lower quality studies, trends, estimates, assumptions, and clinical judgment. The main source of information for proponents of fluoridation is the American Dental Association.[222]

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[219] Appendix 25 Part I Representative Kelly
[220] www.ada.org
[221] www.cdc.gov
[222] Appendix 26 Confounding Factors

XII. PROMOTERS OF FLUORIDATION

No drug is safe for everyone. Fluoride is a protected unapproved drug.

No Government Agency, corporation, or promoters of fluoridation have spoken up in opposition to FDA CDER regulatory oversight other than suggesting fluoridation would not be approved. To be opposed would indicate they might not have "proof" of safety or efficacy. Proponents have not suggested FDA CDER action should be prevented, they suggest action is not needed. However, compliance with Congress and science is needed for the safety of the public.

The CDC/ADA suggest fluoride is "necessary in preventing tooth decay," ignoring the many countries and communities without fluoridation having reduced dental decay rates to similar levels as those with fluoridation.

"ADA Statement
Since 1950, the ADA has unreservedly endorsed the fluoridation of community water supplies as safe, effective, and necessary in preventing tooth decay.

" CDC Statement
CDC has recognized the fluoridation of drinking water to prevent dental decay as one of 10 great public health achievements of the 20th century. Over the past 60 years, optimal fluoridation of community drinking water has been a major factor for the decline in rates of tooth decay.

"Fluoridation is safe. More than 60 years of research and experience have shown that fluoridation at optimal levels does not harm people or the environment. Leading scientists and health professionals, numerous professional organizations, and governments around the world support community water fluoridation.

"Fluoridation is cost-effective. The average cost for a community to fluoridate its water is estimated to range from approximately $0.62 a year per person in large communities to approximately $3.90 a year per person in small communities (2004 dollars). Over a lifetime this is typically less than the cost of one dental filling to repair one decayed tooth. Remember, when it comes to the costs of treating dental disease, everyone pays. Not just those who need treatment, but all of us—through higher health insurance premiums and higher taxes. For most cities, every $1 invested in community water fluoridation saves $38 in dental treatment costs. Through fluoridation, communities can improve the oral health of their residents and save money for all of us.

"The key points to remember about water fluoridation are these:

- Fluoridation is safe.
- Fluoridation of community water supplies benefits everyone.

- Fluoridation is cost-effective because it saves money on dental treatment needs. [223]

The CDC claims fluoridation is safe and *"while it is not CDC's responsibility to determine what levels of fluoride in water are safe, our understanding about the safety of fluoridation is guided by federal regulations, comprehensive reviews conducted by expert panels, and individual studies."*[224] However, the EPA federal regulations used are the wrong regulations and expert panels and individual studies are cherry picked for desired conclusions. Bias at the CDC and EPA is blinding.

A huge red flag and sirens of warning should go off when "absolute" claims of safety for everyone, sperm, egg, fetus, infants, the disabled, and all subpopulations and all animals are made for any substance especially a substance defined as poison by Federal and state laws and unapproved by the FDA CDER. Claims of "prevention" are fraudulent. Absolute statements of safety and prevention are quackery.

The ethics of human subject research without consent on about 200 million people in the USA is one of public health's darkest hours. HHS/CDC should be applauded for opening discussion and once again reviewing laws and science.

How could so many scientists and studies be wrong?

Although most developed countries do not fluoridate public water or their scientists recommend fluoride supplements, hundreds of scientists and scientific studies suggest fluoridation is both safe and effective. However, most scientists asked if they have personally read the research will back off and admit they rely on others to look at the research. Some clinicians (as this author used to) will adamantly claim they see the benefit of fluoridation in their practice. Again, on careful questioning, most will admit they do not correct for known and unknown confounding factors such as socioeconomics, delay in tooth eruption, diet, genetics, or the huge unknown confounding factor which has reduced dental decay by half even before fluoridation was started. Most dentists and their associations admit they do not diagnose medical safety, brain damage, thyroid damage, and other adverse medical risks because those are outside the practice of dentistry. And attempting to determine the contributing effect of chronic toxicant exposure on a person's pathology or death is highly complex and usually speculative.

A good study does not make broad claims such as "fluoridation is safe and effective." With millions of variables for most health theories, the variables need to be limited to one or two and many studies should find a null effect. However, a null effect does not mean the entire theory is wrong anymore than a statistically significant conclusion for a variable means that the conclusion is safe and effective.

For example, the fluoride osteosarcoma connection at first glance is not easy. Numerous studies find no relationship between fluoride exposure and cancer. However, studies looking closer at subpopulations and with better controls, are troubling,

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[223] http://www.cdc.gov/fluoridation/pdf/natures_way.pdf
[224] http://www.cdc.gov/fluoridation/safety.htm

increasing, and do not support safety. Did the cohort actually get fluoridated water to their house when they were growing up? Research indicates about 10% thought they were getting fluoridated water, but when the researcher actually went to the water district and looked up the specific address and dates, the house was not getting fluoridated water on those dates. Did the subject drink the water or bottled water and what was the fluoride content of the bottled water? Did the subject drink soda pop with filtered water or fluoridated water and how much fluoride was filtered out? Did the subject actually consume fluoride supplements or were they prescribed, purchased, used a few times, mostly forgotten, or swallow more toothpaste or had supplements at school? Did the residence not have fluoridated water and the school have fluoridated water? Did the subject's diet have a high fluoride intake from tea, mechanically deboned meat, grapes or pesticides high in fluoride? What was the fluoride content of air? Did the subject ingest more or less lead or other synergistic toxins? Even the list of major and minor confounding factors is unknown.

Because there are many confounding factors, good researchers are moving towards evaluating fluoride exposure based on serum, tooth, urine, tissue fluoride concentrations rather than estimating the impact of fluoride based on the historic and crude guessing of exposure.

Even if the effectiveness of the public health intervention can be measured in the public at large, and fluoridation's benefit is not demonstrated in the public at large, public health agencies should be extremely hesitant to require everyone with the use of state police powers, to be forced against their free will to be experimented on. Such experimentation is against state, national and international laws and codes of ethical research conduct. Until the drug is approved by the FDA CDER, fluoridation should be considered an experiment and crime against humanity.

The explosion of readily available scientific articles, research and information has contributed to revolutions world wide. When people get access to information they demand change, but the change is proceeded by a strong and sometimes violent anger at government agencies and corporations for alleged crimes. Public Health Agencies in their attempt to "do good" and corporations eager to please share holders have been slow to critically measure the harm, or side effects, their "good" is doing. The thought process, policies and rules of public health and government agencies do not promote critical individual thinking, "loose cannons." Few step out of the mold, turn around, and critically review their organization and themselves. Our best drug regulatory agency, the FDA CDER, is known to have made serious regulatory mistakes, even when looking back on the best evidence available at the time. If the FDA CDER has not and would not approve the fluoridated water drug, then the CDC/EPA standards, rules, procedures and policies for fluoridation approval are flawed and not protective.

Even though courts generally give governments a free hand, the HHS/CDC/EPA and all Federal and state health agencies are not exempt from laws even though enforcement is deferred.

If the ingestion of fluoride is effective in reducing dental caries, provide freedom of choice and promote fluoride supplements. Well, fluoride supplements are not FDA CDER approved. Perhaps public health agencies could promote swallowing fluoride toothpaste, except the FDA CDER warns not to swallow fluoride toothpaste.

XIII. ECONOMIC IMPACT[225] OF DAMAGE FROM LACK OF FDA CDER REGULATORY OVERSIGHT OF THE FLUORIDATED WATER DRUG.

NOTE: This economic impact statement has been done to underscore the emergency nature of HHS, EPA, FDA CDER, and CDC action. The amounts shown are conservative estimates and are provided with a justification of how they were derived. The key point is that the overall cost of harm from fluorides significantly outweighs the alleged economic and health benefit.

The half life of fluoride in the body is 20 years. A cessation of fluoridation will take 20 years to significantly reduce the economic impact.

The NTEU testified to the US Senate Committee, 2000, "Fluoride Exposures Are Excessive and Un-controlled."[226] See also Appendixes FF, S, GG and EE.

Pizzo in 2007 confirmed Colquhoun's work, *"In most European countries, where community water fluoridation has never been adopted, a substantial decline in caries prevalence has been reported in the last decades, with reductions in lifetime caries experience exceeding 75%."*[227]

While some at the CDC suggest fluoridation is one of the top ten public health achievements of the 20th Century, other scientists at the CDC suggest, ingestion of fluoride is not likely to reduce tooth decay.[228]

A. Economic Impact from Benefit to Teeth (Appendix 56)

Efficacy of Fluoridation. See www.ada.org and www.cdc.org

1. On one side of the controversy, some Public Health Dentists promoting fluoridation are adamant that fluoridation is safe,[229] causing only some cosmetic effects to teeth. For each of the diseases and risks below, proponents repeat the same statement that fluoridation is safe and discount evidence of risks as not of concern. For brevity, that statement will not be repeated for each disease.

2. Based on estimates of assumptions, proponents claim an economic benefit of from $16 to $38 for every dollar spent on fluoridation.[230] Assuming fluoridation costs average $1.00 per person per year[231] for the 225 million fluoridated, the costs would be $225 million and the savings would be 225 million people X $16 or $38 = $3.6 to $8.4 billion/year), representing a 4% to 9% reduction in the $95 billion

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[225] See also Appendix 27 Fluoridation Costs Clinch
[226] Appendix 14 NTEU 629 Final
[227] Pizzo G, et al. (2007). Community water fluoridation and caries prevention: a critical review. *Clinical Oral Investigations* 11(3):189-93.
[228] CDC (1999). Achievements in Public Health, 1900-1999: Fluoridation of Drinking Water to Prevent Dental Caries. MMWR, 48(41); 933-940, October 22

[229] http://www.ada.org/4378.aspx Accessed 11/19/10
[230] www.cdc.gov/fluoridation/fact_sheets/cost.htm accessed 11/17/10
[231] www.health.state.ny.us/prevention/dental/fluoridation/cost.htm accessed 11/17/10. Costs ranged from $0.06/person in Denver to $2.70/person in communities under 5,000. 35 systems serving more than 20,000 people averaged $0.40/person. However, these costs are usually limited to chemical costs. SEE ALSO APPENDIX KK and CDC at http://www.cdc.gov/fluoridation/pdf/natures_way.pdf which suggests 0.62 to $3.90/person/year with 2004 dollars.

annual cost of dentistry.[232] Proponents generally do not include equipment installation in their calculation of costs, which run from $5 to $20/person.[233]

A possible mitigation of about 4 to 9%[234] of dental costs is based on estimates and assumptions. Perhaps 80% of dentistry is for the treatment of cavities, retreatment of those cavities with more fillings, retreatment of those cavities with crowns, root canals, extractions, bridges, implants, and dentures. In fact, the main components of dentistry mostly unrelated to cavities are orthodontics, cosmetics, some oral surgery, and periodontal treatment (cleaning). After 60 years of fluoridation, preventing 4-9% of dental costs should be easily and repeatedly measured in the community at large and not require estimates based on assumptions.

3. Claims that fluoride actually "prevents" rather than "mitigates" caries is certainly propaganda or fraud, and not honest reality. If fluoridation actually "prevented" dental caries which generates the majority of revenue in a dental practice, many dentists in fluoridated communities would be out of business, move, or not go to fluoridated communities in the first place.

4. Dentists generally have refused to acknowledge any medical risks, claiming there is no absolute proof of harm, despite the fact that there are no randomized controlled trials regarding harm. Further, dentists correctly avoid the issue by claiming dentists do not diagnose medical risks. However, evaluating medical side effects from dental treatments should be part of dental jurisdiction.

5. Proponents of fluoridation generally have a double standard for scientific evidence, accepting low quality studies on efficacy as positive evidence of "proof," yet demanding the highest quality of proof of harm from those harmed.

6. The FFDCA does not require victims to prove harm. The FDA CDER is to regulate those marketing and manufacturing drugs and require manufacturers to provide proof of efficacy and safety, not the consumer, customer or patient.

7. When ranking the 50 states in order of the percent of the whole population fluoridated and comparing the reported very good to excellent teeth (Graph C) little if any benefit from fluoridation is found. Perhaps a 1%-4% for children; however, this slight improvement, if any, could be accounted for with a better population to dentist ratio and does not take into consideration delay in eruption or fractured teeth. Milking a couple of percentage points out of this type of ecological evidence is unwise.

8. The best study on economic impact of measured costs was by Maupome[235] comparing HMO fluoridated and non-fluoridated clinics and reported savings of about half a percent. Applied to the community at large, a half a percent savings was estimated to pay for repairs of the fluoridation equipment but not for the chemicals or installation of the equipment. Children in the two largest communities

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[232] www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=3383
[233] www.cdc.gov/fluoridation/engineering/faqs.htm and Appendix 28
[234] trued for 75% of the population on fluoridated water, estimating costs of $71 billion.
[235] Maupome G, et al, A comparison of dental treatment utilization and costs by HMO members living in fluoridated and nonfluoridated areas. J Public Health Dent. 2007 Fall;67(4):224-33.

showed an opposite effect with a small increase in dental expenses with fluoridation. Based on Maupome's work, an economic impact of half a percent of dental expenses averaging $316/person/year ($1.58 savings per person per year savings) for 225 million on fluoridated water would be about $355,500,000 ($356 Million) dental expense savings. (225 million people X $1.58 savings = $355,500,000)

9. A second study by Kumar[236] of Medicaid claims evaluated a subpopulation, comparing the mean number of restorative, endodontic and extraction procedures per recipient, (procedures related to cavities) and found claims for these procedures to be 33.4% higher in the least fluoridated counties. The author has so far refused to release the data underlying this study for confirmation and evaluation of confounding factors such as socioeconomics, completion of dental treatment, diet habits, brushing, flossing, and average length of time on Medicaid support. A known significant confounding factor of socioeconomics (Medicaid) is not representative of the public at large. Limiting dental expenses to a few procedures does not reflect confounding factors for fractured teeth. Neither the Maupome nor Kumar studies included costs for cosmetic dentistry to correct dental fluorosis damage. Neither study was representative of the general population, although Maupome came closer and cohorts were more representative of the population at large included more procedures. If subgroups of the population do have reduced dental expenses, further study would help define those subgroups and confounding factors.

10. We do not use the Kumar study of Medicaid claims because those cannot be as appropriately related to the nation as a whole.

If fluoridation were effective in reducing dental expenses, economic impact as measured in the community at large should be common and repeatable. If fluoridation were effective in preventing dental decay, communities fluoridated for more than 50 years would not have a crisis of cavities. For example, the American Dental Association awarded Kentucky with an award for virtually 100% fluoridation for 50 years. At the same time, Kentucky held the dubious prize of having the highest percentage of edentulous persons.[237] The loss of teeth is evidence fluoridation is not preventing dental cavities. Boston, Detroit and Connecticut (with 87.5% of the population drinking fluoridated water) report serious problems with cavities even after decades of fluoridation.[238]

The Kumar study underscores the possibility that the ingestion of fluoride may reduce cavities in a subpopulation of the community. However, medicating everyone in an attempt to target only one to eight year olds[239] in poverty (less than 1% of the population) for a noncontageous disease generally considered to be due to bad habits

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[236] Kumar J et al, Geographic Variation in Medicaid Claims for Dental Procedures in New York State: Role of Fluoridation Under Contemporary Conditions, Assocations of Schools of Public Health, 2010 Sep-Oct;125(5)647-654.
[237] 2002 Mortality Weekly Report
[238] http://www.fortwayne.com/mld/newssentinel/7521679.htm?template=contentModules/printstory.jsp
http://www.enquirer.com/editions/2002/10/06/loc_special_report.html
http://www.fluoridealert.org/f-boston.htm
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=13678102&query_hl=1
http://www.nhregister.com/site/news.cfm?newsid=14472801&BRD=1281&PAG=461&dept_id=517515&rfi=8&xb=kasan
[239] Most agree infants should not have fluoridated water and the NRC 2006 report confirmed possible benefit from fluoride would be while the tooth is developing, until age 8.

must be reconsidered. It would be cheaper and provide more freedom to tell people to swallow a pea size of their fluoridated toothpaste. . . except for the fact that the FDA correctly warns those who use fluoridated toothpaste not to swallow it.

11. Fluoridation chemical costs/person average about $1.00/person/year and 225 million fluoridated would have chemical costs of about $225 million.[240] Equipment purchase, plumbing equipment and infrastructure repairs from the strong acid injected into the systems should more than double the $225 million or much more.[241] A conservative estimate of $450 million for chemicals, plumbing, installation, operations and infrastructure repairs is used.

The possibility of limited or lack of economic benefit based on measured evidence becomes readily apparent. A cost benefit based on efficacy may simply be a wash or a loss unless estimates of assumptions are used, only subpopulations considered and damage to the teeth not included.

EPA scientists eloquently summarize concerns and scientific evidence of efficacy (See Appendix II): ". . . the purported benefits associated with it are so small - if there are any at all . . . . ."[242] Appendix II is essential for review. In many studies, fluoridation does not provide benefit.

Several studies find fluoridation cessation does not appear to increase dental decay and that fluoridation is unnecessary.[243]

B. Economic Impact from Damage to Teeth: (Apx. 27, 20, 71, 72)[244]

The FDA CDER professionals have probably experience the tension and consequences of evaluating and then rejecting a NDA and probably even more tension when removing a well accepted drug from the market because of new research. Pressure from industry, politicians and the public to "go along" with incomplete evidence can be significant. The same problem happens with any entrenched scientific theory, such as fluoridation. There is little incentive for a researcher to publish an article which appears to refute the benefits of fluoridation.

1. Repair of cosmetic damage is not usually covered by insurance, offered by HMOs or Medicaid, and therefore cosmetic damage is not fully included in those studies. Cosmetic damage is usually treated only by those who can afford treatment outside of those systems. Should the economic impact include the cost of treating increasing dental fluorosis, now affecting over 40%[245] of 12-15 year olds and increasing at about 1% a year, even though those afflicted with fluorosis cannot afford the treatment? Certainly if someone scratched a car and caused cosmetic damage, that person would be liable. Life-time cosmetic treatment for dental fluorosis can be as high

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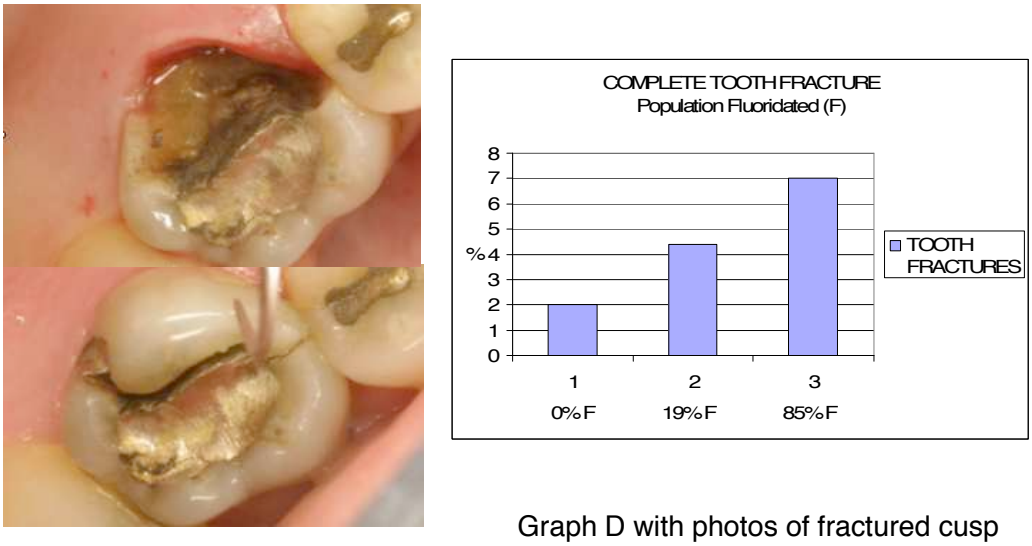
[240] http://www.cdc.gov/fluoridation/fact_sheets/cost.htm
[241] Chemical companies charge public water systems about $1,500/ton but would pay about $7,000/ton to dispose as hazardous waste. Bill Hirzy, Sr. EPA Chemist. Hamilton BOH Report, July 2008.
[242] Dr. J. William Hirzy, Senior Vice-President, Headquarters Union, US Environmental Protection Agency, March 26, 2001. This letter describes some of the harms of water fluoridation as seen by water fluoridation opponents.
[243] Appendix 29 Fluoridation Cessation and Appendix 27 costs.
[244] See additional evidence in Appendix KK Economic Harm and LL Case reports
[245] NCHS DATA Brief No. 53, November 2010, Prevalence and Severity of Dental Fluorosis in the United States, 1999-2004.

as $100,000 per person. An estimate is made here that is based on the following conservative assumptions: An average of only 4 teeth per person will be treated. Assuming a cost of $1,000 per tooth to repair the cosmetic damage (cost range from $100 to $2,000 per tooth). The repair will have to be redone four times over the course of each person's life. The life time cost per person would be $16,000. If each year, 40% of the 4.3 million 15 year olds impacted by mild fluorosis were compensated for damage at $16,000 each, the economic impact would be $27.5 Billion/year, far exceeding any estimate of benefit even the highest $8.4 Billion assumption of benefit from fluoridation.

Proponents of fluoridation claim the cosmetic damage is not really "damage" because it is only "cosmetic" and therefore no compensation is warranted. Currently, those considering their cosmetic effects severe enough to get treatment, would not generally receive cosmetic treatment at medicare/Medicaid or HMO clinics. A conservative estimate of 1% of actual damaged seeking treatment is $275 million/year due to lack of FDA CDER drug regulatory oversight. (See Appendix K).

2. Additional economic damage should be considered for a probable increase in tooth fractures in fluoridated communities. With harder teeth, more fractures are expected. (Graph D)[246]



Graph D with photos of fractured cusp

If three times as many office visits are happening because of fractured teeth in fluoridated communities, one of the more costly dental pathologies, the cost for crowns, root canals, extractions, bridges and/or implants would have a significant impact. A $2,000 crown, root canal, buildup or post visit is 20 times the cost of a $100 cleaning or filling. If triple the number of visits produce 20 times the cost, the difference could be significant. Perhaps an increase in fractured teeth pathology to 10% of the $71 billion dental costs for a negative impact of $7 Billion is our conservative estimate for increased cusp fracture, treatment, retreatment, resulting root canals, extractions, bridges, and implants. More dentists would be needed and could be supported with higher costs from fewer patients with more fractured teeth.

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[246] Appendix 30: Osmunson B , "Water Fluoridation Intervention: Dentistry's Crown Jewel or Dark Hour ... 2 (1998): 103–18, http://www.fluoride-journal.com/98-31-2/312103.htm

SUMMARY OF THE EFFECT OF FLUORIDATION ON TEETH. Precise numbers are lacking. A reduction of caries from fluoridation has been measured at about $0.3 billion and estimated as high as $8 billion. Damage and costs of fluoridation are measured from $0.3 billion and estimated more than $7 billion. Low estimates are a wash and high estimates are close to a wash. Perhaps the reason for lack of measured evidence for benefit.

Fluoridation promoters agree that dental fluorosis "is caused when higher than optimal amounts of fluoride are ingested in early childhood while tooth enamel is forming." The increase of about 1% of children each year with dental fluorosis to currently over 40% does not seem to deter promoters of fluoridation or even give them pause to consider lowering the concentration of fluoride in water. Promoters hang on to 1 ppm as the "holy grail." They agree dental fluorosis is a disruption in enamel formation, although they do not use the term enamel necrosis and consider fluorosis only a cosmetic problem.[247] "

Historically, promoters of fluoridation claimed 1 ppm in water would not cause dental fluorosis. In 2006 Hong reported:

> *"Cumulatively from birth to 36 months, average daily intake of 0.04 mg F/kg BW or less carried relatively low risk for fluorosis (12.9% for maxillary central incisors, 6.8% for first molars)."*[248]

12.9% showing a biomarker of excess fluoride ingestion intake is not a "low" risk.

In other words, in order to only have a 12.9% risk of showing dental signs of excess fluoride ingestion, a 4 kg infant should not ingest more than 0.16 mg of fluoride, 160 ml (5.3 oz) of formula/fluoridated water mix, about half a glass. Infants, however, need about 2-4 oz milk or formula every 1.5 to 3 hours.

C. Economic Impact from Damage to the Thyroid Gland (App. 73)

After review of Appendix L, consider the following:

Those opposed to fluoridation find that compelling evidence of adverse economic impact is serious and grounds for emergency action by the FDA CDER. It is the FDA CDER who has the competent scientists to evaluate the scientific evidence and should no longer delay enforcement action. Governments, without a person's consent, are causing economic damage. The war on illegal drugs does not exempt governments even when governments are the illegal drug pushers.

Determining the degree to which the prevalence of a medical disease is directly related or contributed to by a toxicant is difficult. When two or more toxicants are involved this is even more difficult, and in the case of fluoride it is seldom studied. The synergistic effect of an aggregate toxic burden on a population is without measured data. Therefore, any estimate of economic harm is a best opinion and not a measurement of

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[247] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf

[248] Hong L, et al Fluoride intake levels in relation to fluorosis development in permanent maxillary central incisors and first molars. Caries Res. 2006;40(6):494-500.

fact. These numbers should be disputed both up and down. Several potential adverse effects are hard to quantify in dollars, not because there is no harm but because the percentage of harm associated with fluoride is unclear. The economic harm estimates here are a loud wake up call, a major red flag for emergency action by the FDA CDER. The government agency most competent to make a risk/benefit assessment of drugs such as the fluoride water drug is the FDA CDER.

1. The Fluoride Thyroid Connection.

The economic impact of damage to the thyroid gland from fluoride is far more complex than dental damage. The prevalence of hypothyroidism in the elderly is reported at 5-20% of women and 3-8% of men,[249] and 8-28% overall. Synthroid is reported to be the third most commonly prescribed drug, at 66 million prescriptions per year.[250] A decrease in thyroid activity is causally connected to obesity and diabetes, both of which are easy to measure in the public at large and have plenty of confounding factors. Fluoridated populations appear to have increased obesity and diabetes.

The NRC 2006 report on fluoridation found fluoride to be connected with the following Endocrine Effects:

> "Endocrine Effects: The chief endocrine effects of fluoride exposures in experimental animals and humans include decreased thyroid function, (synthyroid is a very common Rx; low BMR, obesity, skin disorders)
>
> increased calcitonin activity, (opposite parathyroid, reduces Calcium in blood, enhances Ca excretion)
>
> increased parathyroid hormone activity, (increases blood Ca level, from bone & kidney)
>
> secondary hyperparathyroidism, (When Ca blood level too low due to low Vit D or low Ca absorption
>
> impaired glucose tolerance, and (Diabetes, 7% of population, sixth leading killer, six to seven fold increase since 1958 and growing. $217 Billion annual treatment cost) possible effects on timing of sexual maturity." NRC 2006 p.26
> (Our comments in bold)

We are unable to locate demographics directly relating to thyroid function and fluoride intake. Those should be provided by the fluoride water manufacturer. However, we can conservatively assume that obesity and diabetes are in part related to thyroid dysfunction. Certainly thyroid damage causes much more harm than obesity and diabetes, but state reported prevalence of the other diseases has not been found yet. Therefore, obesity and diabetes are the only two diseases we are including in this economic impact, at this time.

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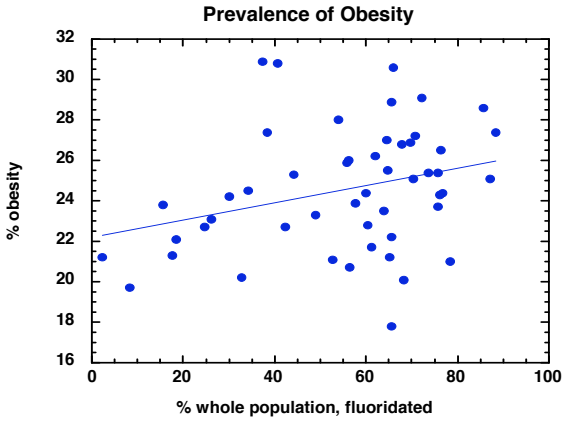
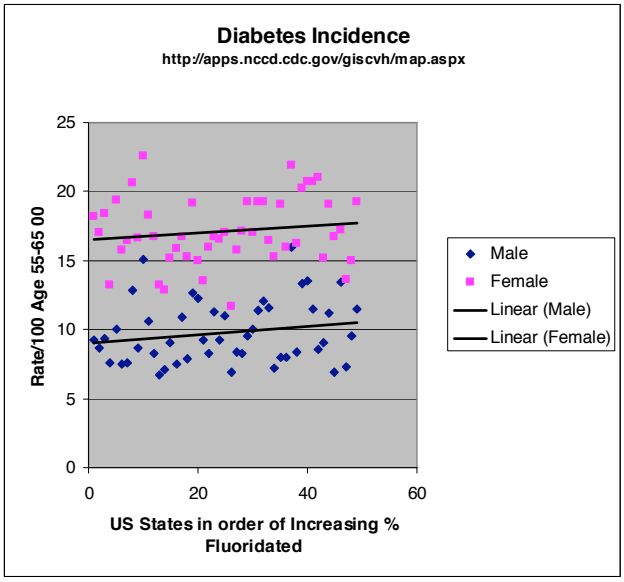
[249] Laurberg P et , Hypthroidism in the elderly: pathophysiology, diagnosis and treatment. Drugs Aging. 2005;22(1):23-38.
[250] http://www.nurse.com/drughandbook/top200.html,

2. Ranking the percentage of the whole population of each state drinking fluoridated water and plotting their percentage of obesity, suggests a 4% increase in obesity with fluoridation[251] (Graph H).



Graph H by Thiessen, K



Graph I, Osmunson B

And 2% increases in diabetes for women (pink) and men (blue) (Graph I).

3. Economic Impact of Fluoride on Thyroid as Measured with Diabetes.

Certainly other factors have contributed to a six fold (600%) increase in diabetes since fluoridation began and too many confounding factors exist for us to suggest, at this time, higher rates of thyroid damage from fluoridation. Even a conservative one percent

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[251] Kathleen M. Thiessen, Ph.D. SENES Oak Ridge, Inc., Center for Risk Analysis 102 Donner Drive, Oak Ridge, TN 37830 E-mail: kmt@senes.com unpublished.

of the population would represent about 3,000,000 additional people with thyroid and endocrine damage from fluoridation. The problem of diabetes is growing.

The cost of reported diabetes is reported at $174.4 billion and the cost of undiagnosed at $218 billion. This represents one in every ten heath care dollars.[252] The contribution of lack of FDA CDER action to the diabetic problem is reasonably estimated at 2% or $8 billion.

Hammond[253] reported 2/3 of USA population over weight and 1/3 obese, as much as 100% higher than healthy adults, and total annual economic impact of $215 billion. If fluoridation increases obesity by 4%, fluoridation's contribution would be about another $8 billion.

Hypothyrodisim, most commonly diagnosed in women over 40, is a serious condition with a diverse range of symptoms including: fatigue, depression, weight gain, hair loss, muscle pains, increased levels of "bad" cholesterol (LDL), and heart disease. The economic impact fluoridation can have in increasing these maladies should also be considered, although no dollar cost is assigned at this time.

Costs for increased calcitonin activity, increased parathyroid hormone activity, and secondary hyperparathyroidism would increase not only health care costs but would also reduce productivity.

Supporters of fluoridation claim, "There is no scientific basis that shows fluoridated water has an adverse effect on the thyroid gland or its function."[254] Supporters of fluoridation provide a study which has the same methodological methods as the studies showing harm that they reject on methodological reasons. When conclusions support their position, ecological studies are just fine. When ecological studies do not support their position they reject the study on methodological flaws.

Supporters of fluoridation continue, "In an effort to link fluoride and decreased thyroid function, those opposed to fluoridation cite one small study from the 1950's. . . "[255] Supporters of fluoridation have negligently failed to do their home work and consider more than 150 studies finding adverse effects of fluoride on the thyroid gland. When victims provide an abundance of evidence of harm, public health promoters of fluoridation refuse to even acknowledge the evidence exists.

D. Economic Impact from Damage to the Mentally Retarded (App 32-55)

1. Some of the Fluoride Brain Connection.

a. Mullenix (1994) reported: "Fluoride exposures caused sex- and dose-specific behavioral deficits with a common pattern. . . One concern that has not been fully investigated is the link between fluoride and effects on the central nervous system (CNS).... Many years of ubiquitous fluoride exposure have not resulted in obvious CNS problems such as seizures, lethargy, salivation, tremors, paralysis, or

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[252] http://www.diabetesarchive.net/advocacy-and-legalresources/cost-of-diabetes.jsp
[253] Open Access full Text Article at brookings.edu. The economic impact of obesity in the United States, 17 August 2010.
[254] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf Question 30
[255] ibid

sensory deficits. Still unexplored, however, is the possibility that fluoride exposure is linked with subtle brain dysfunction."[256]

b. The latest report from the American Dental Association (ADA) finds, "There is no generally accepted scientific evidence establishing a causal relationship between consumption of optimally fluoridated water and central nervous system disorders, attention deficit disorders, or effects on intelligence." The ADA dismisses the Mullenix peer reviewed study based on a letter to the editor "that the observations made can be readily explained by mechanisms that do not involve neurotoxicity . . . inadequate experimental design. . . were the result of analytical error."[257] However, the ADA does not provide details. The ADA reported one 1986 study finding no effect[258] and concludes, "The research conducted by Mullenix et al. . . has not been replicated by other researchers."[259]

c.. He reported a study of 16 artificially aborted fetuses, 10 controls: "The results show that fluorine levels in tissues are obviously high, especially brain, calvarium, and femur."[260] (See also Li at Appendix 39)

d. Du reported a study of 15 artificially aborted fetuses, 16 controls: "Stereological study of the brains showed. . . .The numerical density of volume, the volume density, and the surface density of the mitochondria were significantly reduced. The results showed that chronic fluorosis in the course of intrauterine fetal life may produce certain harmful effects on the developing brain of the fetus. . . . Purkinje cells of fetuses from the endemic fluorosis area were abnormally disorganized and had a thicker granulated layer in the cerebellum. Other dysmorphology, including higher nucleus-cytoplasm ratio of brain cones, hippocampus cones, and Purkinje cone cells, supports the theory that fluoride has an adverse effect on brain development."[261]

e. Ren reported lower IQ,[262] Wang G reported lower IQ,[263] Wang S reported lower IQ,[264] Li reported a possible mechanism for reduced mental capacity due to a decrease of 5-hydroxyindoleacetic acid and the increase of norepinephrine and "the mental work capacity of the two groups of children with grade 3 dental fluorosis was lower than the two groups with no dental fluorosis. . . This indicates that early, long-term exposure to excess fluoride causes deficits in memory, attention, and reaction time, but 12-13 year-old children with only recent exposure show no major effects. Studies (on human fetuses) have already shown that the developing brain is one of the ripest targets for disruption by fluoride poisoning. Given that before six years of age the human brain is in its fastest stage of development, and that around seven and eight basic structural development is completed, therefore the brain is most vulnerable to damage from excess fluoride intake before this age.[265]

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[256] Appendix 31 Mullenix Rats
[257] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf
[258] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf Shannon FT et al, Exposure to fluoridated public water supplies and child health and behavior. N Z Med. J 1986;99(803):4 16-8.
[259] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf
[260] Appendix 32 He Human Fetus, Complete Study Provided. Permission at Appendix 24
[261] Appendix 33 Du Human Fetus, Complete Study Provided. Permission at Appendix 24
[262] Appendix 34 Ren 8-14 year olds, Complete Study Provided. Permission at Appendix 24
[263] Appendix 35 Wang 4-7 year old lower IQ, Complete Study Provided. Permission at Appendix 24
[264] Appendix 36 Wang S lower physical development and IQ, Complete Study Provided. Permission at Appendix 24
[265] Appendix 37 12-13 year olds and animals, Complete Study Provided. Permission at Appendix 24

f. Li discusses long-term intake of fluoride reducing the body levels of zinc, "likely a case of absorption antagonism between the two trace elements. . . . On the whole, this suggests that interference with zinc metabolism caused by prolonged intake of excess fluoride leading to lowered levels of zinc in the body is perhaps one of the mechanisms by which fluoride affects mental work capacity.[266]"

g. Yang reported, "high levels of fluoride and iodine have a serious damaging effect on the body"[267](5 point lower IQ.) As does a high fluoride and lack of iodine reported by Dahi. The level of iodine intake appears to become more specific with a high level of fluoride intake.

h. Burgstahler, Neurath provided a summary[268] of 12 articles originally published in Chinese research journals. The fact that so many articles over 20 years have been published by public health Professionals in China brings out surprise and admiration. We are a global community and can be grateful for scientists in other cultures and languages who ask questions we have failed to ask. Meanwhile, America buys China's toxic fluoride waste and drinks it.

i. 1990 Qin[269] reported lower IQ comparing children on 0.1-0.2 ppm, 0.5-1.0 ppm, and 2.1-4.0 ppm natural fluoride water and found a "non-monotonic pattern."

j. 1991 Chen[270] compared children's IQ raised with 4.55 ppm and 0.89 ppm fluoride and reported almost 4 IQ points higher with 0.89 ppm water.

k. 1991 Guo[271] reported lower IQs of 7-13 year olds with dental fluorosis. Subject community had 60% of adults and 86% of children with dental fluorosis, from coal burning, water was tested at 0.5 ppm. Fluorosis about double the rate of USA average. Compared to controls, 7-9 yr/olds had 6 IQ loss, 10-11 yr/olds 5 IQ loss, 12-13 yr/olds 2.5 IQ loss.

l. 1995 Wu[272] tested rats with higher dosages of fluoride and found no physical abnormalities, four dams failed to produce enough milk and pups starved, also differences with motor coordination, auditory reaction, pain sensitivity, and other cognitive responses.

m. 1996 Yu[273] tested brain tissue of aborted fetuses and reported levels of norepinephrine, 5-hydroxytryptamine, and α1-receptor were lower, and the level of epinephrine was higher.

n. 1999 Zhang[274] decreased learning-memory ability of mice.

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[266] Appendix 38 and 39 Li
[267] Appendix 40 Yang F & I, Complete Study Provided. Permission at Appendix 24
[268] Appendix 41 Editor Complete Article Provided. Permission at Appendix 24
[269] Appendix 44 Qin Complete Article Provided. Permission at Appendix 24
[270] Appendix 45 Chen Complete Article Provided. Permission at Appendix 24
[271] Appendix 46 Guo Complete Article Provided. Permission at Appendix 24
[272] Appendix 47 Wu Complete Article Provided. Permission at Appendix 24
[273] Appendix 48 Yu Complete Article Provided. Permission at Appendix 24
[274] Appendix 49 Zhang Complete Article Provided. Permission at Appendix 24

o. 2000 Liu[275] comparing children in 3.15 ppm and 0.37 ppm communities found an 11 IQ drop in the higher fluoride area.

2000 Sun[276] reported a cerebral function decrease in mice with increased fluoride ingestion.

p. 2001 Guo[277] reported various effects of occupational fluoride exposure on the central nervous system.

q. 2001 Hong[278] compared fluoride and iodine intake on the IQ of children 8-14 years of age. Control ingested 0.75 ppm fluoride and high fluoride was considered 2.85 ppm fluoride in water. About a 2 point IQ drop for the higher fluoride area, 3 point IQ drop for high fluoride high iodine area, 14.4 IQ drop for high fluoride low iodine area, and a 7 IQ drop for low fluoride low iodine area.

r. 2003 Li Y.[279] reported an average 8.12 IQ point lower in the area with dental fluorosis.

s. 2004 Li J.[280] comparing mothers on well water ranging between 1.7 and 6.0 ppm with mothers with well water of 0.5-1.0 ppm, reported their babies had significant reduction in directional reaction to vision and audition, weight, length, passive, passive muscle tension, primary and general reactions were similar.

t. A search of Pub Med was done, 12/3/10, no research was found resulting in a null effect or lowest ingestion level where fluoride did not contribute to brain disorders.

u. EPA Professionals testified to the Senate in 2000:

"Brain Effects Research Since 1994 there have been six publications that link fluoride exposure to direct adverse effects on the brain. Two epidemiology studies from China indicate depression of I.Q. in children (11,12). Another paper (3) shows a link between prenatal exposure of animals to fluoride and subsequent birth of off-spring which are hyperactive throughout life. A 1998 paper shows brain and kidney damage in animals given the "optimal" dosage of fluoride, viz. one part per million (13). And another (14) shows decreased levels of a key substance in the brain that may explain the results in the other paper from that journal. Another publication (5) links fluoride dosing to adverse effects on the brain's pineal gland and pre-mature onset of sexual maturity in animals. Earlier onset of menstruation of girls in fluoridated Newburg, New York has also been reported (6)[281].

v. Kanneex reported the relationship of fluoride and aluminum in the early onset of forgetfulness (dementia). "The presence of fluoride enhanced the bio-availability of aluminum (Al) causing more aluminum to cross the

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[275] Appendix 50 Liu Complete Article Provided. Permission at Appendix 24
[276] Appendix 51 Sun Complete Article Provided. Permission at Appendix 24
[277] Appendix 52 Guo Complete Article Provided. Permission at Appendix 24
[278] Appendix 43 Hong Complete Article Provided. Permission at Appendix 24
[279] Appendix 38 Li Complete Article Provided. Permission at Appendix 24
[280] Appendix 39 Li Permission at Appendix 24
[281] Appendix Appendix 14 NTEUC 280 Hirzy 2000

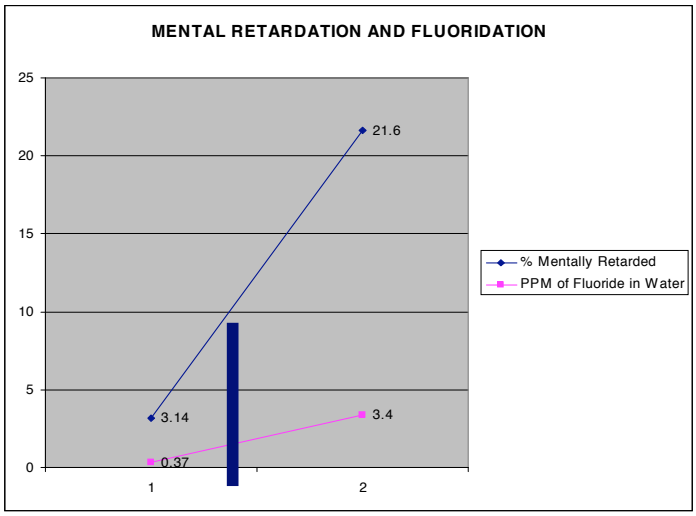
blood-brain barrier and become deposited in the brain. . . . The pathological changes found in these cultured neurons incubated in aluminum-fluoride were similar to the alterations found in the neurons of people with Alzheimer's disease and other forms of dementia. . . Our initial experiments also indicated that primary maximum contaminant level (MCL) for fluoride in drinking water which is 4 mg/L is toxic for neuronal culture of both hippocampus and cortex of mammals. 1-2 mg/L of fluoride in the presence of aluminum not only inhibits theneuronal growth but also decreases the number of growth cones and synapses."[282]

w. Tang (2008) selected sixteen case-controlled studies from 1988 through 2008 and reported, "The children who live in a fluorosis area have five times higher odds of developing a low IQ than those who live in a nonfluorosis area or in a slight fluorosis area."[283]

2. Effect of Fluoride on the Brain: Estimating IQ Drop.

a. Consistent with other studies above, Tianijn[284] reported a 21.6% mental retardation rate with water fluoride content of 3.14 ppm of fluoride and a 3.4% mental retardation rate at 0.37 ppm of fluoride.

b. Graphing the increases reported by Tianijn below and assuming a linear increase of mental retardation, fluoride at 1 ppm in the USA could represent more than a doubling of mental retardation. Remembering that water represents about half the total fluoride ingestion in the USA, triple the number of mentally retarded is reasonable.

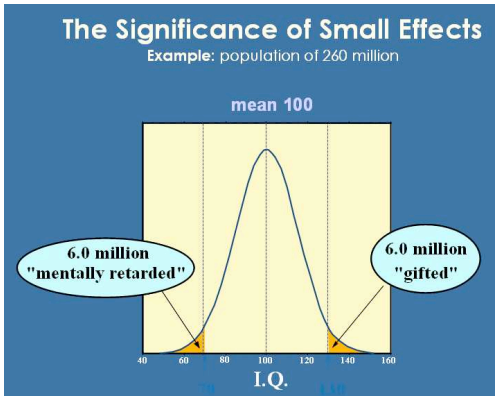


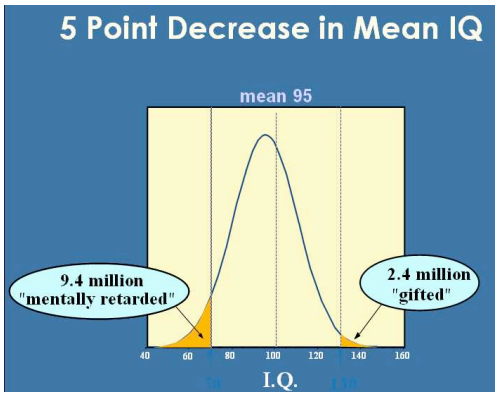
[282] Appendix 55 Kaneez
[283] Appendix 42: Tang Fluorosis & lower IQ
[284] Appendix 56: Spittle, Fluoride Vol. 33 No. 2 49052 2000, Editorial 49 Fluoride 33 (2) 2000 http://www.fluoride-journal.com/00-33-2/332-49.pdf

Graph J Mental Retardation

c. Tang (2008) reported a 5 fold chance of lower IQ in fluorosis communities. (40% of US children now have dental fluorosis), again consistent with more than a doubling of mental retardation with fluoridation.

d. If fluoridation doubles mental retardation, then it would be causing more than a 5 point drop in IQ. Physicians for Social Responsibility use Graph K1 and K2 (immediately following). A 5 point decrease in IQ would be about a 63% increase in the number of mentally retarded, halving the number of gifted with a reduced IQ throughout the population. The entire Bell Curve, of most of us on the fluoridated water drug, moves left.





Graph K1 and K2

e. Li (2003) reported 8.12 IQ lower and Qin (1990) found a reduction in intellectual development even at “less than 0.2 mg/L” fluoride in water. These are studies of the effect of naturally occurring (often) calcium fluoride, not artificially added hydrofluorosilicic acid, which is much more toxic than naturally occurring fluoride. Nor do these studies measure the other sources of fluoride ingested, such as fluoridated toothpaste, dental products, post-harvest fumigants and fluoride pesticides. Nevertheless, the trends and in some cases the intake would be comparable with the USA. Because artificially added hydrofluorosilicic acid is much more potent than naturally occurring calcium fluoride, outcomes would be expected to be more severe in the United States than in these studies.

f. Ranking the 50 USA states in order of whole population fluoridated and plotting the reported rate of mentally retarded 6 – 17 year olds, (Graph L) reveals an increase in mental retardation from about 50/10,000 to 160/10,000 of the population.[285] This ecological evidence suggests an increase of more than 1%, in effect, more than doubling the number of mentally retarded and a more than 5 point decrease in IQ.

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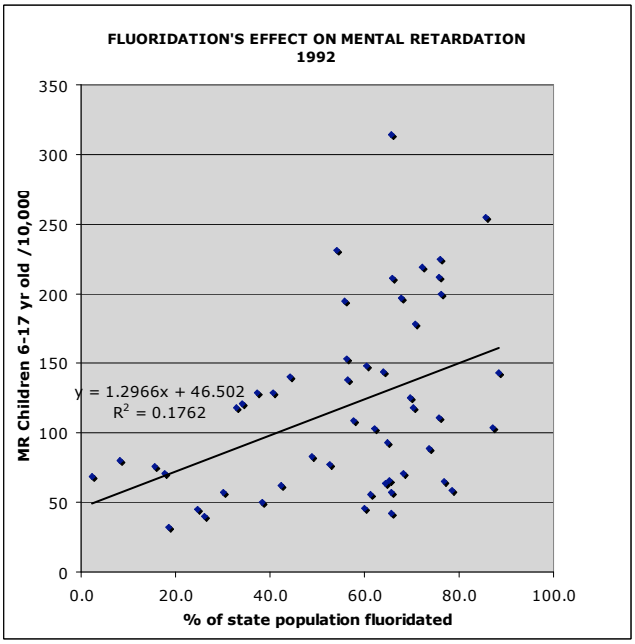
[285] Appendix 30: Osmunson B, WATER FLUORIDATION INTERVENTION: DENTISTRY’S CROWN JEWEL OR DARK HOUR? Guest editorial, Fluoride 40(4)214-221 October-December 2007.



Graph L[286]

A tripling of the mentally retarded population in fluoridated communities compared to isolated communities in developing countries, which are the subjects of the IQ studies discussed above, is possible given that fluoridated water represents about half an individual's fluoride exposure.[287] (See NRC 2006 Figure 2-1 and on page 45 above.)

Evidence that fluoride crosses the placenta to the fetus[288] contributing to harm[289] and higher blood lead levels in fluoridated communities could explain part of the risk of higher mental retardation rates in fluoridated communities. And once again hydrofluorosilicic acid is more toxic than naturally occurring fluoride such as CaF.

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[286] Although this data was from 1992, that is the latest state survey of mental retardation we can find. More current studies use special education rates and the graphs are similar. Certainly MR data must be available but was not found to date. http://apps.nccd.cdc.gov/giscvh/map.aspx http://apps.nccd.cdc.gov/nohss/FluoridationV.asphttp://pubs.usgs.gov/circ/2004/circ1268/htdocs/table05.html http://www.cdc.gov/mmwR/preview/mmwrhtml/00040023.htm

[287] Appendix 57

[288] Appendix 32, 33, 48

[289] Appendix 39

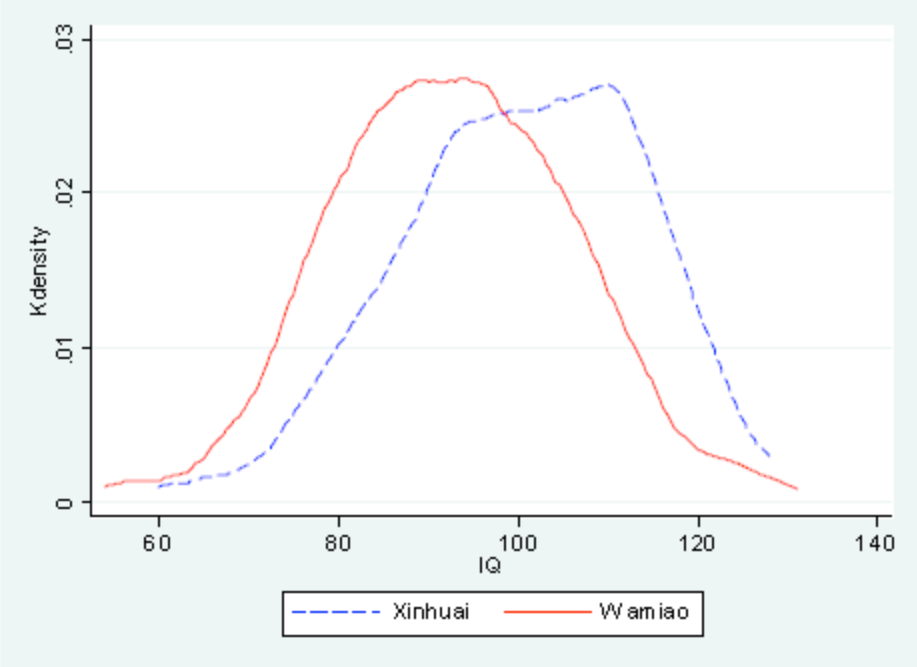

Figure 2 Kdensity distribution of children's IQ in Wamiao and Xinhuai village

Xiang (2003 and 2005)[290] compared two villages, one with 0.04 ppm fluoride in fasting serum and the other with 0.08 ppm fluoride in fasting serum. The graph above illustrates the lower IQ of about 8 points found with the higher fluoride.

Fluoride serum concentration in the USA general population is not well documented. Some individuals certainly exceed 0.08 ppm serum fluoride levels and 0.04 ppm may not be safe.

If better controls were available, then other factors could be considered such as states without fluoridation, fluoride supplements, fluoride toothpaste, fluoride post-harvest fumigants, fluoride dental and medical products, and fluoride pesticides. If these other factors were considered, then confidence levels would be higher and the effect from fluoride exposure would probably be higher. Confounding factors of smoking, income, poverty, Alzheimer deaths, and race[291] have been considered for this ranking of

[290] Appendixes 16 and 19. Xiang presented the referenced graph of the 2003 and 2005 data in 2010. The 2010 was withdrawn because it was substantially similar to his earlier work.
[291] Appendix 119 Race and Fluorosis Meier 2010

the 50 states and little effect was noted.292 Critics are concerned that most recent studies showing brain damage have been done in China. Indeed, they are warning us that their waste product we are purchasing is not safe. However, we are not doing our own research on the effects of fluoride on the brain.

g. Comparing the USA with other Countries. The Organization for Economic Co-operation and Development reported (2000) the prevalence of disability (not just mental retardation) in some European Countries and the USA:

> "The United States Category A prevalence rate was 5.62%, as compared to European rates of: 1.33% for Austria, 2.53% for France, 1.45% for Germany, 2.57% for Ireland, 2.13% for Italy, 1.77% for the Netherlands, 2.56% for Spain, and 1.62% for Switzerland."[293]

Ireland has higher mental retardation than the USA and a higher percentage of the population drinking fluoridated water. European countries with less fluoridation have lower mental retardation, except for Italy which has higher mental retardation and less fluoridation. A doubling or more of mental retardation with fluoridation is consistent when comparing the USA with other countries less fluoridated. [294]

h. On the other side of the controversy, the CDC suggests, "Right now, we do not know how to prevent most conditions that cause intellectual disability."[295] However, the dental part of the CDC actively promotes fluoridation[296] and the CDC specifically states they do not determine the safety of fluoridation.[297]

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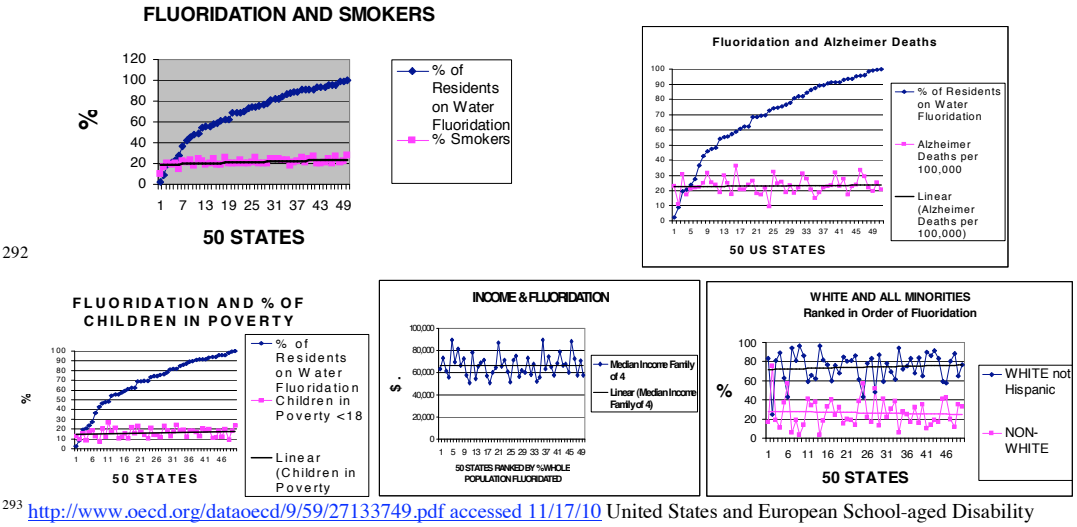

[293] http://www.oecd.org/dataoecd/9/59/27133749.pdf accessed 11/17/10 United States and European School-aged Disability Prevalence: An Investigative Study to Elaborate Differences, Dec 2000, Funded from the Office of Special Education Programs.

[294] http://www.oecd.org/dataoecd/9/59/27133749.pdf accessed 11/17/10 United States and European School-aged Disability Prevalence: An Investigative Study to Elaborate Differences, Dec 2000, Funded from the Office of Special Education Programs.

[295] The terms mentally retarded and intellectually disabled appear to be used interchangeably by the CDC and researchers.

[296] http://www.cdc.gov/fluoridation/benefits.htm

[297] "it is not CDC's responsibility to determine what levels of fluoride in water are safe" http://www.cdc.gov/fluoridation/safety.htm

3. Economic Impact of Mental Retardation

a. In 2000, Muir estimated economic impact for the USA with a 5 point IQ loss between $375-$425 billion/year.[298]

b. The FDA Division of Neurotoxicology appropriately summarizes the potential economic impact of neurological disability:

> "Fifty-million Americans have a permanent, neurological disability that limits their daily activities. One in three will experience some form of mental disorder during their lifetime. Health care, lost productivity, and other economic costs associated with brain-related diseases are estimated to exceed $500 billion a year. . . .
>
> The number of neuroactive chemicals that require FDA regulation is estimated to be in the thousands. Thus, identifying methods and approaches for assessing neurotoxicity is critical for the development of guidelines for the assessment of neurotoxic risk. Chemicals that are known or suspected causes of brain-related disorders are vital to the national economy and our quality of life. However, the challenge is to determine at what doses, or exposure levels, and under what conditions these compounds can be used effectively while minimizing the likelihood that they will cause adverse effects on the nervous system."[299]

c. National average cost for state care of a mentally disabled person is reported at $128,000/person/year.[300] Those in private homes require about half that amount but certainly additional costs for special education, counseling, and family support should be included. To argue on behalf of the disabled and their parents, a dollar cost of $50,000 to $180,000 a year for care does not cover other costs such as time, grief, and care provided by teachers, employers, friends and especially the harm to those whose lives have been irrevocably changed by loss of mental functioning. The loss of income for the intellectually disabled as well as their family members should also be included in economic costs.

d. Using a conservative number of $70,000/year in added care costs and $30,000/year in reduction of wages, an estimated economic impact of $100,000/year/person is reasonable. A per person cost of $100,000 applied to only 1% of the 225 million people in the USA drinking fluoridated water drug represents a $225 billion economic impact due to lack of FDA CDER drug regulatory oversight.

Nevertheless, proponents of fluoridation maintain that fluoridation is safe.[301]

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[298] MUIR, T. and ZEGARAC, M. "Economics of Health Costs due to Environmental Disease." Presentation at the 2001 Conference of the International Association of Great Lakes Research. Authors' Address: Great Lakes Environment Office, Environment Canada - Ontario Region, 867 Lakeshore Road, Burlington, ON, L7R 4A6 Reported at http://www.foxriverwatch.com/economic_damage_pcb.html

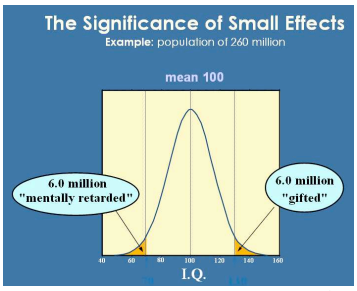
[299] http://www.fda.gov/downloads/AboutFDA/CentersOffices/NCTR/ResearchAccomplishmentsPlans/UCM200349.pdf 11/16/10

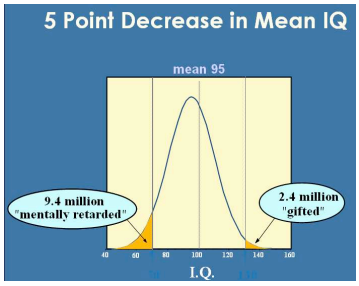
[300] http://virginia.watchdog.org/629/virginia-pays-more-to-serve-fewer-developmentally-disabled/

[301] http://www.ada.org/4378.aspx accessed 10/18/10

E. Economic Impact from Damage to the "Gifted" Brain (App 32-55)

1. Effect of Fluoride on the Brain for the Gifted.





Graph K1 and K2 are considered Again for the Gifted

Population damage from toxins is considered to shift the entire population of the "Bell Curve" of IQ down, (Graph H) resulting in a reduction of the number of the intellectually gifted in half.

2. Economic Impact of Gifted IQ Reduction.

i. The effect of IQ on income is controversial. However, most agree that manipulating IQ to a significant degree, except for child adoption, has not been successful. Intelligence is largely (40% to 80%) genetically heritable, or at least strongly related to the mother's intelligence. Correlating IQ with economics should include many factors, such as decrease in wages, increase in divorce, incarceration to at least the next generation. Herrnstein and Murray outline the effect below:

Economic and social correlates of IQ

IQ	<75	75-90	90-110	110-125	>125
US population distribution	5	20	50	20	5
Married by age 30	72	81	81	72	67
Out of labor force more than 1 month out of year (men)	22	19	15	14	10
Unemployed more than 1 month out of year (men)	12	10	7	7	2
Divorced in 5 years	21	22	23	15	9
% of children w/ IQ in bottom decile (mothers)	39	17	6	7	-
Had an illegitimate baby (mothers)	32	17	8	4	2
Lives in poverty	30	16	6	3	2
Ever incarcerated (men)	7	7	3	1	0
Chronic welfare recipient (mothers)	31	17	8	2	0
High school dropout	55	35	6	0.4	0

Values are the percentage of each IQ sub-population, among non-Hispanic whites only, fitting each descriptor. Herrnstein & Murray (1994) pp. 171, 158, 163, 174, 230, 180, 132, 194, 247-248, 194, 146 respectively.

3. Murrey reported lower earnings with lower IQ, graph below.[302]

Relation between IQ and earnings in the U.S.

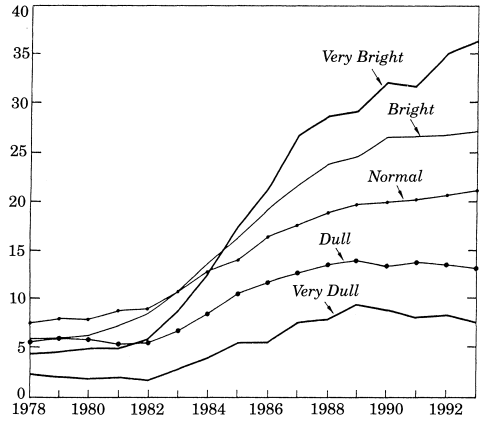
IQ	<75	75–90	90–110	110–125	>125
Age 18	2,000	5,000	8,000	8,000	3,000
Age 26	3,000	10,000	16,000	20,000	21,000
Age 32	5,000	12,400	20,000	27,000	36,000

Values are the average earnings (1993 US Dollars) of each IQ sub-population.

Using economic impact as a measurement for the gifted has several indirect economic considerations. After the basics of food and lodging are satisfied, the gifted may be more motivated with more cognitive challenges than economic gain. For example, scientists both in private and government agencies, such as the FDA CDER, and University Professors are almost exclusively drawn from the top 10% of the IQ distribution; however, their incomes are not exceptional. And it is well known in the dental profession that the top 10% of the class do not necessarily have the greatest economic success. Social skills are more important than IQ for patient trust. To reduce the IQ of those who mentor the next generation as professors, or a single government regulatory employee who stands up for justice, or a complex judgment on a medical diagnosis can have serious indirect economic impact far greater than the care of one mentally retarded person. The economic value of IQ in both academics and the market place has increased, as graphed by Murray with NLSY data[303] Figure 2-1.

CHARLES MURRAY ♦ 7

FIGURE 2–1
MEDIAN EARNED INCOME BY COGNITIVE CLASS, 1978–1993
(thousands of $ 1993)



[302] Murray, C. (1997). IQ and economic success. Public Interest, 128, 21–35.http://en.wikipedia.org/wiki/The_Bell_Curve
[303] http://www.aei.org/docLib/20040302_book443.pdf accessed 11/26/10 Very Bright = IQ 120+; Bright = 110 -119; Very Dull IQ under 80. Dull = 80-89 IQ;

4. What is the economic impact of a 5% lower IQ for the President of the United States, a Chairman of the Federal Reserve, or FDA CDEA regulators? Those people simply can't have too much intellectual "horsepower." An unfortunate decision by one of those, perhaps to needlessly go to war, provide unsecured loans, defer regulatory action, or inspire and educate the next generation can create trillions in direct and indirect economic harm or good. The direct and indirect economic impact of the gifted can be exponentially higher than the mentally retarded.

The economic impact of a 5 IQ point decrease on the gifted is conservatively estimated at double the impact on the mentally retarded, $450 billion due to lack of FDA CDER drug regulatory oversight.

F. Economic Impact from Damage to the "Normal" Brain (App 32-55)

Suppose someone found an IQ pill and offered it for sale at auction. What would you or I pay for one more IQ point, 5 or 10 more IQ points? One more IQ point might enhance memory, reasoning, compassion, love, or creativity. Is one more IQ point worth $1 a day, $10 a day, $100 a day? Would we trade the avoidance of a cavity for an extra IQ point? What would employers pay for their employees to have perhaps 5 more IQ points? We would certainly pay a great deal for more IQ horsepower for the FDA CDER.

Dentists can fix teeth. No one can fix damaged IQ.

Murray reports an increase of $453 -$892/year in wages per increased IO point, independently of parental socio-economic status.[304]

Economic Impact from lack of FDA CDER oversight for the middle 90% of the public losing about 5 IQ points is estimated in excess of $3,000/person/year for 200 million people, at a conservatively estimated $600 billion/year.

G. Economic Impact from Damage to Those on Fluoridation or Fluoride Supplements.

A confounding factor for fluoride ingestion is the percentage of people in fluoridated areas who drink bottled water instead of tap water or who drink distilled water or water filtered through reverse osmosis filters. Another confounding factor is the fact that some who live in non-fluoridated communities work or go to school in fluoridated communities, take fluoride supplements, swallow toothpaste, or eat foods high in fluoride. These additional sources of fluoride make it even more essential that the FDA CDER regulate fluoridated water.

H. Economic Impact from Increased Cancer Damage (App 74, 75)

Burk,[305] head of the cytochemistry section of the National Cancer Institute in 1974, took 20 large comparable US cities, 10 nonfluoridated controls (5.3 million population) and 10 nonfluoridated experimental (11 million population) which became

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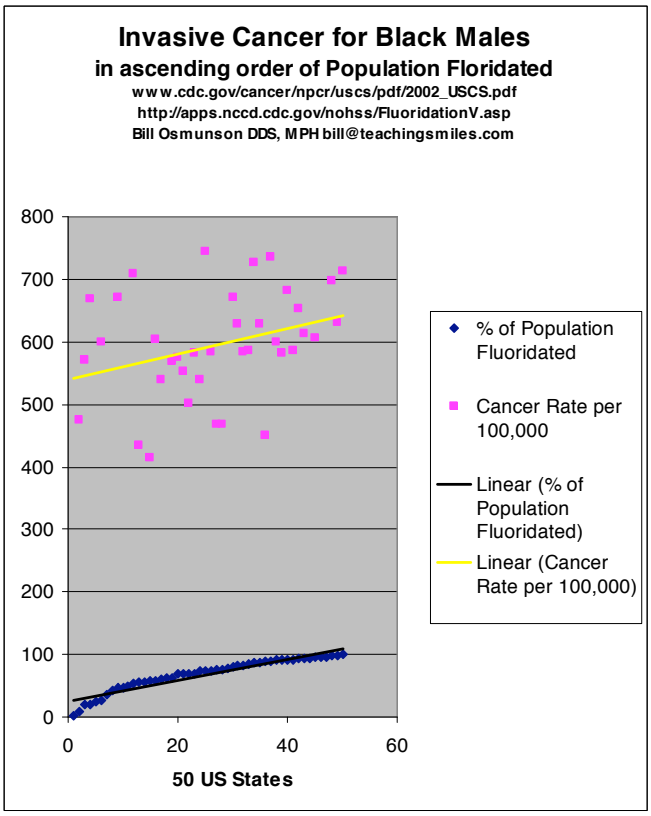
[304] http://www.aei.org/docLib/20040302_book443.pdf page 10.
[305] Appendix 28 for more details

fluoridated and compared cancer rates. His study stopped in 1969 because the control cities became fluoridated. The resulting data of cancer deaths (CDRo) resulted in 31.3 excess cancer deaths per year per 100,000 persons after 15-20 years of exposure. Critics of Burk's work were found to have used flawed data and shown to be in error. The percentage increase in cancer was confirmed at about 16%.

In 2009, the National Institutes of Health estimated the 2008 overall annual cost of cancer was around $228 billion.[306] Using Burke's conclusion that 16% of cancers are caused by fluoridation and assuming that 75% of the public is now drinking fluoridated water, the yearly economic impact of fluoridation on cancer would be estimated at $228B x 16% x 75% = around $27 Billion due to lack of FDA CDER drug regulatory oversight.



Graph M

Research and Graph M[307] above is consistent with the work by Burk, and shows perhaps a 16% increase in cancer for black males. The general population shows a lower increase than black males. The increase is lower for females than for males. However, an increase in fluoride toothpastes, fluoride pesticides, fluoride post-harvest fumigants, fluoride dental and medical products – all part of the aggregate fluoride exposure - are significant confounding factors for total fluoride ingestion. Because this $27B number does not even take into consideration the negative halo effect, this number maybe conservative.

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[306] http://www.cancer.org/cancer/cancerbasics/economic-impact-of-cancer Accessed 11/16/10
[307] http://apps.nccd.cdc.gov/nohss/FluoridationV.asp; http://www.cdc.gov/cancer/npcr/uscs/pdf/2002_USCS.pdf

The significant increase in fluoride exposure from new sources and other confounding factors have minimized a comparison between fluoridated and non-fluoridated populations. Our estimate here will use 16% of the $228 billion total cancer economic expense and estimates $27 billion[308] economic impact from lack of FDA CDER oversight.

In contrast, the CDC agrees with the American Dental Association report:

"According to generally accepted scientific knowledge, there is no association between cancer rates in humans and optimal levels of fluoride in drinking water."[309]

In 1977 Burk presented that "Fluoride causes more cancer deaths, and causes it faster, than any other chemical." In 1982, as expert witness, testified, "I know of absolutely no, and I mean absolutely no means of prevention that would save so many lives as simply to stop fluoridation, or don't start it where it is otherwise going to be started. There you might save 30,000 or 40,000 or 50,000 lives a year, cancer lives."[310]

Fluoridation promoters[311] claim more than 50 epidemiologic studies have failed to demonstrate an association between fluoridation and a risk of cancer and references historical NAS statements. Fluoridation promoters criticize Burk's work but fail to check their flawed raw data.[312] Regardless of whether cancer went up or not, promoters suggest the level of industrialization in the fluoridated cities created the higher rate of cancer.

It is not the victims, consumers or patients who are required by the FFDCA to prove harm to an absolute certainty.

The FDA CDER is the most competent agency to evaluate the risks and benefits of fluoridation. Proponents of fluoridation demand high quality studies to demonstrate risks, but accept lower quality studies evaluating benefit. In fact, the opposite should occur. Proof of safety should be of a higher quality than proof of efficacy. And providing proof of both safety and efficacy should be required of those promoting fluoridation and not required of the victims.

I. **Economic Impact from Increased Kidney Damage** (App 84)

See short video http://www.youtube.com/watch?v=utB94Jee0Os

The kidney is the primary method for elimination of fluoride and is the primary target organ for fluoride toxicity, as Dote and other scholars point out. "Whenever renal

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[308] Criticisms of Burk's study were drummed up by pro-fluoridationists. Burk's study was valid as far as it goes, but it is not the only type of study that should be done. It was not meant to answer all questions about fluoridation. Nevertheless, much can be learned from it. It is now 36 years old, and it is time to redo it. We are fortunate it was done. Much can be learned from Burk's study, and its ardent supporters should raise money and redo it.

[309] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf 12/2/10

[310] Dean Burk, PhD, Judicial hearing, 1/14/1982, Safe Water Foundation vs. City of Houston District Court of Texas, Harris County 151st Judicial District.

[311] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf

[312] Appendix 28 Cancer Major Health Risk

function is significantly impaired, urinary F excretion decreases, and serum F concentrations increase. . . ."[313]

Direct and indirect damage to the kidneys as well as damage to other organs and systems from a reduction of fluoride elimination should be considered and are sometimes difficult to separate. (See Appendix T)

In 2008, the National Kidney Foundation withdrew their support of fluoridation.[314] That withdrawal was equivocal because the NKF is a recipient of the CDC, however, note that tucked away in the withdrawal are these important words: "Individuals with CKD (chronic kidney disease) should be notified of the potential risk of fluoride exposure…." NRC's "withdrawal" was not equivocal – but their new stance not taking a position on fluoridation may reduce the negative impact on gaining grants.

In 2002, Trivedi et al estimated the direct (not including indirect) savings from a slowing of the progression of kidney disease over a 10 year period. (GFR glomerular filtration rate)

> "If the rate of decline in GFR decreased by 10%, 20%, and 30% after December 31, 1999, in all patients with GFRs of 60 mL/min or less, cumulative direct healthcare savings through 2010 would equal approximately $18.56, $39.02, and $60.61 billion, respectively. For a 10%, 20%, and 30% decrease in the rate of decline in GFR in all patients with a GFR of 30 mL/min or less, estimated cumulative savings through 2010 equal $9.06, $19.98, and $33.37 billion, respectively."[315]

An estimated 26 million adults in the USA have CKD (chronic kidney disease).[316]

If we conservatively attribute only 5% of the total MEDICARE CKD and ESRD (end-stage kidney disease) costs to effects from fluoridation, using numbers from the U.S. Renal Data Service we have: (57.5B + 35.3 B)(.05) = $ 4.64 billion. Indirect costs from loss of income, family support and death would increase those costs perhaps 10 to 50%.

The NRC 2006 Report, stated, "Several investigators have shown that patients with impaired renal function, or on hemodialysis, tend to accumulate fluoride much more quickly than normal."[317] The NRC 2006 Report further reported, "Early water fluoridation studies did not carefully assess changes in renal function. It has long been suspected that fluoride, even at concentrations below 1.2 mg/L in drinking water, over the years can increase the risk for renal calculi (kidney stones)."[318]

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[313] http://www.fluoride-journal.com/00-33-4/334-210.pdf and Kono K, Yoshida Y, Harada A. Urinary excretion of fluoride in chronic renal failure and hydrofluoric acid workers. Toxicol Ind Health 1984;125:91-9.
[314] http://www.kidney.org/atoz/pdf/Fluoride_Intake_in_CKD.pdf accessed 11/27/10
[315] Trivedi HS, Pang MM, Campbell A, Saab P. Slowing the progression of chronic renal failure: economic benefits and patients' perspectives. Am J Kidney Dis. 2002 Apr;39(4):721-9
[316] http://www.kidneytrust.org/learn/ckd-public-health-crisis/ accessed 11/27/10 Reported in 2007 JAMA
[317] NRC 2006 Report Chapter "Patients with Renal Impairment"
[318] NRC 2006 Chapter "Does Fluoride in Drinking Water Contribute to Kidney Stones?"

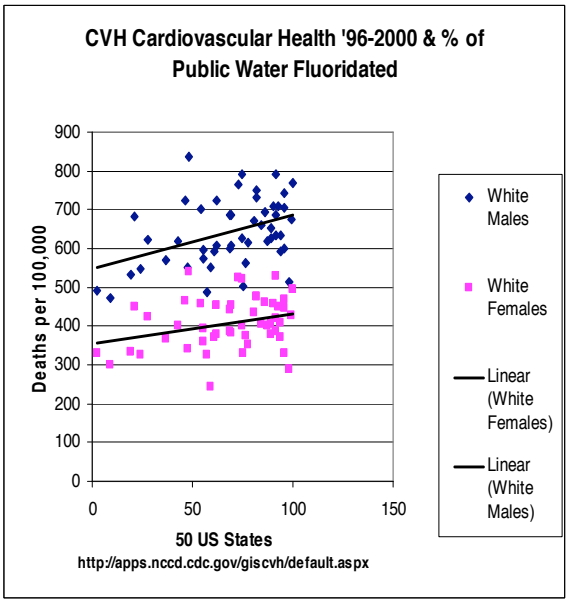
Promoters of fluoridation agree about half of fluoride ingested is removed from the body by the kidneys. To conclude that "the consumption of optimally fluoridated water has not shown to cause or worsen human kidney disease," promoters use inadequate community-based studies with inadequate and flawed methodology referencing historical studies. Manufacturers must be required to provide evidence of safety for the kidneys.

A very conservative estimate of the cost of kidney damage from the addition of fluoride to public water is used: $4.6 billion/year from FDA CDER deferred action.

J. Economic Impact on Cardiovascular Disease (CVD) (App 77, 124)

Cardiovascular disease is considered the number one killer in our society. Arteriosclerosis (calcification of the arteries) by fluoride has been demonstrated since the 1980s. Low calcium is directly related to impaired heart function. Elevated blood-fluoride levels lower available body calcium and lower calcium can affect the heart and calcification of the arteries. Extremely low calcium causes cardiac arrest. The heart beat rate slows, and heart rate abnormalities increase, in direct proportion to increasing fluoride levels. Recent research shows fluoride affects the aorta (main artery) and heart in ways that lead to increased heart attacks (Varol et al 2010). As with an increase in kidney stones, fluoride increases calcification of arteries.

A few studies suggest an effect of fluoride ingestion on CVD. (Appendix 77 and 124). Graph N below suggests an increase in CVD of 17%-18% for both men and women. Fluoride appears to exacerbate or increase the existing pathology similarly for men and women.



Graph N

Promoters of fluoridation defend fluoridation by saying, "Drinking optimally fluoridated water is not a risk factor for heart disease."[319] Safety is based on the opinion

[319] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf Question 39

of the National Heart and Lung and Blood Institute of the NIH who looked at ecological evidence comparing cities fluoridated with those non-fluoridated, (not unlike a comparison of states in the graph above) in 1972 on heart deaths in Antigo, Wisconsin and examination of "persons exposed to a lifetime of naturally occurring fluorides or persons with high industrial exposures, and from broad national experience."[320]

A 1972 Antigo, Wisconsin study and broad national experience is hardly adequate evidence to conclude "safety." Certainly manufacturers must be held to a higher standard of evidence than they have provided.

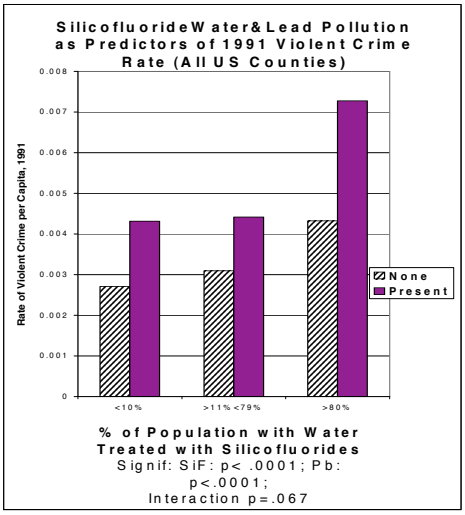
The FDA CDER must compare the evidence of promoters with the evidence presented in Appendix W of more than 60 published studies raising concerns of risk from increased exposure from fluoridation on cancer. Remember, fluoridation contributes about half of the fluoride exposure and contributes to excess fluoride intake.

Economic impact of CVD is $503 Billion.[321] An estimate of 17% increase in CVD for the 225 million fluoridated equals $64 Billion CVD economic impact due to lack of FDA CDER oversight.

K. Economic Impact from Increase of Crime

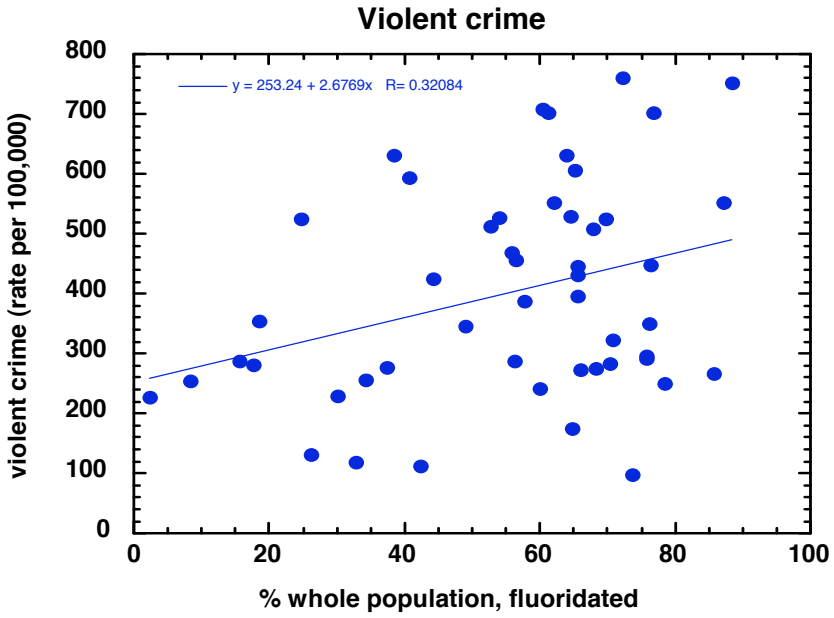
1. Masters reported an increase of 71% in violent crime when comparing counties in the United States with more than 90% of the population on fluoridated water and lead pollution, Graph O.[322]

Graph O



[320] ibid
[321] http://www.cdc.gov/chronicdisease/resources/publications/AAG/dhdsp.htm
[322] Masters, R.D. (2002). (Westport: Praeger), pp. 275-296 Ch. 15 See also Appendix M-4 Niu Effects of Fluoride and Lead on Locomotor Behavior and Expression of Nissl Body in Brain of Adult Rats 2008

2. We again ranked the 50 states in order of the increasing percentage of the whole population fluoridated and violent crime, Graph P, and found a doubling of crime.



Graph P

In 1999, Masters reported:

"For the period 1977 to 1997, levels of violent crime and teenage homicide were significantly correlated with the probability of prenatal and infant exposure to leaded gasoline years earlier. Across all U.S. counties for both 1985 and 1991, industrial releases of heavy metals were -- controlling for over 20 socio-economic and demographic factors -- also a risk-factor for higher rates of crime. Surveys of children's blood lead in Massachusetts, New York, and other states as well as NHANES III and an NIJ study of 24 cities point to another environmental factor: where silicofluorides are used as water treatment agents, [also known as water fluoridation] risk-ratios for blood lead over 10μg/dL are from 1.25 to 2.5, with significant interactions between the silicofluorides and other factors associated with lead uptake. Communities using silicofluorides also report higher rates of learning disabilities, ADHD, violent crime, and criminals who were using cocaine at the time of arrest."[323]

"For NHANES III Children 3-5, mean blood lead is significantly associated with fluoridation status (DF 3, F 17.14, $p < .0001$) and race (DF 2, F 19.35, $p < .0001$) as well as for poverty income ratio (DF 1, F 66.55, $p < .0001$). Interaction effect between race and fluoridation status: DF 6, F ;3.333, $p < .0029$; . . .

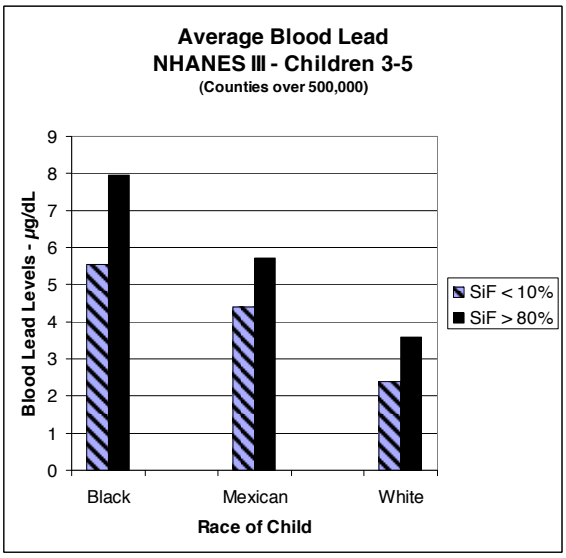
[323] Roger D. Masters, Department of Government, Dartmouth College, Foundation for Neuroscience and Society, Research conducted with Myron J. Coplan (Intellequity, Natick, MA) and Brian Hone under grants from the Office of Criminal Enforcement, Forensics and Training, Environmental Protection Agency, the Earhart Foundation, and the Rockefeller Center for the Social Sciences, Dartmouth College

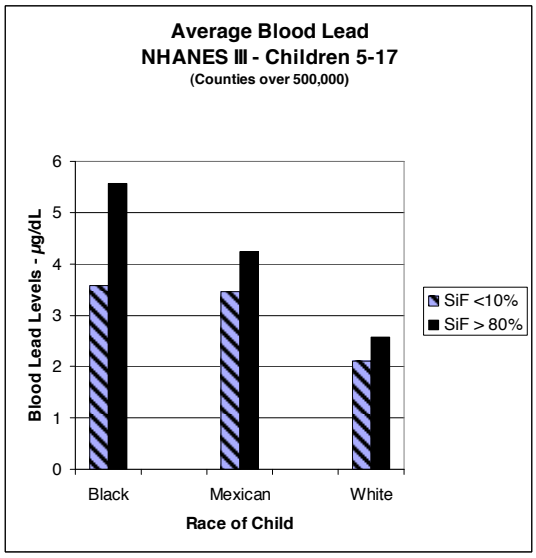
"Among 30,000 criminals in 24 cities studied by NIJ, those living where SiF is in water were more likely to have been using cocaine at the time of their arrest (H2SiF6 = 44%; Na2SiF6 = 43%; non-fluoridated = 32%). . .

"Crime rates in the cities using SiF were significantly higher than in non-fluoridating cities (H2SiF6 = 1486 per 100,000; Na2SiF6 = 1480 per 100,000; non-fluoridated = 1100 per 100,000), as were rates of death from alcoholism (H2SiF6 = 56.1 per 100,000; Na2SiF6 = 53.8 per 100,000; non-fluoridated = 44.1 per 100,000). . .

"Minorities are especially at risk. In high SiF exposure counties, blood lead levels average 6.26 μg/dL among Black children, 4.86 μg/dL among Mexican-Americans, and 3.05 μg/dL among Whites; in low SiF exposure counties, Blacks average 4.37μg/dL, Mexican-Americans 3.86μg/dL, and Whites 2.03μg/dL (risk ratios between 1.26 and 1.50). For both 3-5 and 5-17 age-groups, the interaction effect between a child's race and SiF exposure as factors in higher blood lead is highly significant ($p < .0001$). A. The brain is the most sensitive chemical organ in the body. While discussions of toxins heretofore focused on cancer and disease, ADD/ADHD, alcoholism, substance abuse, and crime need to be studied in terms of the latest biology and neuroscience of early development and brain function. . .

"In contemporary society, these effects take on a different character. Environmental pollution and dangerous water treatment procedures are human activities whose results are both economically costly and morally unjust. Innocent children should not be poisoned by public water supplies."[324]





Graphs O and P

[324] Ibid

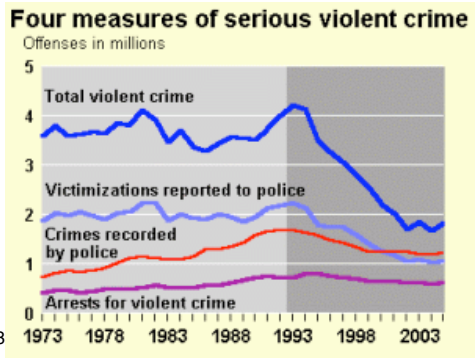
Critics suggest this evidence lacks appropriate methodology. However, the lack of evidence does not refute the meager evidence available. The American Dental Association finds, “Generally accepted scientific evidence has not shown any association between water fluoridation and blood lead levels.”[325] Masters responded to his critics, “Given the costs of incarcerating violent criminals, these side-effects justify a moratorium on using silicofluorides for water treatment until they are shown to be safe.”[326] The FDA must certainly recognize that it is not the victims who must prove the safety of drugs or foods.

The most conservative estimate of increased crime rate appears to be the work of Masters, finding the rate of crime goes from 1486 per 100,000; Na2SiF to non-fluoridated = 1100 per 100,000. A 35% increase in crime. The highest estimate is a doubling of crime with fluoridation.

Estimating cost of incarceration.

“In 2007 per capita income in the United States was $38,611, according to the U.S. Bureau of Economic Analysis, while the annual economic impact of crime was, by one estimate (described below), $5,125 per capita. In other words, more than 13 percent of Americans' income is allocated to crime-related expenditures.”[327]

Graph Q[328]



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[325] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf Question 37 The ADA references Urbansky who suggested the methodology was faulty and “intentionally biased towards what appears to be a preconceived conclusion.” Connett M correctly pointed out the FDA CDER h has never approved ingestion of any fluoride product. Masters responded that fluoride is an untested compound. Lack of evidence is not proof of safety. Briggs provided a reasonable discussion of the controversy which is found at http://www2.fluoridealert.org/Alert/United-States/Vermont/Contradictory-scientific-studies-raise-questions-about-fluoride-safety.

[326] Appendix 37 Masters Moratorium will save millions.

[327] http://www.frbatlanta.org/pubs/econsouth/econsouth_vol_11_no_1_paying_for_crime_and_punishment.cfm?redirected=true

“Crime trending upward?

The $5,125 annual per capita cost of crime cited earlier is an estimate—adjusted for inflation using the consumer price index—of a statistic originally calculated by David Anderson, a professor of economics at Centre College. In 1999, Anderson's study "The Aggregate Burden of Crime," published in the *Journal of Law and Economics*, set the cost at $4,118. According to the National Center for Policy Analysis, Anderson's research was a landmark because it considered costs not included in previous studies. Some of the new factors were opportunity costs of time lost by victims, criminals, and prisoners, as well as the cost of private deterrence (such as home security systems) and losses related to the fear of being victimized. His model also included decreases in property values of real estate and buildings because they are located in high-crime areas as well as the costs associated with commuting to the suburbs to avoid crime in the city center.”

[328] http://en.wikipedia.org/wiki/File:Ncsucr2.gif 11/27/10

Using $5,125 per person per year direct and indirect costs for 225 million would be would be about $1.15 trillion. If a conservative estimate of a quarter of the crime is due to fluoridation (35%-100%) the economic impact would be $288 billion from FDA CDER deferring regulatory action.

L. Economic Impact from Other Pathologies

Studies show increased bone and joint disorders resulting from fluoridation.[331] The elderly are impacted the most by bone and joint disorders. These are serious problems for elderly patients. However, it can be argued cynically that because the elderly are not generally economically productive, their early demise is of relatively low economic impact, with the costs and "benefits" of water fluoridation balancing each other off:

Arthritic like symptoms,[332] allergic reactions,[333] gastrointestinal,[334] and immune system[335] damage from excess fluoride is well known, although the economic impact directly related to fluoridated water is less clear but not negligible.

Reproductive damage[336] was reported as low as 3 mg/day by Ortiz-Perez. Shusheela reported lower testosterone levels with increased fluoride intake. Ferni reported decreased total fertility rate when comparing communities with fluoride levels of at least 3 ppm. Critics claimed the study has "serious limitations in design and analysis" but have failed to provide any better studies and conclude from the lack of evidence acceptable to them, that "there is no credible evidence that fluoridation has an adverse effect on human reproduction, fertility or birth rates"[337] The FFDCA requires the manufacturer to provide adequate evidence of safety, not the consumer, patient or victim. Critics have appropriately set a high standard of quality for acceptable research and the FFDCA requires the FDA CDER to demand quality research from the manufacturer.

The Pineal Gland[338] has the highest concentration of fluoride of any body tissue. Again, the economic impact from this high concentration and the role of fluoridated water is unclear. Studies need to be done on whether an increased fluoride exposure resulting in higher fluoride concentrations in the Pineal Gland reduce the output of melatonin. Melatonin appears to affect sleep patterns and the difficulty in falling asleep, fatigue, mood changes, confusion, dizziness, drowsiness, hallucinations, headache, other hormone changes, high blood sugar, eye pressure and much more.

Regarding the pineal gland, critics claim, "Generally accepted science does not

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[331] Appendix 58 Bone Damage
[332] Appendix 59 Arthritic Like Symptoms
[333] Appendix 60 Allergy
[334] See Above
[335] See Above
[336] See above
[337] http://www.ada.org/sections/professionalResources/pdfs/fluoridation_facts.pdf Question 34
[338] See Above

suggest that water fluoridation causes the early onset of puberty." True, no studies have been done controlling for the effect of fluoride just from water fluoridation, and if such studies are required, then they must be provided by the manufacturer, not the victims. Critics reference an historical 1956 study of pediatric findings as evidence of safety. In the last half century more studies have become available suggesting harm,[339] although suggesting an economic impact from altered pineal gland function is difficult.

Historically fluoride was experimented with to alter motivation, hyperactivity, and other behavioral changes with reported success. Today, one of the components of some ADD drugs is fluoride.

The relative economic impact of these other disorders from fluoride is harder to quantify but not negligible. If future study demonstrates that economic impact to the brain, cancer, thyroid or teeth is not as high as estimated, the negative impact on the pineal gland, on bone fractures, and in causing arthritic like symptoms and other damage will more than make up the difference.

A small but increasing percentage of the population is experiencing mild to severe immediate adverse reactions to fluoridated water. The exact number is unknown because most do not seek a specific diagnosis and the condition is not accurately tracked. See Dr. Bruce Spittle's book, Fluoride Fatigue for studies on adverse reactions.[340] Many of these chemically sensitive individuals are children. Individuals suffering adverse reactions to fluoridated water incur huge costs obtaining fluoride-free water, installing reverse osmosis filtration systems, and for some, being forced to move from cities that fluoridate, even abandoning jobs to avoid fluoridated water. The household cost of eliminating and/or avoiding fluoridated water is extremely difficult to estimate, but highly significant to those it affects. Economically, these costs are likely offset by the sizable fluoride-filtration industry.

Confounding Factors

Because fluoride is more toxic than lead and there is no known safe level of lead ingestion, then the ingestion of any fluoride should be of equally or greater concern. The debate will go on for generations as to how small an amount of toxic substances such as arsenic, lead, strychnine, and fluoride is needed to create adverse effects in some individuals. We have enough scientific evidence to raise serious caution that fluoride ingestion should be reduced to as close to zero as possible.

Ecological evidence is not the best evidence; however, the FDA CDER needs to judge the evidence provided by the drug manufacturers. The FDA CDER must obey the law and not force the victims and patients of the illegal drug to provide the research of harm. The estimate of economic impact is used here as an illustration of the critical importance for regulatory action and the specific numbers are estimates to demonstrate the potential severity of the lack of regulatory oversight. The point is one of law. Congress has mandated the FDA CDER with drug regulatory oversight approval.

An emergency crisis is taking place with long term effects. This estimate of

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[339] See Above Pineal GI and see also http://www.fluoridealert.org/health/pineal/
[340] http://www.pauapress.com/fluoride/files/1418.pdf

economic impact is summarized here:

ECONOMIC SUMMARY:

Economic Benefit to Teeth (Range $3.6M-$4.2B)	$	(356,000,000) (Million)
Less Chemicals, equipment repair, operations	$	675,000,000 (Million)
Net Economic LOSS after Fluoridation Costs	$	319,000,000 (Million)

The most optimistic estimates based on assumptions, not including risks, claim perhaps $8 billion of dental cost savings.

B. Damage to Teeth, Cosmetics and Fractures	$	3,750,000,000 (Billion)
D. Damage to the Thyroid (Diabetes & Obesity)	$	16,000,000,000 (Billion)
E. Damage to Intellectually Disabled	$	225,000,000,000 (Billion)
F. Damage to Gifted	$	450,000,000,000 (Billion)
G. Damage to General Population IQ	$	600,000,000,000 (Billion)
H. Fluoride Supplements & "Halo" Effect	$	16,000,000,000 (Billion)
I. Damage from Cancer	$	27,000,000,000 (Billion)
J. Damage to the Kidneys	$	4,600,000,000 (Billion)
K. Damage from Cardiovascular Disease	$	64,000,000,000 (Billion
L. Damage from Crime (Range of $288B-$1.2T)	$	288,000,000,000 (Billion)

Congress mandated the FDA CDER to require drug (and food) manufacturers to provide evidence of efficacy and safety, not the victims.

Regardless of whether there is several trillion, billion, million, thousand, or no economic impact of damage, the FDA CDER must take enforcement action and require manufacturers of the drug to make a NDA.

The inescapable fact of fluoridation's so called "proven safety and efficacy" is seriously contested and the FDA CDER is the most competent agency to regulate fluoride when used for the prevention of disease.

Confounding factors in fluoridation research are numerous with many unknowns. One conclusion at the 2001 "NIH Consensus Development Conference on Diagnosis and Management of Dental Caries Throughout Life" found the evidence "incomplete" for all non surgical management methods, with two exceptions with use of fluoride varnishes the evidence was fair.

The preponderance of the evidence of harm, although incomplete, is above the level used by the FDA to regulate caffeinated alcohol beverages.

XIV. FLAWS IN EPA DRA/RSC REPORTS

It has taken 8 years for the NRC and DRA reports and the public has been given a short 90 days to respond. We agree with the urgency. Due to catastrophic harm to the public from excess fluoride ingestion, immediate emergency action on the part of HHS and the EPA is essential. However, appropriate action by the EPA must be taken to protect the public rather than protecting the polutant.

A. The RSC May Not Protect People Drinking More Water than the 90th percentile.

Only protecting to the 90th percentile of the public, in other words, placing the most vulnerable 10% such as infants in harm, makes no sense, is contraindicated and not within the SDWA. Congress did not authorize the EPA or CDC to make a benefit risk analysis for contaminants in water or substances used with the intent to prevent disease.

Considering only dental fluorosis, the RSC summarized "Comparison of the age-specific total estimated exposure for the 90th percentile drinking water consumer to the daily reference dose suggests that some children at ages less than seven years old may be at risk for severe dental fluorosis." RSC (2010) xiii. On page 105 of the RSC report,the graph below is presented.

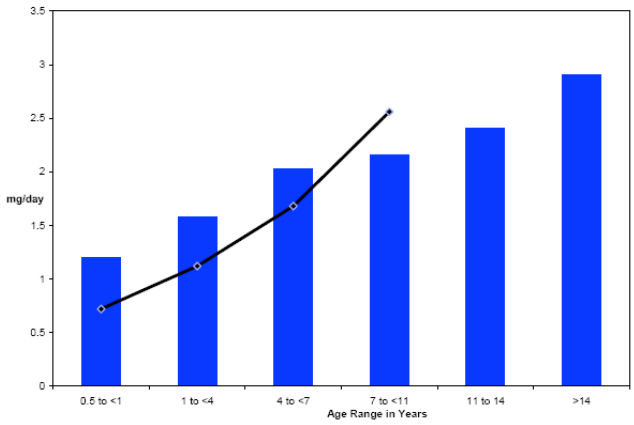

Figure 8-1. Total Daily Fluoride Intake Estimates Relative to the Proposed RfD Using 90th Percentile Drinking Water Intake Data for Consumers Only and the Mean Drinking Water Fluoride Concentration (0.87 mg/L)

Hold the horses, the EPA makes no sense. What Congressional authorization, moral concept, or administrative rule permits the EPA to disregard some children at ages less than seven years old from safety? None. The EPA must correctly determine RfD to be protective of all ages including infants birth to six months which are not even included in this graph. We are not talking about a substance which is hard to remove from water. Most of the harm to infants and children is caused by the CDC's and EPA's and HHS's intentional promotion of the addition of the toxic contaminant to public water. All we have to do is have the CDC, EPA and HHS stop shooting our children in the brain, thyroid, teeth and bodies with fluoride. Please, we are begging, stop promoting the unapproved fluoride drug.

Again on page 4 of the Peer Review of RSC (Comment-Response Summary Report for the Peer Review of the Fluoride: Exposure and Relative Source Contribution Analysis Document), in response to Dr. Fox, the EPA said, *"The absence of discussion of public health implications in Chapter 8 was a deliberate omission because* ***the public health implications extend beyond the purview of the EPA*** *and impact fluoridation guidelines (Centers for Disease Control) as well as the role of the Food and Drug Administration with its oversight of toothpaste, bottled water, and food labeling."*

The EPA clearly admits that the public health implications are beyond the purview of the EPA, but the EPA insists on regulating fluoride with the assumption of efficacy which is outside the purview of the EPA. However, the CDC has no authority to regulate fluoride unless FDA CDER approved.

The EPA is correct that determining the efficacy of fluoride drugs such as toothpaste, bootled fluoridated water and labeling of foods and drugs is outside the purview of the EPA and CDC. The "implications" of efficacy referenced by the EPA is an assumption which does not have FDA CDER approval. Until FDA CDER approval, fluoride is a poison, an illegal drug, and CDC and EPA are assisting in the commission of the crime of pushing an illegal drug.

Peer Review RSC page 6, the EPA's response to Dr. Abbott "that the use of the 90th percentile value for drinking water intake and use of the average body weight were Agency policy" is simply no excuse and without scientific support. Agency policy to abandon 10% of the population might apply to toxins when a safety factor of 10 or 100 times is used. When no safety factor is used, the EPA has no authority to abandon 10% of the public and place them at risk. The SDWA does not permit the EPA from exempting a significant portion of the population. EPA policy is flawed and must be changed or not applied in this situation without a margin of safety. At a minimum, the EPA should recommend a warning for adults not to drink more than for example one liter of public water a day so they do not over dose on fluoride. And a warning should be made for children under 7 years of age not to use public water for drinking. Certainly FDA CDER label approval would have a maximum dosage and a warning label.

B. Determining the Level of Confidence of Risk: The EPA is Mandated to Determine Risk at Which No Adverse Health Effects are "Likely," "Possible," or "Anticipated" AND an Additional "Margin of Safety" is Provided. Instead EPA has Required Those Harmed to Prove "Total Certainty" of Harm.

1. The EPA states, The SDWA "sole" focus is on "possible health risks" and the "no adverse health effects are likely to occur"and an "adequate margin of safety." The overriding force behind the SDWA is safety to protect ALL the public and the EPA is not compliant with the SDWA. However, the EPA fraudulently represents to the Peer Reviewers that it is agency policy that the SDWA applies only to 90% of the public. The Peer Reviewers should have objected to such high handed arbitrary harmful policies.

A margin of safety is essential to account for synergistic effects of other toxins, individual sensitivities, and for what we don't know. If scientists in most developed countries have rejected fluoridation, perhaps HHS and EPA should not be so arrogant as to protect fluoride without any margin of safety. The evidence provided in these comments demonstrate a likely, possible, and anticipated harm to a significant portion of

the public with an RfD of 0.08 mg/kg/bw/day and 0.7 ppm fluoride in public water.

The DRA (2010) report is limited in large part on the NRC (2006) report: "Fluoride in Drinking Water: A Scientific Review of EPA's Standards,"[341] which started out in violation of the SDWA. *"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'."*[342]

The SDWA only requires a "reasonable expectation," of harm or "may have any adverse effect on the health of persons"[343] for the EPA to take action. The EPA restates Congress's mandate to the EPA, *"In 1974, Congress passed the Safe Drinking Water Act. This law requires EPA to determine the level of contaminants in drinking water at which no adverse health effects are likely to occur. These non-enforceable health goals, based solely on possible health risks and exposure over a lifetime with an adequate margin of safety, are called maximum contaminant level goals (MCLG)."*[344]

The EPA has no justification or authority to openly, clearly and directly contradict the SDWA and place 22 million people (the 10% drinking over the 90%) in harm from a MCLG of fluoride in water higher than zero ppm. However, those 22 million are those drinking the most water and do not include those with poor kidney function, genetic sensitivity, or synergistic effects with other chemicals.

The SDWA does not require those being harmed to generate enough scientific evidence to prove with absolute confidence they are being harmed. Confidence of harm only needs to rise to the level of likely or possible to occur and EPA must add an adequate margin of safety. The patient should not have to spend their money to fight their tax supported protection of the fluoride pollutant. The CDC has determined less than 0.02 ppm fluoride serum and some individuals are at 0.02 ppm fluoride serum without fluoridated water. As with arsenic and lead, the MCLG for fluoride must be zero so these individuals do not ingest even more fluoride because of CDC and EPA neglegence.

2. Building on the misdirected NRC (2006) report, the EPA again misdirected the Authors and Peer Reviewers in the current DRA (2010) report and charged them at #12:

> *"Do you support the OW's conclusion that an RfD of 0.07 mg/kg/day will be protective for severe dental fluorosis in children and skeletal effects in adults while still providing for the beneficial effects of fluoride?"*

Hang on there. In chapter 8 the EPA finished saying, ***" the public health implications extend beyond the purview of the EPA"*** and now the EPA asks the Reviewers to ensure the dosage will be ***"still providing for the beneficial effects of***

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[341] Appendix 61 Carton, Fluoride, NRC 2006 report.
[342] Appendix 61 Carton NRC (2006)
[343] Title 42 Chapter 6A Subchapter XII § 300f(B)
[344] http://water.epa.gov/drink/contaminants/basicinformation/fluoride.cfm Accessed 1/24/11

***fluoride*."** Confidence in the EPA OW is lost with double speak. Either the EPA needs to discuss the public health implications and then ask the reviewers whether the level will still provide beneficial effects, or the EPA OW must remove the risk benefit analysis question. The travesty of fluoridation persists because the EPA is not honest with the SDWA. Either the public health implications are outside the purview and benefits are not discussed, or the EPA includes a review of the benefits and asks the question. Assumptions do not protect the public.

The EPA makes no sense and the Peer Reviewers should have shouted, "NO." In one breath the EPA says, that some children at ages less than seven years old may be at risk for severe dental fluorosis" RSC (2010) xiii. And the in the next breath the EPA asks "will the RfD of 0.07 (actually 0.08) be protective? The answer is "NO."

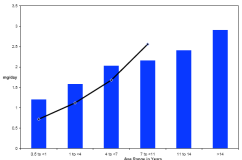

Figure 8-1. Total Daily Fluoride Intake Estimates Relative to the Proposed RfD Using 90th Percentile Drinking Water Intake Data for Consumers Only and the Mean Drinking Water Fluoride Concentration (0.87 mg/L)

The EPA has said the RfD is not protective of severe enamel fluorosis for some children under seven. At least for some children under seven, the OW's conclusion that the RfD is protective is not correct. And it is not protective because the EPA is assuming purview of efficacy.

a. The question should be asked of the FDA CDER, not the OW Reviewers. The Peer Reviewers are not authorized by Congress to make an authoritative response to the question of drug safety for an unapproved drug. In other words, the Peer Reviewers were asked a question outside their jurisdiction. Congress, in the FFDCA, has mandated the FDA CDER to evaluate the beneficial effects of substances used with the intent to prevent disease. Therefore, an assumption that fluoride is beneficial, a benefit risk analysis, is not within the jurisdiction of the EPA or the Peer Reviewers and must be removed from the question. The Peer Reviewers are not the FDA CDER and not authorized to weigh the safety versus efficacy of any drug.

b. OW's conclusion is for an RfD based on unsupported assumptions. The RfD excludes 10% of the public at most risk, excludes fluoride exposure from fluoridated toothpaste, fluoride mouth washes, fluoride dental and medical products. And the RfD assumes only an additional 0.01 mg/kg/day of fluoride from foods will be ingested.

c. The SDWA does not only mandate the EPA to determine whether a level "will be protective," but rather will fluoride at 0.08 mg F/kg/day have a possibility of health risks and include a margin of safety. The EPA and Peer Reviewers have no choice but to answer, "NO" for the 10% excluded by the EPA. The OW is outside the authorization of the SDWA with the wording of their question.

d. By assuming fluoride provides a beneficial effect in the prevention of dental caries, the EPA becomes in effect the formulator and drug regulatory authority of the fluoride drug. And without FDA CDER drug approval, the EPA formulates and regulates an unapproved and therefore illegal drug and the Peer Reviewers must raise objection.

3. Judgment regarding scientific studies should be approached differently by the EPA and FDA CDER. Until the confidence level of scientific research for an existing contaminant reaches the level of possible health risks, the EPA leaves a

substance in the water. In simple terms, “we don’t know what we don’t know and the absence of evidence may not generate action to remove the contaminant.”

4. In contrast, the FFDCA requires the manufacturer of the substance marketed with the intent to prevent disease to provide evidence of efficacy and also safety. In simple terms, the FDA CDER does not permit marketing of a drug until “manufacturers reasonably find out what we don’t know.” Manufacturers of the fluoride drug, such as the EPA, raising and lowering the concentration of fluoride with the intent to prevent disease, have circumvented both the FFDCA and SDWA. Circumventing laws does not protect the public. Until FDA CDER approval, the EPA must remove any reference to “benefit” from their scientific evaluation of fluoride in public water. Until FDA CDER approval, the EPA RfD for fluoride must be the same as lead and arsenic.

5. The CDC is not authorized to determine the efficacy of drugs.

In the case of fluoridation, the patient is hit a triple blow of a nearly impossible burden of proof. First, the EPA/CDC requires the patient to provide the scientific evidence of harm and lack of efficacy rather than the manufacturer. Second, the EPA/CDC requires the patient to provide a confidence level of research to be with absolute certainty (or close). Third, the EPA/CDC requires the patient to prove to the EPA that the CDC has not determined efficacy and prove to the CDC that the EPA has not provided safety.

Costs associated with those three burdens are enormous and pulled from patients who’s money has been spent treating the damage from excess fluoride. The overriding purpose of the FFDCA is to protect patients from charlatans and quacks selling unapproved and illegal drugs - - such as the unapproved fluoridated water drug pushed by the CDC and protected by the EPA.

5. The FDA CDER should (and generally does) require manufacturers of substances used with the intent to prevent disease to provide adequate scientific evidence to ensure safety and efficacy. The FDA also requires the manufacture to monitor adverse effects and change or withdraw the drug if necessary and reporting of adverse effects are part of the regulatory process and should not be ignored. Enforcement laws include liability to the manufacturer. Use of an unapproved drug is sometimes considered assault and battery. The EPA/CDC evade Congresses mandate for FDA CDER approval.

6. The FDA CDER should continue to insist that the patient has reasonable information to make an informed consent and guidance is provided to both the doctor and patient with warning labels and dosages. In part, the informed consent and safety is supported with warning labels and regulation of marketing of the substance to ensure the patient understands that for example, pregnant women, infants, children, those with heart problems, cancer, kidney or other complications and risks do not use the substance and consult with their doctor. The legal intermediary of the doctor is preserved for the protection of the patient with FDA CDER approval; however, protection is absent with fluoridation. When the doctor makes a mistake, that patient is harmed. When an EPA or CDC public health practice mistake is made, millions of patients can be

harmed.[345] The magnitude of harm from public health errors at the Federal level is hard to comprehend and the EPA/CDC have caused trillions of dollars in damage from assuming efficacy and safety of fluoride when ingested with the intent to prevent disease.

7. In the case of fluoride and the DRA, the EPA relies on the CDC and IOM to provide evidence of efficacy. The CDC and IOM do not have authority to approve highly toxic substances, poisons, used as drugs for health related purposes. The EPA must rely on the FDA CDER or specifically state in their web page that the EPA does not determine the safety or efficacy of the addition of fluoride to public water.

C. The DRA (2010) is Confusing and Needs to Provide Clarity with Specificity in What the DRA Covers (Includes) and What the DRA Does Not Cover (Excludes) and the Overriding Basis for the RfD for Fluoride.

The overriding basis for the DRA report is an alleged "therapeutic value in the prevention of dental caries"[346] rather than a level at "which no adverse health effects are likely to occur."[347]

1. The DRA is confusing because the reader expects the EPA to have an overriding principle of safety as required by the SDWA. However, without FDA CDER review of benefit, the EPA has used an assumption of an overriding principle of benefit. The Authors and Peer Reviewers of the DRI must insist a clear statement of the overriding basis of the DRA report is stated to clear up the confusion as to whether the overriding purpose of the DRA report is to protect people or protect the fluoride pollutant.
The DRA page 94 at 5.1

> *"Nutritional Guidelines. Risk assessment for elements such as fluoride with beneficial as well as adverse properties is a challenge, especially when there is a narrow boundary between the doses that are beneficial and those that have adverse effects."*

In Chapter 8, the EPA stated, "***the public health implications extend beyond the purview of the EPA***." Now the EPA is again assuming "beneficial" effects of fluoride which is outside the purview of the EPA. Fluoride is not a food. Foods are not defined by laws as poisons and not restricted by sale to prescription. Bottled water with fluoride added is not FDA CDER approved. The FDA Food section was notified based on fraudulent incomplete evidence. The EPA makes a flawed assumption that there are other elements as toxic as fluoride which are considered nutrients. No food fits within the Federal or state definitions of poison or highly toxic substance. Foods for ingestion are not sold at the pharmacy by prescription only.

Dental decay is not due to a lower concentration of fluoride in that part of the tooth which gets decay or an inadequate fluoride serum level. Due to the controversy and difficulty for the EPA in determining the *"narrow boundary between doses that are theoretically considered beneficial by some and doses which have adverse effects,"* the

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[345] Appendix 75 Holtgrave, Public Health Errors Costing Lives, Millions . . .
[346] DRA (2010) p xiv
[347] http://water.epa.gov/drink/contaminants/basicinformation/fluoride.cfm Accessed 1/24/11

EPA would protect the public by regulating fluoride the same as arsenic and lead (0 MCLG). The IOM and NRC have no jurisdiction over drug regulatory approval and the EPA is flawed to rely on those fine organizations for something they are not authorized to approve and have not adequately determined.

2. The DRA is confusing the public, scientists and health agencies by not clearly explaining the difference between total exposure and the relative contribution of fluoride from water (and some food) used by the EPA and which Agencies have jurisdiction over the various contributions of fluoride to water and total exposure.

3. The DRA report must clearly state congressional authority for fluoridation and the overriding intent of fluoridation. Any assumed efficacy of fluoride is not within the purview or jurisdiction of the EPA and all marketing references of the unapproved drug's assumed efficacy must be removed from the DRA and RSC reports until the substance is approved by the FDA CDER. Sanitizing the fluoride drug as a nutrient is in violation of poison laws. Authors and Peer Reviewers must be instructed to evaluate the safety of fluoride according to the SDWA and without bias of assumed or speculation of therapeutic value unless the FDA CDER approves fluoride for ingestion with label and dosage. The EPA must not stack review committees with dentists who assume efficacy.

4. The SDWA repeatedly requires the EPA to protect the public, the water and prevent contamination.[348] Nothing in the SDWA or Amendments authorizes the SDWA to consider beneficial effects of contaminants or highly toxic substances intended to prevent disease and further to protect the pollutant based on assumptions, and the EPA agrees, "***the public health implications extend beyond the purview of the EPA***." Yet the current (reported 2011) DRA and RSC reports clearly weigh the assumed and speculated incomplete biased opinion of a benefit of decay prevention vs. a limited incomplete scope of adverse effects. The EPA has cherry picked the science of benefits and risks and reviewers only in support of fluoridation for a predetermined result.

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[348] Title 42 Chapter 6A Subchapter XII Safety of Public Water http://water.epa.gov/lawsregs/guidance/sdwa/theme.cfm Accessed 1/24/11 SDWA Amendments
DR. DONAHUE made a presentation August 12, 2003 to the NRC committee on Fluoride in Drinking Water:
"We have a mandate to protect all sensitive populations that we can protect through the drinking water regulations. . . (COMMITTEE MEMBER:) Will you just review the charge for me again here - we're looking at adverse effects of anything added to water other than (DR. DONAHUE:) No, no, no. EPA deals with what is already in the water from other sources. And we tell people that when they exceed the MCL they must treat the water to remove it. It does not involve addition to water. (COMMITTEE MEMBER:) OK. But you are specifically looking at disinfection and disease control. (DR. DONAHUE:) No. That's caveat in the Safe Drinking Water Act. It says the Act for EPA does not deal with the addition of any substance to water except for -and it covers it by disinfection for disease control. (COMMITTEE MEMBER:) And then how do you define disease control insofar as it can be viewed as having an [UNCLEAR] (DR. DONAHUE:) I can't identify that. The Act was done by Congress. That's one sentence in the Act. I didn't give it to you exactly. And I cannot tell you what they had in mind with they wrote that one sentence. But it is one sentence. And I'll be happy to provide you with the one sentence. (COMMITTEE MEMBER:) About the source of [UNCLEAR] . I want to make sure that I understand this. The way the regulations were written it assumes a hundred percent of fluoride intake comes from water, but.. (DR. DONAHUE:) Of that 20 milligrams that was tied to it ... (COMMITTEE MEMBER:) But do you have mechanisms that so if you can decide that, say, fifty percent comes from water, or you have half that number, is that what you're saying? (DR. DONAHUE:) In other regulations, in many other regulations, we have what you call a relative source contribution factor. When the data are from a study that only looked at the amounts in water, you don't find that. So in, otherwise, take the case for barium, the basis for our barium regulation is just based on barium in the drinking water. And it doesn't deal with how much is in the diets for the individuals that were involved. And so we have no relative source on that one either. So fluoride is not alone. . . (COMMITTEE MEMBER:) The current standards are based on the assumption that one hundred percent of the fluoride comes from water? (DR. DONAHUE:) Well, that 20 milligrams per liter was estimated from drinking water -a retrospective trying to get how much it was- that the people who got the crippling skeletal fluorosis were exposed to, and as far as I can tell it was from what was in the water although the records ascribed a small amount of it to food, when it gets into IRA there's a small portion that's ascribed to food. (COMMITTEE MEMBER:) Is this true for the SMCL as well? (DR. DONAHUE:) The SMCL was just based on the drinking water from what I can tell." http://www.fluoridealert.org/pesticides/nrc.aug.2003.epa..html Accessed 1/25/11

D. The Preface of the DRA Report References the NRC (2006) Report includes various endpoints and not just fluorosis and fractures. *"In light of the collected evidence of various health endpoints and total exposure to fluoride, the committee concludes the EPA's MCLG of 4 mg/L should be lowered."*

1. DRA report is confusing because it does not clearly state that the DRA does **NOT** cover all the *"various health endpoints and total exposure to fluoride"*[349] as required by the (NRC 2006 report.) The DRA report should be clear and concise and include the basis for the exclusion of cancer and the other health endpoints listed by the NRC (2006) report. Who will include cancer and when? When will the other health endpoints be reviewed and included for a risk analysis (not a benefit risk, but a risk analysis)? Silence does not protect the public and is not within the jurisdiction of the EPA and does not help the credibility of the EPA or CDC.

2. The DRA Report Executive Summary essentially sets a foundation, an overriding basis of therapeutic value, assuming, *"At low intake levels, fluoride has been shown to have therapeutic value in the prevention of dental caries. . .* .(and further down the page references the IOM for dosage and authority for preventing caries) dose level of 0.05 mg/kg/day which had been recommended as an Adequate Intake (AI) by the Institute of Medicine (IOM, 1997) for "optimal anticaries protection."[350] Those assumptions are ***"beyond the purview of the EPA."***

The DRA is flawed when relying on the IOM for oversight and regulation of highly toxic substances used with the intent to prevent disease and defined by Congress as a drug. And further, the EPA must provide current evidence 0.08 mg/kg/day is safe and does not increase adult blood serum levels above 0.02 ppm recommended by the CDC and 0.01 which includes a minor factor for safety.

The IOM does not determine drug safety or quality and clearly states:

> *"As used in this study, the phrase "drug safety and quality" did not include known risks associated with the medication itself, product purity, or integrity, that are the subject of extensive FDA oversight and regulation through the drug approval process and good manufacturing practice (GMP) regulations and guidance."*[351]

E. The SDWA does Not Appear to Permit the Selection of a Maximum Contaminant Level Goal Excluded Millions From Protection.

1. The DRA would have us believe subpopulations need not be provided a Constitutional right of protection to pursue life.

2. The DRA must clearly state the approximate percentage of the population who will not likely be protected, are likely or possibly to be harmed with a proposed RfD of 0.08 mg F/kg/day. The EPA should provide warnings and cautions for these people to restrict their use of the fluoridated water drug. Eliminating research

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[349] (DRA) Fluoride: Dose-Response Analysis For Non-cancer Effects; Dec 2010 p i.
[350] DRA (2010) p xiv
[351] http://iom.edu/Activities/Quality/MedicationErrors.aspx Accessed 10/16/10

determining fluorosis below 0.05 mg/kg/day and adding another 0.03 mg/kg/day onto that number is not protective. *"Any doses that were less than or equal to the 0.05 mg/kg/day, the EPA eliminated from consideration as the threshold dose for severe dental fluorosis."*[852] Assuming 0.05 mg/kg/day is the threshold, then 0.08 mg/kg/day is above the threshold. The scientific basis for adding more than the determined threshold, places the public in harm and makes no sense.

3. And the DRA must clearly state how 0.05 mg F/kg/day or 0.08 mg F/kg/day would change if an estimated total exposure (ingestion) from all sources is considered. On the scientific level: CDC's NHANES' survey of dental fluorosis in the US found that approximately 3.6% of children have moderate or SEVERE dental fluorosis.[353] This is for the population (of 12-15 year olds) as a WHOLE. While the CDC did not separate out the rates for moderate vs severe, the summary suggests the ratio may be roughly 2 to 1. Therefore, the rate of severe dental fluorosis among 12-15 year olds at 0.8 ppm in public water would reasonably be expected to exceed an estimated 0.5%.

4. Each author and each internal and external Peer Review member must be able to "stake the farm" and assure the public (or remove their name) that the DRA will meet Congress's mandate in the SDWA that for fluoride, the *"maximum contaminant level goal established under this subsection shall 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 SDWA does not exclude infants, children, those with renal disorders, genetic problems or 10% of the population who drink more water than usual.

5. The DRA should determine an estimated range of fluoride concentration in serum, plasma, urine, hair, nails, and other organs and systems of the body which is expected to result from an 0.08 mg F/kg/day RfD from the contribution of water and also from total exposure to fluoride for the various age groups and all consumption levels. Neither the FDA nor CDC have evidence that 0.08 mg F/kg/day RfD will result in serum fluoride levels <0.02 ppm as recommended by the CDC.

Measuring, determining and adjusting fluoride concentration in water without knowing or including known fluoride serum levels and tooth concentration directly places many in harm.

6. The DRA report acknowledges confounding factors such as "diet, climate, altitude and possibly genetics"[354] but does not include these confounding factors in a determination for RfD and is a violation of the SDWA.

F. The RfD Must be Lowered to 0 mg F/kg/day for Infants, 0.002 mg F/kg/day for Children and 0.01 mg F/kg/day for Adults with the MCLG for Fluoride in Public Water the Same as Arsenic and Lead.

1. The EPA's last RfD (NOEL [No Observed Effect Level]: 1 ppm

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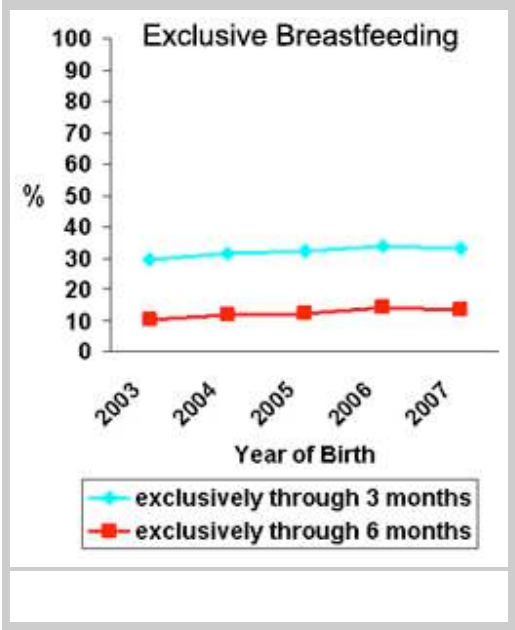
[352] DRA (2010) p xv
[353] (See figure 3 on page 3 at http://www.cdc.gov/nchs/data/databriefs/db53.pdf)
[354] page 97 DRA Report

0.06 mg/kg/day)[355] and the proposed is 0.08 mg/kg/day is for "pitting" fluorosis.

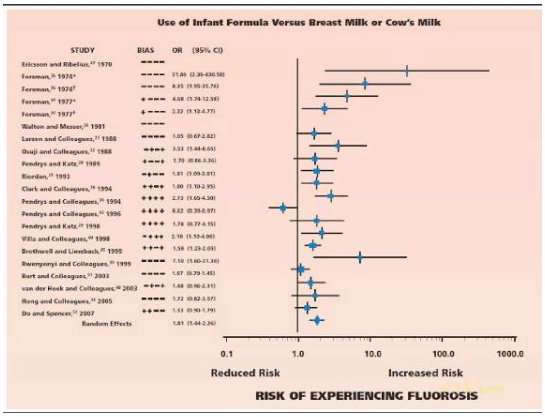
2. In most samples of mother's milk, the fluoride concentration is not detected or is extremely low. Mother's milk at 0 mg/kg/day should be set as the RfD for infants. The RfD must be 0 mg/kg/day unless the EPA has proof mother's milk is flawed and defective or is directed otherwise by the FDA CDER.

3. The CDC reports about 13% of infants are exclusively breast fed through 6 months.[356] Support of fluoride by the CDC and EPA places 87% of infants at risk of excess fluoride ingestion with formula made with fluoridated water.



4. The EPA, DRA, and HHS/CDC must not exclude infants. A warning not to use fluoride for infant drinking or mixing with formula is inadequate and not protective of all infants but a reasonable start.

Hujoel (2009)[357] (graph below) summarizes studies evaluating infant fluoride ingestion and all but one reports infants ingesting too much fluoride and at risk.



[355] http://www.epa.gov/iris/subst/0053.htm Accessed 2/2/2011
[356] http://www.cdc.gov/breastfeeding/data/NIS_data/ Accessed 4 15 11
[357] Appendix 66: Hujoel JADA (2009) http://jada.ada.org/cgi/reprint/140/7/841

3. Levy (2010) concluded, *"Greater fluoride intakes from reconstituted powdered formulas (when participants were aged 3-9 months) and other water-added beverages (when participants were aged 3-9 months) increased fluorosis risk. . . ."*[358]

4. Villa (2010) considered a reasonable concept to evaluate a measured balance of fluoride retention where there is a "neutral" balance between intake and excretion. Homostasis is a reasonable concept and unless HHS/CDC and the EPA determine a scientific requirement for increased fluoride later in life, a neutral balance between intake and excretion should be the normative value for children and adults. "Neutral fluoride balances were predicted when the TDFI (total daily fluoride intake) was equal to approximately 0.07 mg F/day for children and 0.8 mg F/day for adults."[359] Note, the above dosages are total daily dosages not dosages per kg/day.

a. RfD for a child based on "neutral fluoride balance" should be 0.002 mg F/kg/day,[360] (35 kg X 0.002 mg/kg/day = 0.07 mg F/day) and is double the mean concentration of fluoride in mother's milk. In contrast, the EPA has chosen 0.08 mg/kg/day for children which would result in 2.8 mg F/day (35 X 0.08 mg/kg/day) rather than 0.07 mg F/day recommended by Villa (2010).

b. RfD based on "neutral fluoride balance" for an adult should be 0.01 mg F/kg/day. (0.01 mg F/kg/day X 80 kg = 0.8 mg F/day) Any additional fluoride does not have justification that a life time of increasing retention of fluoride is both safe and required for all organs and tissues of the body, even teeth. The EPA is about 6 to 8 times higher than recommended by Villa (2010).

5. The DRA report is confusing. After determining an RfD based on benefit of ingesting fluoride, the DRA proceeds to explain that, *"the primary function of fluoride in drinking water in reducing tooth decay is topical."*[361]

Indeed the EPA in this case is correct. Any benefit from fluoride is topical and ingesting fluoride does not appear to prevent dental decay. However, minimal, if any contact time of water on teeth during drinking with about 0.7 ppm or 1 ppm of fluoride concentration has virtually no topical effect. For topical effect, fluoride toothpaste usually has in excess of 1,000 ppm of fluoride. There is no pharmacokinetic evidence for the topical benefit of fluoridated at 1 ppm topical application for insignificant amounts of contact time during drinking. If fluoride's primary effect is topical, then the EPA and CDC should consider marketing toothpaste. Fluoridated toothpaste is an approved FDA CDER drug, fluoridated water is not. The CDC and EPA could promote swallowing a pea size of toothpaste and freedom of choice would be protected. Of course the FDA warns not to swallow fluoridated toothpaste.

6. EPA based a significant amount of credibility on the historical1942

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[358] Levy S et al, Associations between fluorosis of permanent incisors and fluoride intake from infant formula, other dietary sources and dentifrice during early childhood. JADA 2010; 141(10) 1190-1201.
[359] Appendix 115 Villa A et al, Relationships between Fluoride Intake, Urinary Fluoride Excretion and Fluoride Retention in Children and Adults: An Analysis of Available Data. Caries Res 2010:44:60-68.
[360] 0.07 mg F/day divided by 30 kg = 0.0023 mg F/kg/da
[361] DRA (2010) p 3 quoting Fejerskov et al 1994.

research of Dean. Dean's work is reportedly *"relatively free of confounding factors associated with the widespread use of fluoride-containing consumer products introduced after that time."* It is precisely those confounding factors which make Dean's work incomplete for 2011.

Rather than evading total current exposure, the EPA MUST become inclusive of all fluoride sources. Why? Because state and city health agencies, public water systems and the public assume the EPA is inclusive. If for some reason the EPA determines they cannot be inclusive of all sources of exposure, then the EPA must be very precise in stating exactly what is included and what is not included in the EPA's RfD and MCLG.

Dean's work has minimal value in an historical era without fluoridated toothpastes, fluoride dental products, fluoride medical products, etc. Dean's threshold for severe dental fluorosis at 1.87 mg/L is similar to the total fluoride exposure commonly found in the population today (one to two mg of fluoride from water and almost that much again from foods, toothpastes and other sources). Dean's work is historic, flawed and actual drinking water intakes were not collected and later estimated based on data collected 40 years after Dean's research. And then the EPA (2010) determined exposure to the 95% percentile. Dean's estimate exposure range of 0.04mg/kg/day to 0.19 mg/kg/day of fluoride in 1930-1940 does not include today's new sources of fluoride.

G. For the Safety of the Public, EPA should be Clear on Jurisdiction.

1. In the DRA report, the EPA appears to assume some jurisdiction over the addition of the fluoride as a drug to water.

2. State agencies look to various Federal Agencies such as the FDA, EPA, and/or CDC to determine the safety of total fluoride exposure. Examples:

a. The Washington Board of Pharmacy explains that fluoride is exempt from poison laws when used with the intent to prevent disease and is a prescription drug regulated as a legend drug under Federal laws.[362] The FDA CDER regulates drugs, not the HHS, EPA or CDC.

b. The Washington State Board of Health (WBOH) states: *"For standards regarding the safety of drinking water, the Board relies predominantly on the U.S. Environmental Protection Agency (EPA). For setting the allowable concentration range for fluoride when a water district's board of commissioners chooses to artificially fluoridate its water under RCW 57.08.012, it relies also on guidance from the Centers for Disease Control and Prevention (CDC).*[363]

WBOH is jurisdictionally correct in relying on the EPA to determine when naturally occurring fluoride concentration is too high. However, the EPA is prohibited from adding contaminants and must not base safety on assumed efficacy.

c. And again, the WBOH states,*"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."*[364] However, neither the CDC nor the EPA have jurisdiction in determining the efficacy, safety, formulation of drugs or drug

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[362] Appendix 6 WA State Board of Pharmacy.
[363] Appendix 61 WA BOH Denial to Reduce Concentration
[364] Appendix 63 WA BOH Denial to state Intent of fluoridation

legend. The FFDCA gave the FDA CDER jurisdiction over substances used with the intent to prevent disease and both the CDC and EPA need to be concise and clear up the confusion of jurisdiction.

3. HHS must provide the list of scientific reports, evidence based analysis and studies HHS used to determine that a decrease in the fluoride drug concentration in water was needed and that the safety and efficacy of the fluoridated water drug is approved. The references provided are incomplete.

H. For the Safety of The Public, The DRA Report Should Clearly State What is Not Included In The DRA Report So Local Governments Understand What Aspects of Fluoridation They Must Regulate. In Effect and without scientific support, the DRA doubled the RfD for fluoride.

1. The Authors and Peer Reviewers should clearly state that the NRC 2006 committee raised concerns about other risks which are not covered in the DRA report, such as other possible dental effects, musculoskeletal effects, reproductive and developmental effects, neurotoxicity and neurobehavioral effects, effects on the endocrine system, effects on the gastrointestinal, renal, hepatic, and immune systems, genotoxicity and carcinogenicity. (All listed in the NRC 2006 Report) The DRA must clearly give a cut off date for research included under review.

2. The DRA must address why fluoridated dentifrice, fluoride medical and dental products, fluoride mouth washes, fluoride chewing gum and other fluoride sources are not included in the RfD. *"The combination of the drinking water and dietary estimates thus became the basis for the OW inorganic fluoride Reference Dose (RfD) estimate of 0.08 mg F/kg/day."*[365] Clearly total exposure, total dosage, total ingestion is not included in the EPA's RfD. In section VIII we present NRC (2006) evidence the DRA includes only about a quarter of the non-water fluoride exposure. In effect, the DRA RfD is about 0.1 mg F/kg/day.

3. The DRA must address an appropriate label. All drugs, substances used with the intent to prevent disease, are required by the FDA CDER to provide a label to ensure informed consent. No "label" was suggested by EPA or reviewers as warning or caution for pregnant mothers to protect their fetus or infants ingesting formula made with water containing fluoride. Children drinking more than one glass of water a day, chemically sensitive individuals, those with renal insufficiencies, swallowing fluoridated toothpaste, taking fluoride medications, inadequate iodine intake, renal insufficiency or drinking over the 90th percentile of water need cautions.

4. The DRA report must clearly state that the EPA is not authorized to approve the addition of any drug or substance to water added with the intent to prevent disease and the FDA CDER should be contacted for further advice.

5. The DRA report must clearly state that the lethal dose or toxicity of fluoride is not considered, or the DRA report should include such evaluation of research.

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[365] DRA (2010) ii

6. The DRA report must clearly state that in vitro studies of safety and toxicity are not considered and such studies should be reviewed at the local level.

7. The DRA report must clearly state that local and federal laws relating to highly toxic substances, poisons, and state laws requlating poisons are not considered.

8. The DRA report must clearly state that animal studies of toxicity and safety have not been considered.

9. The DRA report must include an evaluation for higher risk subgroups based on race. Martinez-Mier (2010)[366] compared White and African American 7-14 year old children, dental fluorosis, water, urine and saliva fluoride content. *"Fluoride concentration of water and saliva was not different for the two groups; however, the fluoride content in urine was significantly higher in African Americans than in Whites [P < 0.05; 1.40 +/- standard deviation (SD) 0.65 ppm versus 1.08 +/- SD 0.28 ppm]."*[367]

10. The DRA must state that the EPA does not evaluate the effect of fluoride on antioxidative enzymes and dental fluorosis *"Excessive fluoride ingestion has been identified as a risk factor for fluorosis and oxidative stress. . . Caspase 8, caspase 3, Bax, Bid increase expression and more TUNEL positive cells in both experimental groups than control, suggest that apoptosis induced by fluoride is related to oxidative stress due to reduction of the enzymatic antioxidant."*[368]

11. The DRA report fails to include more specific studies covering the relationship between dental fluorosis and serum, plasma, urine, hair, nail and other physiological systems and tissues. The DRA report needs to return to the scientific studies and evaluate studies measuring fluoride concentrations in the body with all end points.

12. The DRA failed to make a clear distinction between the contaminant fluoride as regulated by the EPA and artificial fluoridation added as a drug with the intent to prevent disease. The EPA regulates determining when to remove the naturally occurring fluoride contaminant and the FDA CDER regulates the artificially fluoridated water drug when manufactured with the intent to prevent disease.

13. Consideration was not made whether other nutrient intakes may limit the harm measured in prevalence of dental and skeletal fluorosis and fractures and not limit the harm from other diseases such as increased tooth fractures, neurological, endocrine, or kidney risks.

14. The synergistic effects of other toxicants was not included and a

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[366] Appendix 219 Martinez-Mier 2010

[367] Martinez-Mier EA, Soto-Rojas AE. Differences in exposure and biological markers of fluoride among White and African American children. J Public Health Dent. 2010 Summer 70(3):234-40. Appendix 219

[368] Jacinto-Alemán LF, Hernández-Guerrero JC, Trejo-Solís C, Jiménez-Farfán MD, Fernández-Presas AM. n vitro effect of sodium fluoride on antioxidative enzymes and apoptosis during murine odontogenesis. J Oral Pathol Med. 2010 Oct;39(9):709-14. doi: 10.1111/j.1600-0714.2010.00918.x. Epub 2010 Aug 3.

margin of safety was not included in the DRA.

15. The DRA must address concerns that studies used to determine RfD did not fully include:

a. At least one Randomized Controlled Trial
b. Socioeconomic status was usually not controlled
c. Adequate study 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

I. Toxicology versus Pharmacology, A Paradigm Shift: Determining Whether a Substance is Safe to Treat People is More Protective than Determining Whether a Substance is Harmful Enough to Be Removed From Water.

1. The DRA report must clearly state that the EPA determined health effects based on the need to remove excess fluoride from water rather than to a much stricter approach of determining safety as required by the FDA CDER.

2. The DRA report must clearly explain why the EPA relies on the IOM 1997 report (Institute of Medicine) for determining the efficacy of fluoride for the prevention of dental caries rather than to the FDA CDER (Food and Drug Administration Center for Drug Evaluation and Research) who is mandated to regulate fluoride when used with the intent to prevent disease. In other words, EPA must provide the authority Congress has given the IOM to determine the efficacy and safety of listed drugs, specifically fluoride used with the intent to prevent disease, and provide evidence the IOM accepts jurisdiction and authority over determining the efficacy, safety and/or dosage of fluoride.

J. The DRA States: *"This document provides a detailed review of available dose-response data from published and peer-reviewed studies for the following endpoints as they relate to fluoride exposure from drinking water: Dental fluorosis, Skeletal fluorosis, Skeletal fractures."*[369]

1. The DRA report, especially the title, should be clearer and more specific as to what the report does and does not include. For example, cancer is an endpoint which must be included, but at least the DRA title is clear and concise when it states, "Non-cancer Effects." The DRA should clearly state that it does not include other possible endpoints. The DRA title should be changed to read:

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[369] DRA (2010) p i.

2. To protect the public, the PREFACE should clearly state that the RfD "Dose" does or does not include the relative contribution of fluoride from fluoride toothpastes, fluoride mouthwashes, fluoride pesticides, fluoride from air or dirt, fluoride dental or medical products, or fluoride drugs, etc. In other words, is the RfD inclusive of all fluoride exposure for all people? Apparently the EPA only protects up to the 95th percentile. The EPA must advise states of a more protective RfD which would protect to the 99th percentile and then the ultimate RfD which would be protective of all. In other words, what if the Constitution of the US applied to everyone? What would the ultimate RfD be?

3. The IOM report of 0.05 mg/kg/day refers to total fluoride exposure rather than the relative contribution of fluoride from water. Therefore, we can reasonably assume the IOM was referring to total exposure of all the substances under review and was not limited to water and a relative contribution of pesticides to some food. The DRA must stick either with total exposure from all sources or relative exposure from water. The DRA is flawed to take a total exposure and assume the relative exposure of water is the total exposure. For example, IOM suggests total exposure of 0.05 from all sources and in contrast DRA suggests 0.07 is safe for water with an additional 0.01 from (pesticides' contribution to) food and fails to include other sources.

4. The EPA protected fluoride at 0.05 mg/kg/day and then arbitrarily added 0.02 mg F/kg/day. The EPA chose 0.07 mg F/kg/day dose from water and another 0.01 mg/kg/day from food for a total Reference Dose (RfD) of 0.08 mg F/kg/day. What about toothpaste? The RfD is not based on possible risk of harm or safety but *"a reasonable difference in exposure (0.02 mg/kg/day) between it and the IOM (1997) AI of 0.05 mg/kg/day . . . The dietary contribution of 0.01 mg/kg/day was added."*[370] No evidence for the basis of 0.02 mg/kg/day or 25% "reasonable difference" is understood. A margin of safety would decrease the RfD, not increase the RfD. The EPA does not explain whether the difference is between "toxicological and pharmacological" evaluations, IOM and EPA evaluations, efficacy and safety, or the difference between the IOM and what some are experiencing. Protecting the public does not appear to be as important as protecting the policy. If a careful review of the studies is made, the DRA appears to be protecting the pollutant rather than the public.

5. The DRA estimate of dietary fluoride contribution of 0.01 mg F/kg/day is not supported by Maguire (2007)[371] who reported mean 0.031 mg/kg bw/day, 0.038 mg/kg bw/day and 0.047 mg/kg bw/day for 6 to 7 year old children and found,

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[370] DRA (2010) p xv See also DRA (2010) page 101 and evidence disqualified.
[371] Appendix 64 Maguire A, et al. Fluoride intake and urinary excretion in 6 to 7 year old children living in optimally, sub-optimally and non-fluoridated areas. Community Dent Oral Epidemiol. 2007 Dec;35(6):479-88.

"Fluoride retention was not correlated with the fluoride concentration of home water supply, but was strongly positively correlated (P < 0.001) with total daily fluoride intake."

6. The DRA must address the concerns of fluoride's action on protein. *"The mechanisms by which excessive fluoride modifies tooth development are not fully understood, but it appears that alterations in protein metabolism disrupt crystal organization in the developing tooth."*[372] Specifically, if fluoride alters protein metabolism for the crystal organization in the developing tooth, then the EPA must explain why fluoride is unable to alter the protein metabolism in brain, kidneys, thyroid, and other tissues at the same concentrations?

7. The DRA report must ensure powdered infant formula reconstituted with fluoridated water does not exceed the fluoride intake of infants on mother's milk. Mother's milk is ideal for infants and more than half of mother's milk tested contains no detectable fluoride. If infants are not a subgroup the EPA DRA are able or willing to protect, the DRA report must clearly state the risk to this subgroup and provide a caution or warning on the fluoridated label or water bill that the water should not be used to reconstitute infant formula. If a notice or warning to protect infants is not within the jurisdiction of the EPA, the DRA report should clearly state the agency under who's authority the protection of infants from excess fluoride in public water stands.

Levy (2010) reported the median fluoride intake of infants 3-9 months on formula made with fluoridated water was 0.440 milligrams per day, no actual measurements of the children's serum, plasma, urine, hair or nail fluoride content is provided. A 5 kg infant would ingest 0.088 mg/kg/day, above the DRA RfD of 0.08 mg/kg/day. All 5 kg children above the median intake would be above the RfD and no margin of safety is provided. In other words, more than half of all children will not be protected by the EPA's proposed RfD. The EPA must clearly state that it does not protect infants and provide Congressional justification for abandoning infants.

K. Dental Fluorosis is a Disease and a Sign of Fluoride Toxicity and Effect on Antioxidative Enzymes and Apoptosis.

1. The EPA (2010) report reviewed only one aspect of dental-skeletal fluorosis, a sign of chronic fluoride poisoning and fractured bones. The EPA then made a damage analysis and determined dental fluorosis is a cosmetic problem. For example, if the EPA found a high rate of obesity in a community and only looked at the immediate obesity problem, the EPA could rightly determine that obesity is simply a cosmetic problem. However, obesity is a clinical sign of a higher risk for diabetes, stroke, and other medical problems. Significant research finds the clinical sign of excess fluoride exposure (dental fluorosis) is an indication that the person has ingested too much fluoride and has other health harm.

b. Tang: *"Children who live in a fluorosis area have five times higher odds of developing low IQ than those who live in a nonfluorosis area or a slight fluorosis area."*[373]

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[372] Levy S et al, Associations between fluorosis of permanent incisors and fluoride intake from infant formula, other dietary sources and dentifrice during early childhood. JADA 2010; 141(10) 1190-1201.

[373] Appendix 42 Tang QQ, DuJ, Ma HH, Jiang SJ, Zhou XJ, Fluoride and children's intelligence: a meta-analysis, Biol Trace Elem Res. 2008 Winter: 126(1-3):115-20

c. Li found, *"The development of intelligence appeared to be adversely affected by fluoride in the areas with a medium or severe prevalence of fluorosis. A high fluoride intake was associated with a lower intelligence."* SOURCE: Li XS. (1995). Effect of Fluoride Exposure on Intelligence in Children. Fluoride 28:189-192

d. Dental fluorosis, excessive fluoride intake since early childhood indicates reduced mental work capacity. The EPA needs to acknowledge the research and refute it or explain why mental capacity is not important.

2. We agree with the DRA report that excess fluoride ingestion can possibly result in problems which include, *"enamel defects ranging from barely discernable markings to brown stains and surface pitting."*[374] Dental fluorosis is a sign of past protein disruption during the development of the tooth, fluoride toxicity for those cells. Because fluoride disrupts protein in the developing tooth, it is reasonable to consider the disruption of fluoride at the same concentration in other tissues, such as brain (IQ loss), thyroid (hypothyroidisum), kidney, liver, heart (CVD), red blood cells (Alzheimvers), etc.

3. There is no logical or scientific evidence that systemic fluoride only affects the protein of the teeth during development. Dental fluorosis is not only a "cosmetic" sign of excess fluoride ingestion for the teeth but also a sign of possible and likely cosmetic damage, possible tooth damage (increased dental decay and increased dental fractures), neurological damage (lower IQ and increased mental retardation), endocrine damage (increased obesity and diabetes), cancer, skeletal damage, skeletal fractures and other possible medical harm to all protein and all cells. Dental fluorosis is a sign of other likely harm and the DRA must include these endpoints.

4. The NRC 2006 report provided evidence that fluoride at 0.08 mg/kg/day *"may have any adverse effect on the health of persons."*[375] Studies since 2006 must be included and cancer must not be taken off the table.

5. The DRA dose-response analysis without measuring the fluoride concentration in blood, serum, plasma, hair, nails, pineal gland, brain, kidney tissue and all other tissues is incomplete and crude. The DRA report failed to consider direct measured fluoride concentrations of body parts and fluids and failed to determine "normal" concentrations for each fluoride and tissue. To understand dental fluorosis, the concentration of fluoride in serum, urine, hair and nails of cohorts must be included in studies and dental fluorosis compared to actual measurements of the cohorts.

6. Urine fluoride concentration is also an acceptable measurement assessment.[376] Rathee[377] provides the graph below comparing urinary stones, urine and serum of stone formers compared to those without symptoms. Both HHS and EPA must

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[374] DRA (2010) p xiv
[375] Title 42 Chapter 6A Subchapter XII § 300f(B)

[376] http://www.cdc.gov/niosh/docs/2003-154/pdfs/8308.pdf Accessed 2/3/2011
[377] http://medind.nic.in/iaf/t04/i2/iaft04i2p100.pdf Accessed 2/3/2011

report and determine a no adverse urine fluoride concentration, or require manufacturers of fluoride drugs to provide the evidence.

Table 1. Fluoride content in urinary stones, urine and serum of stone formers compared to normal

Type	Urine (mg/l)	Serum (mg/l)	Drinking water (mg/l)	Urinary Stone (mg/g)
N (25)	1.04±0.043	0.025±0.001	0.89±0.01	-
S.F. (100)	1.88±001 p < 0.001	1.12±005 p < 0.01	2.3±0.01 p < 0.05	0.5±0.001

Data are Mean ± S.E.
p<0.001 - highly significant
p<0.01 - definitely significant
p<0.05 - probably significant

Correlation coefficient (r) for fluoride content between

Urine and stone (r=0.88)
Urine and serum (r=0.54)
Serum and stone (r=0.6213)
Drinking Water and stone (r=0.846)
Urine and water (r=0.831)
Serum and water (r=0.505)

Indian Journal of Clinical Biochemistry, 2004 101

L. Protection and Safety versus Policy.

The EPA's December 2010 DRA report, "Fluoride: Dose-Response Analysis For Non-cancer Effects" is a violation of the SDWA, FFDCA, Reasonable Scientific Judgment, Scientific Evidence, Ethics, and Common Sense. The Report Must Be Rejected and Reviewed in Light of Laws and Current Research and Inclusive of Stakeholders Based on Correct Direction (Charge) to Committees.

2. The Title, "Fluoride: Dose-Response Analysis For Non-cancer Effects" (EPA 2010) is misleading and the EPA (2010) report must be rejected based on the fact that the report is not a dose-response analysis for non-cancer effects. There are more non-cancer effects of fluoride than just dental/skeletal fluorosis and fractured bones. The title claims far more than the report provides.

3. The Peer Reviewers for dental fluorosis consisted of one Epidemiologist and three Dentists. Clearly the EPA cherry picked dentists to peer review these reports to ensure a bias of effectiveness was included. The lack of Toxicologists, Pharmacologists, Neurologists, Physicians, Psychologists, Special Education Teachers, and Parents of the mentally retarded is of grave concern. For example, Dentists do not diagnose brain damage or lower IQ. Ask a parent of a mentally retarded child if they would trade half a filling for 8 IQ points?

Even with the biased limited evidence used by the EPA, more than half of infants are at risk of excess fluoride exposure. For example, water consumption dose rates for children ranged from 0.04 mg/kg/day to 0.19 mg/kg/day, significantly higher than 0.05-0.08 mg/kg/day proposed by the EPA.

Without a margin of safety and inclusion of all sources of fluoride, policy is not in keeping with the SDWA to protect everyone. The public is demanding protection from forced mass medication of an illegal drug without individual consent.

M. EPA's Selection of Authors and Peer Reviewers was Biased

The authors, internal and external reviewers were not representative of stakeholders and were skewed towards those supporting the assumption of efficacy. For example, dental fluorosis is generally considered a cosmetic effect; however, no cosmetic dentists were included. Dental fluorosis is a sign of other pathologies outside the oral cavity and reviewers do not appear to have a background in endocrinology, pharmacology, law, nephrology, neurology, and are perhaps unfamiliar with human subject research ethics. Scientists and stakeholders who have concerns the scientific evidence for efficacy and safety is inadequate were not represented. Bias of authors and reviewers started from the position of assumed efficacy and safety rather than approaching the science from a position assuming harm and lack of efficacy and requiring the science to prove safety as would be required of a drug evaluation.

"The Responsibility for proving a drug's harm is not on the Patients, Consumers, or Victims. Rather, the proof of efficacy and safety is on the manufacturer."

N. The Lack of Mutagenic Consideration is a Violation of EPA Cancer Guidelines

1. The EPA's Guidelines for Developmental Toxicity Risk Assessment[378] (GDTRA) suggests 70% of children born with developmental defects, 70% are from unknown causes or combination of causes. Of particular concern is the lowering of IQ throughout the entire population which except for the lowest IQ would not be included in the developmental defects.

The EPA GDTRA (p. 1) states, *"First, it is assumed that an agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans following sufficient exposure during development."* Appendix 87 provides ample evidence fluoride produces an adverse developmental effect.

The EPA GDTRA (p. 2) states, *"It is assumed that all of the four manifestations of developmental toxicity (death, structural abnormalities, growth alterations, and functional deficits) are of concern. . . Thus, a biologically significant increase in any of the four manifestations is considered indicative of an agent's potential for disrupting development and producing a developmental hazard."* Appendix 87 provides both animal and human evidence of biologically significant increase in developmental hazard from fluoride ingestion. The EPA assumes the most appropriate species to estimate human risk is human. These comments provide human studies of human risk. The NRC (2006) called for additional studies, which have been done and the EPA should include the additional studies.

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[378] http://www.epa.gov/raf/publications/pdfs/DEVTOX.PDF Accessed 4/16/11

The EPA has not disputed fluoride is a developmental toxicity risk, they simply fail to include all infants and fetuses in the reports.

Of the four major manifestations of developmental toxicity, death, structural abnormality, altered growth, and functional deficit, all four are caused by fluoride exposure. Unless a toxic spill or unusual dosage, seldom do people die from acute fluoride toxicity.

2. EPA Cancer Guidelines[379]

[379] Appendix 120

XV. PERMITTING (EPA) VS PREVENTING (FDA CDER)

The EPA PERMITS a contaminant until science demonstrates "proof" of harm. The FDA CDER PREVENTS a drug from going to market until science demonstrates "proof" of efficacy and safety. The difference in starting points is substantial, material and requires a different level of confidence from the science. The EPA Toxicologists are not Pharmacologists and the CDC should not consider their Toxicologists to have determined safety to the level of Pharmacologists. No Pharmacologist appears to be listed as author or reviewer of any of these reports.

For example, the EPA considers water safe until scientific evidence rises to the level of confidence to "prove" the contaminant, such as naturally occurring fluoride, is harmful. The EPA appropriately requires "proof" of harm. In contrast, the FDA CDER and Pharmacologists should consider a contaminant (proposed drug such as fluoride) is harmful until the manufacturer provides adequate science to "prove" the contaminant (proposed drug) is safe and has an approved label. The FDA CDER requires "proof" of efficacy and safety. The EPA should not be a sham drug approval agency and the FDA CDER should not wait for proof of harm or a popular uprising to regulate the use of fluoride with the intent to prevent disease, as a drug. Therefore, the EPA must include specific disclaimers. For example wording could include, "An evaluation of fluoride's efficacy was and has not been determined by the EPA and artificial fluoridation is not under the jurisdiction of the EPA. Recommendations of removing the contaminant should not be construed to indicate any safety or recommendation for the manufacturing of the artificially fluoridated water."

Before any laws or science are considered and in order to weigh the scientific evidence, the above concept must be firmly rooted as a cornerstone in the mind of the HHS, CDC, FDA, and EPA and clearly delineated in the reports. Flawed conclusions will be made and the intent of the SDWA violated if the level of confidence of "proof" of harm has to rise to the level of absolute confidence. Proof of harm is still debated for tobacco products. Proof of harm is very difficult. In contrast, proof of safety by the manufacturer must be provided to the FDA CDER before artificial fluoridation is started. After all, fluoride is the only mass medicated drug without consent and the level of confidence of both safety and efficacy must at least meet or even exceed FDA CDER New Drug Application criteria. The EPA reports are not clear whether the EPA is considering only naturally occurring fluoride or also the addition of fluoride to water with the intent to prevent disease, artificially fluoridated water.

We, the patients, demand protection under the FFDCA and SDWA that the FDA CDER prevent the marketing of fluoride in all forms until the manufacturers provide proof of safety and efficacy and approved by the FDA CDER. We do not give our consent to be fluoridated or medicated without our consent.

We also request the EPA take enforcement action against states who have contracted to uphold the SDWA which forbids the addition of substances intended to prevent disease other than the disinfection of water.

The laws and scientific evidence presented here must be judged not from the paradigm of "does this constitute enough evidence to stop fluoridation" but rather "does the evidence from both sides of this controversy rise to the level to start fluoridation." There are no randomized controlled trials of fluoridation. The evidence for efficacy is historical, limited to subpopulations, and contains serious flaws. The empirical evidence

of safety is lacking. Absence of evidence may not cause EPA action, but absence of evidence is not proof of safety for the FDA CDER.

Public health professionals should be charged with crimes against humanity and present their defense before judges when they violate Congress's mandate for FDA CDER drug approval, International Conventions on Human Subject Research[380] and force us to ingest an unapproved drug when we are shouting our refusal as loud as we can.

[380] "Human subjects asked to contribute their time and effort to research should consent to do so freely. The consent should be given only after the subject understands what he or she is consenting to, and any risks that may be involved. Subjects should be assured that there will be no penalties for declining to participate, and that they are free to withdraw from the research at any time after they have given their initial consent." University of Washington http://www.washington.edu/research/hsd/hsdman4.html

XVI. MAJOR SOURCES OF FLUORIDE EXPOSURE P 49 NRC 2006

A. The CDC in one place reports the incidence of dental fluorosis has increased from 22 to 32% in children[381] and more recently suggested approximately 41% of adolescents aged 12 to 15 and 36% aged 16 to 19 years had enamel fluorosis. Moderate and severe fluorosis was observed in less than 4% in both age groups.[382] "On a per-body-weight basis, infants and young children have approximately three to four times greater exposure than do adults,"[383] a significant sign many are ingesting too much fluoride.

B. NO practical method of removing fluoride from water is available to households, placing everyone at risk. Neither boiling nor home water filters remove fluoride. Bottled water is not labeled for fluoride content, and all contain some fluoride with some exceeding EPA MCL (maximum contaminant level) limits even for adults.

C. The lowest socioeconomic group in fluoridated communities suffer the greatest financial burden as well as the greatest barriers to purchasing, supplying, or transporting non-fluoridated water. In practical terms this represents an unreasonable requirement for low income parents without a car, using public transportation or walking, carrying babies, groceries, and now adding bottled water.

Based on Table 2-9, the NRC estimates the average person ingests from non-water inorganic sources: a 10 Kg child averages 0.39 mg., a 20 Kg child 0.68 mg., a 70 kg adult about 1 mg. In contrast, the DRA uses 0.01 mg F/kg/day for food, about 25% the non-water NRC estimate.

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[381] http://www.cdc.gov/fluoridation/safety/infant_formula.htm

[382] ***Prevalence of Enamel Fluorosis Among 12-19 Year-Olds, U.S., 1999-2004***
http://iadr.confex.com:80/iadr/2007orleans/techprogram/abstract_92598.htm
Table below presents percentages (standard errors) and prevalence of fluorosis, including very mild or higher severity.

Cycle:	1999-2000		2001-2002		2003-2004		1999-2004	
Age:	12-15	16-19	12-15	16-19	12-15	16-19	12-15	16-19
Unaffected & questionable	60.63 (4.66)	66.25 (4.32)	65.95 (3.18)	70.57 (3.33)	51.58 (3.78)	55.10 (4.59)	60.12 (2.28)	64.55 (2.40)
Very Mild	26.17 (2.99)	21.16 (2.94)	24.82 (2.62)	20.63 (2.32)	34.58 (2.65)	31.96 (3.75)	27.98 (1.61)	24.10 (1.76)
Mild	8.67 (1.49)	6.98 (0.84)	6.57 (1.14)	6.47 (1.05)	10.31 (1.57)	9.67 (0.88)	8.34 (0.81)	7.58 (0.53)
Moderate & severe	4.53 (1.22)	5.61 (1.44)	2.66 (0.40)	2.33 (0.61)	3.52 (0.85)	3.27 (0.94)	3.56 (0.51)	3.78 (0.64)
Prevalence	39.37 (4.66)	33.75 (4.32)	34.05 (3.18)	29.43 (3.33)	48.42 (3.78)	44.90 (4.59)	40.60 (2.23)	36.29 (2.45)

[383] ." NRC 2006 Summary p. 4

XVII. NRC (2006) RECOMMENDED EPA's MCLG IS NOT PROTECTIVE.

The NRC (2006) recommended the EPA should:

- *"Apply current approaches for quantifying dose-response where feasible,*
- *Consider susceptible populations,*
- *Characterize uncertainties and variability, and*
- *Provide better estimates of total exposure for individuals."*

The EPA DRA has failed all four EPA NRC (2006) recommendations. The EPA failed to include current approaches for quantifying dose-response such as urine, serum, plasma, milk, spinal fluid, lymph, or any other tissue fluide fluoride measurements.

"EPA identified a point of departure (POD) of 1.87 mg F/L for severe dental fluorosis based on benchmark dose modeling of theprevalence for severe dental fluorosis associated with specific drinking water fluoride concentrations as reported by Dean (1942)." (DRA 2010)

The NRC (2006) told the EPA to use "current approaches" and the EPA's opinion of "current" is seven decades old. The EPA failed. Data seven decades old is not current. The EPA's so called "current" literature is older than employees at the EPA.

Dean's (1942) evidence indicating 1.87 mg F/L POD is historic prior to the use of fluoridated toothpastes and many other sources of fluoride and did not take into consideration the fluoride concentration of mother's milk or other body fluids and tissues. Dean (1942) did not include "susceptible populations" such as fetuses and infants. The majority of infants receive all or some of their nutrients from formula.

The EPA relied on the IOM (1997) 0.05 mg/kg/day AI and "Any doses that were less than or equal to the 0.05 mg/kg/day were eliminated from consideration as the threshold dose for severe dental fluorosis." (DRA xv)

The EPA has no jurisdiction to evade evidence based on an assumption the IOM has authority to approve drugs. The FDA CDER approves drugs and the EPA is to determine risks of contaminants not defer to other non-drug regulatory agencies for drug approval.

The HHS/CDC have found 1ppm fluoridation is too high and lowered that to 0.7 ppm. Just on that evidence alone, the EPA's MCL must be 0.7 ppm and based on other sources of fluoride exposure, serum, urine, pineal gland, and tooth fluoride concentrations the MCLG must be set at 0.0 ppm the same as lead and arsenic.

The EPA uses Hong (2006a) to suggest less than 0.06 mg/kg/day fluoride did not cause severe dental fluorosis and then increases that level by a third as a "reasonable difference of exposure."

The EPA references the WHO for increased bone fracture of greater than 14 mg/day of fluoride.[384] However, WHO has no official position on artificial water but recommends lowering the fluoride concentration of water when intake of fluoride exceeds 6 mg/day.[385] An 80 kg adult ingesting 0.08 mg/kg/day would ingest 6.4 mg/day of fluoride. Therefore, the OW proposed RfD of 0.08 mg/kg/day is not consistent with either the NRC (2006) report or WHO benchmarks.

Cherry picking evidence to support fluoridation is not the intent of the Safe Drinking Water Act.

[384] DRA p xv
[385] Appendix 74

XVIII. PUBLIC CONFIDENCE IN THE FDA IS AT STAKE

A. The FDA, EPA and CDC scientists would be wise to consider the EPA scientists quotation of ethics (Appendix DD),

"The first rule set forth by the Code of Ethics for Government Service is that Government employees should
I. Put loyalty to the highest moral principles and to country above loyalty to persons, party, or Government department."

B. Congress and State Laws Defined Drugs and Fluoridaton is a Drug.

C. Congress has Mandated the FDA CDER to Regulate Drugs.

1. Hundreds, perhaps thousands of scientific studies on fluoride confirm fluoride is hazardous, a poison and can cause harm even in small amounts, especially to subpopulations.
2. Most developed countries provide their citizens with freedom and do not fluoridate public water.
3. In more than half of referendums held on fluoridation the public has voted against fluoridation, in itself a statement that they do not trust the drug regulatory oversight by the FDA CDER nor the false assurances of the EPA and CDC.
4. There is substantial evidence that fluoridation exacts a heavy economic toll.
5. The lack of drug regulatory oversight by the FDA CDER is of greater negative impact on the health and economy than any other drug. Even if fluoridation were stopped tomorrow, the damage will continue for at least a generation. However, the sooner we begin, the sooner the damage will end.
6. A highly qualified task force in Fairbanks Alaska just completed a review of fluoridation and recommends to the City to no longer fluoridate public water. Their conclusions in Appendix 106 are worth consideration by the FDA CDER, EPA, and CDC.

D. The Public has a Right to Doubt the Logic and Even the Ethics of the Scientific Establishment (you and me) with the Haphazard Regulation of the Illegal Fluoride Drug:

1. Exempt from poison laws if regulated as a drug, but CDC and EPA ignore drug laws and call fluoride a food which is not exempt from poison laws.
2. Mostly undetected in mother's milk (Appendix FF, EE, S) but no warning for infant formula made with high fluoride containing water.
3. Defined as a prescription drug, (WA Board of Pharmacy) but CDC and EPA act as though drug laws do not apply to them and persist in being the biggest illegal drug pushers in the USA.
4. Marketed for ingestion as a supplement without FDA approval in 3.75 mg capsules and tablets (Mericon's Fluorical) 15 times the "do not swallow" dosage of the toothpaste warning,
5. Marketed for ingestion with notification to FDA as a "food" but not as a drug with disease prevention claims in bottled water and chewing gum.
6. Marketed for topical use with FDA approval but warning not to swallow (0.25 mg of fluoride) the same amount in unlabeled chewing gum and one glass of fluoridated water, and the same amount forced into everyone without consent in fluoridated water,

7. Undisputed risk of dental fluorosis (enamel and dentin necrosis) costing many thousands of dollars per person for those seeking treatment,

8. Hundreds of research articles raising health concerns and others claiming benefit,

9. Opposition by EPA scientists yet regulated as a protected pollutant,

10. Report by “Drug Digest 1975” that the FDA had rejected several NDAs for fluoride due to lack of evidence of efficacy, yet claimed to be one of the 20th Centurey’s greatest public health achievements,

11. Mass medicated in an uncontrolled experiment without cohort consent; and therefore in violation of Title 45, state laws, and fundamental declarations of medical ethics such as the Nurenberg trials and all subsequent medical research ethics boards which say, “The investigator must terminate the experiment if its continuation may be detrimental to the patient.”

The standard of protection is “may be detrimental to the patient” and does not need to reach the level of any probable certainty or absolute certainty.

XIX. "BURDEN OF PROOF" SHOULD NOT BE ON THE PATIENT

A. Congress has Mandated the Burden of Proof for New Drug Efficacy and Safety be on Industry Before Marketing and as an Independent Third Party, the FDA CDER Evaluates the Science Provided by Industry.

1. The weight of scientific evidence is incomplete for fluoridation and would probably not be approved by the FDA CDER. Rather than protect the public and perform the necessary research to gain NDA (New Drug Application) approval, public health agencies, HHS/CDC/EPA and public water systems have evaded Congress by assuming a quasi fluoridation drug regulatory process shared between agencies with no single agency assuming jurisdiction. Therefore, all agencies can point the regulatory finger at other agencies and no one is responsible.

2. Public Health Agencies' errors are multiplied millions of times[386] compared to a doctor's error with a single patient. Caution is critical.

B. In Contrast, the Burden to Show Proof of Efficacy and Safety for Fluoridation is Not Accepted by "Industry" (Public Health Agencies) and We the Patients are Obliged to Prove Lack of Efficacy and Harm with Absolute Certainty to Government Health Agencies, "Industry." HHS/CDC/EPA should Recommend FDA CDER NDA.

In the case of fluoridation, "industry marketers" and formulators of fluoride concentration with intent to prevent disease such as HHS/CDC/EPA public health employees and public water systems require the patient to provide scientific absolute proof of harm and proof of lack of efficacy for fluoride.

1. Public Health Officials have no personal liability or risk in not following drug laws or failing to protect the public from adverse effects of fluoridation or lack of efficacy or excess exposure. The American Dental Association promoting fluoridation has testified in court they have no duty to protect the public, they only provide information. Public health employees promoting the illegal drug will usually have their jobs, pension, and position regardless of the lack of FDA CDER approval and have no liability for harm. The public is without unbiased protection or advocate.

2. In effect, the patient must convince "industry," those government agencies with vested interest, to fund unbiased balanced research, evaluate the research without bias, and for "industry" to make a virtually impossible unbiased judgment determining themselves wrong and contributing to serioius harm. The patient is placed with a hopelessly high bar to hurdle, without a legal intermediary, and without third party review, and without financial resources to fight what their tax dollars are funding.

3. Without deep financial pockets of liability, lawyers are reluctant to take on expensive suits.

4. The FDA CDER, CDC and EPA, in effect the patient's doctor, are to protect the patient. However, with fluoridation all have failed.

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[386] Appendix 75 Holtgrave

XX CURRENT APPROACHES FOR QUANTIFYING DOSE-RESPONSE INCLUDE MEASURED CONCENTRATIONS IN SUBJECT TISSUES

Traditional measurements of fluoride exposure and metabolism have usually been estimates based on fluoride concentrations in water, food, air, and drugs such as toothpaste and estimating the concentration in the body, teeth and bones.

A. Estimations of Exposure from Multiple Sources are Crude and Lack Individual Specificity.

The more sources of exposure we have, the more complex the variables. The more potential variables in quantity ingested from each source, the more complex, crude, and virtually impossible the estimates of exposure become. Subpopulations with compromised health, inadequate kidney function, age, diet, weight, ingestion habits, genetics and even altitude of residence add significant complexity to an already improbable individual exposure estimate. The more toxic the substance, the more precise the estimate must be. The lower the range of safety, the more complex the estimate becomes. The lack of an established optimal concentration of the drug in the target organ, the more complex an estimate of exposure. Therefore, the approach by EPA of limiting "dose-response" based on estimates of exposure from water is hopelessly inadequate, incomplete and indeed historically crude. No one should be surprised research estimating total exposure or relative exposure of fluoride from water is no longer considered reasonable or adequate. Actual measured concentration in the body rather than estimates of assumptions with many variables is the current scientific standard and the EPA has avoided those studies. Reliance on research of the 1940's and 1950's as the best available science for fluoride safety is unacceptable.

The ingestion of fluoride with the intent to prevent disease is far more complex than most drugs and even more caution and margin of safety should be used. With most drugs, the major source of exposure is the pill being taken by the patient prescribed by the doctor as legal intermediary for each specific patient.

B. The Intent of Ingesting Fluoride is to Reduce Dental Caries.

Several measurements should be made: the concentration and amount of fluoride in substances ingested, the amount of fluoride absorbed, the concentration and amount of fluoride excreted, and the concentration of fluoride in the blood, fluids, and body tissues such as teeth. At each step on the pathway to the target organ (teeth,) the concentration and amount of fluoride should be determined and "normal" or "optimal" fluoride concentrations determined.

To date, the fluoride concentration in water has been held sacred as though the water were being treated and little attention (by HHS/CDC/EPA) seems to have been given concentrations in substances such as serum, urine, hair, nails, organs, tissues, cells, and most important the target organ the teeth. The EPA must include measurements of fluoride concentration in all these tissues and their health effects.

C. Skeletal Fluorosis:

The Office of Water did not identify any studies that were good candidates for dose- or concentration-response modeling, in part because current assessment methods no longer limit assessment to the inaccurate, crude and historic method of estimating exposure. Too many sources of fluoride exist to reasonably estimate a relative exposure for specific individuals and excretion of fluoride is variable. The issue of efficacy and safety of ingesting fluoride is far too complex to limit consideration to a relative concentration of fluoride from water. The scientific gold standard for measuring fluoride exposure is to include measured fluoride concentrations serum/plasma, urine and tissues in subjects. The EPA is looking for "horse and buggy" measurements in the 21st Century and did not find current horse and buggy measurements. Assuming safety and efficacy without inclusion of current assessment methods puts the public in harm.

The Office of Water is simply out of their jurisdiction, purview, and out of their expertise to assume a benefit from fluoride based on an assumed health related benefit and then to suggest a RfD without current assessment standards of measured fluoride concentrations in human and animal systems.

D. How Much Dental Fluorosis, If Any, is Desired?

EPA must answer the question how much dental fluorosis is desired, if any. The proposed EPA RfD of 0.08 mg/kg/day will probably result in more than half of maxillary central incisors having fluorosis. If the EPA desires half, why not 100%? What is the dental fluorosis goal of the EPA?

> *Levy (2006)[387] "Cumulatively from birth to 36 months, average daily intake of 0.04 mg F/kg BW or less carried relatively low risk for fluorosis (12.9% for maxillary central incisors, 6.8% for first molars). Average daily intake of 0.04-0.06 mg F/kg BW showed a significantly elevated risk for fluorosis (23.0% for maxillary central incisors, 14.5% for first molars), while fluorosis risk was even higher for average intake above 0.06 mg F/kg BW (38.0% for maxillary central incisors, 32.4% for first molars)."*

Dental fluorosis is a biomarker of excess fluoride exposure and a sign of other adverse effects from excess fluoride ingestion. The EPA is not protecting the public.

See Appendix 101 Prystupa (2011).

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[387] Appendix 97 Levy (2006)

XXI. TEETH: INCREASED FLUORIDE CONCENTRATIONS IN TEETH DO NOT REDUCE DENTAL CARIES

A. The CDC reported, *"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."*[388]

1. Without an endpoint, target, goal, or objective of a specific efficacious "optimal" fluoride concentration in a tooth, all other discussion and measurements are meaningless. In other words, the increased or decreased concentration of fluoride in teeth from fluoridated water is similar for teeth with or without dental caries. High fluoride concentrations placed topically show some benefit, but not ingestion of fluoride. First, the CDC must determine an optimal fluoride concentration for the enamel and dentin and then work back to serum concentration and then total exposure.

2. *"Fluoride incorporated during tooth development is insufficient to play a significant role in caries protection."*[389] *"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."* 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.

3. *"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."* Adair SM. (1999). Overview of the history and current status of fluoride supplementation schedules. Journal of Public Health Dentistry 1999 59:252-8.

4. *The case is essentially a risk-benefit issue - fluoride has little preeruptive impact on caries prevention, but presents a clear risk of fluorosis."* Burt BA. (1999). The case for eliminating the use of dietary fluoride supplements for young children. Journal of Public Health Dentistry 59: 260-274.

5. *"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."* Featherstone JDB. (1999) Prevention and Reversal of Dental Caries: Role of Low Level Fluoride. Community Dentistry & Oral Epidemiology 27: 31-40.

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[388] 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.
[389] Featherstone, JDB. (2000). The Science and Practice of Caries Prevention. *Journal of the American Dental Association* 131: 887-899.

6. *"[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."* 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.

7. *"[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."* 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.

8. *"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."* 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.

9. *"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 legible benefit in ingesting it."* Diesendorf, M. et al. (1997). New Evidence on Fluoridation. Australian and New Zealand Journal of Public Health 21 : 187-190.

10. *"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."* Ekstrand J, et al. (1994). Fluoride pharmacokinetics in infancy. Pediatric Research 35:157–163.

11. *"It is now well-accepted that the primary anti-caries activity of fluoride is via topical action."* 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.

12. "*I have argued in this paper that desirable effects of systemically administered fluoride are quire minimal or perhaps even absent altogether."* Leverett DH. (1991). Appropriate uses of systemic fluoride: considerations for the '90s. Journal of Public Health Dentistry 51: 42-7.

13. *"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..."* Wefel JS. (1990). Effects of fluoride on caries development and progression using intra-oral models. Journal of Dental Research 69(Spec No):626-33;

14. *"[E]vidence has continued to accumulate to support the hypothesis that the anti-caries mechanism of fluoride is mainly a topical one."* Carlos JP. (1983) Comments on Fluoride. Journal of Pedodontics Winter. 135-136.

15. *"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."* 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.

16. *"Fluoride is most effective when used topically, after the teeth have erupted."* Cheng KK, et al. (2007). Adding fluoride to water supplies. British Medical Journal 335(7622):699-702.

17. *"it is now accepted that systemic fluoride plays a limited role in caries prevention."* 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.

18. *"the major anticaries benefit of fluoride is topical and not systemic."* National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 13.

19. *"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."* 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.

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."* Hellwig E, Lennon AM. (2004). Systemic versus topical fluoride. Caries Research 38: 258-62.

21. *"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." Fejerskov O. (2004). Changing paradigms in concepts on dental caries: consequences for oral health care. Caries Research 38: 182-91.

22. *"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."* Warren JJ, Levy SM. (2003). Current and future role of fluoride in nutrition. Dental Clinics of North America 47: 225-43.

23. *"[T]he majority of benefit from fluoride is now believed to be from its topical, rather than systemic, effects."* 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.

24. *"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."* Zimmer S, et al. (2003). Recommendations for the Use of Fluoride in Caries Prevention. Oral Health & Preventive Dentistry 1: 45-51.

25. *"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."* Aoba T, Fejerskov O. (2002). Critical Review of Oral Biology and Medicine 13: 155-70.

26. *"[F]luoride's predominant effect is posteruptive and topical."* 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.

27. Vieira, Limeback (2003)[390] reported a correlation in unerrupted 3rd molars between dentin fluoride concentration and dental fluorosis but not enamel fluoride concentration and dental fluorosis and no correlation between dentin and enamel fluoride concentrations in the same tooth. Viera, Limeback (2003) suggest dentin fluoride concentration maybe the best biomarker for chronic fluoride ingestion. Vieira, Limeback (2003) Part A and B of Figure 2 below.

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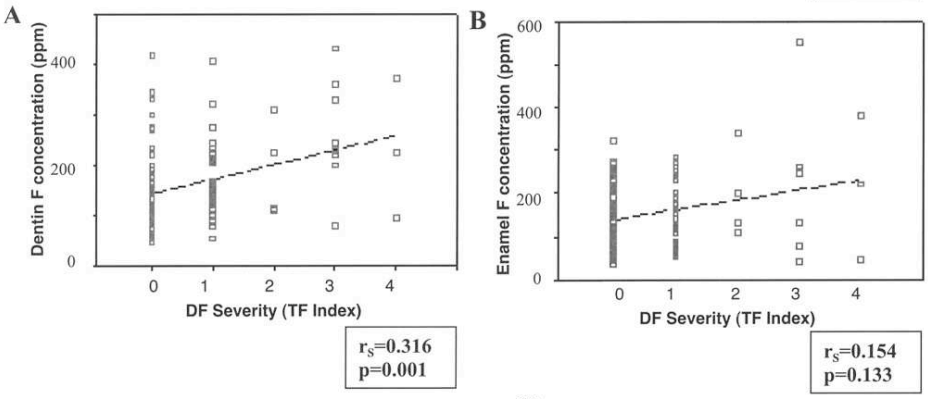
[390] Appendix 108 Vieira (2003) http://jdr.sagepub.com/content/83/1/76.full accessed 2/26/11



Both dentin and enamel appear to reflect a higher concentration of fluoride with dental fluorosis, but there does not appear to be a fluoride concentration in enamel or dentin which would "prevent" dental fluorosis. Getting fluoride concentrations in dentin and enamel below 100 ppm would certainly reduce dental fluorosis but not eliminate the occurrence.

28. Arnstrong (1963) reported, *"enamel fluoride of sound or carious third molars was not found to be different in persons of comparable age."*[391]

29. A confounding factor is fluoride contributing to a delay in tooth eruption found in some studies.[392] Studies compare chronological age rather than dental age. A delay in tooth eruption would protect the tooth for a few months; however, a life time benefit does not necessarily follow.

Without a relationship between fluoride concentrations in tooth structure and dental caries, recommendations for optimal fluoride concentrations in teeth are not possible, yet absolutely essential. Not until an optimal fluoride concentration in the teeth is determined can an optimal serum or optimal daily intake be determined. Serum fluoride levels should be based on safety rather than efficacy.

HHS/CDC and the EPA need to clearly and publicly show how they determine and publicly state their conclusion on the optimal fluoride concentration for dentin, enamel, serum, water and total exposure for the prevention of dental caries.

B. Dental Fluorosis is a Sign, a Biomarker, of Previous Excess Fluoride during the Development of the Tooth.

1. Jimenez-Farina (2011)[393] reported, *"The dose-response association between intake and dental fluorosis in permanent teeth suggests that the critical limit of 0.05-0.07 mg/kg body weight is not safe."* The new increased EPA RfD to 0.08 mg/kg/day is a relative consideration, does not include all sources or all persons,

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[391] Armstrong WD, Singer L. Fluoride contents of enamel of sound and carious human teeth: A reinvestigation. J dent Res 1963;42(1):133-6.
[392] Appendix 99 Delay in Tooth Eruption
[393] Jimenez-Faran M, et al. Fluoride Consumption and Its Impact on Oral Health, Int. J. Environ. Res. Public Health, 2011, 8, 148-160. Open access as of 2/25/11 http://www.mdpi.com/1660-4601/8/1/148/pdf

and certainly not safe.

2. Although dental fluorosis is principally found in areas with excess endemic fluoride in water, dental fluorosis is now reported in over 40% of USA children.

3. Again, EPA must determine what percentage of children are expected to have dental fluorosis and other harm from excess fluoride ingestion at an RfD of 0.08 mg/kg/day.

4. The Jimenez-Farina (2011)[394] dental examiners were confident that only 4.4% of the children were without dental fluorosis. Only 22% consumed fluoridated salt. The urine fluoride concentration indicated the children were consuming a "normal" (currently considered normal) amount of fluoride but the vast majority were showing signs of excess fluoride ingestion. Either "normal" is too high or unknown confounding factors, such as synergistic chemicals, are increasing risk.

5. Jimenez-Farina (2011)[395] reported a reduction in DMFT (decayed missing filled teeth) with children positively having dental fluorosis; however, the relative reduction out of a total of 128 surfaces was only about half a percent. With a moderate fluoride concentration in water of 0.18-0.44 ppm, significant dental fluorosis just from the water would not generally be expected and HHS proposed 0.7 ppm F in water is about double the concentration which was found not safe. The study did not include the confounding effect of delayed tooth eruption with fluoride exposure.

6. Elevation: The moderately high altitude of about 7,000 feet could be a factor for the excessively high dental fluorosis. If so, EPA needs to provide warnings for those at high elevations.

7. Toothpaste: Children with dental fluorosis generally brushed twice a day with toothpaste covering the brush both increasing fluoride exposure and toothbrush exposure.

8. Caries reduction: The reduction of dental caries could be a sign of more frequent home dental hygiene and have nothing to do with increased fluoride intake as seen with the dental fluorosis. In other words, the dental fluorosis could be a sign of more brushing rather than efficacy of fluoridation.

9. Caries reduction: The children with less fluorosis maybe using less topical toothpaste which is shown to reduce dental caries.

10. Other medical conditions such as calcium deficiency, pH disorders, urinary flow disturbances, and renal management of fluorides and diet over long term were not considered for confounding effects.

11. Eruption time of the teeth was not considered. Some have

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[394] Jimenez-Faran M, et al. Fluoride Consumption and Its Impact on Oral Health, Int. J. Environ. Res. Public Health, 2011, 8, 148-160. Open access as of 2/25/11 http://www.mdpi.com/1660-4601/8/1/148/pdf

[395] Jimenez-Faran M, et al. Fluoride Consumption and Its Impact on Oral Health, Int. J. Environ. Res. Public Health, 2011, 8, 148-160. Open access as of 2/25/11 http://www.mdpi.com/1660-4601/8/1/148/pdf

reported a delay in tooth eruption with excess fluoride ingestion and the reduction of tooth decay could be simply a matter of less time of the tooth exposed to the oral environment.

Dental fluorosis is a sign, a biomarker of excess fluoride ingestion. For example, obesity is a sign of excess ingestion of calories and must not be considered the only adverse effect of an imbalance of caloric intake. Likewise, dental fluorosis is a sign of excess fluoride ingestion and must not be considered the only adverse effect of an imbalance of fluoride intake. It is scientifically irrational to expect a highly toxic enzymatic substance like fluoride to show a direct biomarker sign of excess intake with damage limited to only teeth (as considered by HHS) and bones (included by EPA).

XXII SERUM: ITSDA CDC RECOMMENDED SAFE ACUTE SERUM FLUORIDE LEVEL <0.02 PPM SHOULD INCLUDE <0.01 PPM CHRONIC LEVEL FOR ADULTS AND < 0.005 PPM FOR INFANTS AND CHILDREN.

With no apparent benefit from increasing serum fluoride concentrations, safety should be the primary determining factor for concentration.

A. Serum Fluoride Concentrations are an Essential Measurement of Individual Fluoride Burden.

3. The CDC reasonably reports,

"Normal serum fluoride levels are <20 mcg/L. . . "[396] (<0.02 ppm).

Less than 0.02 ppm fluoride serum should be protective for most adults if the concentration is acute; however, <0.01 ppm fluoride fasting serum concentration should be a target normal. Infants and children should have a normal fluoride fasting serum <0.005 ppm. Achieving those levels is possible and reasonable and will give patients and doctors a target to reduce risks for high risk individuals. Fetal fluoride serum concentrations may need to be even more protective and must be determined to protect development of the fetal brain.

2. Itai (2010)[397] found mean serum fluoride concentrations at 0.009 ppm. Our 10% higher target of <0.01 ppm is certainly achievable.

3. Hossney (2003)[398] *"the fluoride levels in mothers' milk reflected the serum levels of their own infants."* More than half of mother's milk tested in a Canadian study [399]had no detectible fluoride and a mean 0.004 ppm for mothers not on fluoridated water. Our recommended <0.005 ppm serum fluoride concentration is a reasonable target at this time.

4. Villa (2010) considered a reasonable concept to evaluate a measured balance of fluoride retention where there is a "neutral" balance between intake and excretion. *"Neutral fluoride balances were predicted when the TDFI (total daily fluoride intake) was equal to approximately 0.07 mg F/day for children and 0.8 mg F/day for adults."*[400]

With a "neutral fluoride balance" our recommended serum fluoride levels are perhaps high.

A 14 kg child at our recommended <0.005 mg/kg/day TDFI would ingest

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[396] http://www.bt.cdc.gov/agent/sulfurylfluoride/casedef.asp Accessed 2/9/11

[397] Appendix 17: Itai K et al, Serum ionic fluoride concentrations are related to renal function and menopause status but not to age in a Japanese general population. Clin Chim Acta. 2010 Feb;411 (3-4):263-6.

[398] Hossney E, Reda S, Marzouk S, Diab D, Fahmy H. Serum fluoride levels in a group of Egyptian infants and children from Cairo city. Arch Environ Health. 2003 May;58(5):306-15.

[399] NRC (2006)

[400] Villa A et al, Relationships between Fluoride Intake, Urinary Fluoride Excretion and Fluoride Retention in Children and Adults: An Analysis of Available Data. Caries Res 2010:44:60-68.

0.07 mg F/day and have a reasonably "neutral" balance but heavier children would not be protected. In contrast, the EPA proposed RfD of 0.08 mg/kg/day would be sixteen times higher.

An 80 kg adult at our recommended <0.01 mg/kg/day TDFI would ingest 0.8 mg F/day. In contrast, the EPA proposed RfD of 0.08 mg/kg/day X 80 kg = 6.4 mg/day would be eight times higher than a "neutral fluoride balance" or homeostasis.

5. To the question of what is a safe serum fluoride level, the CDC suggests less than <0.02 ppm and research would suggest a chronic serum fluoride concentration goal of <0.01 ppm (Sandhu 2009, Xiang 2005, Villa 2010, Hossney 2003, etc). An upper limit of 0.02 ppm serum fluoride suggested by the CDC with a goal of <0.01 ppm serum fluoride or 0.01 mg F/kg/day appears to be reasonable for adults.

6. Sandhu used controls with mean fluoride serum at 0.0421 ppm, and reported bone-forming tumors at 0.072 ppm and osteosarcoma at 0.143 ppm. Sandhu's controls were too high. Rathee[401] (below) reported serum fluoride for controls without stones at 0.025 ppm (close to CDC's 0.02 ppm) and subjects at 0.12 ppm. Historically, Singer[402] reported a value of 8 micromolar (0.15 p.p.m.) as a "normal" serum fluoride level which is no longer considered "normal" or safe.

7. The NRC (2006) report for the EPA refereneced fluoride serum levels over 300 times in their report and serum fluoride concentrations must be considered by HHS/CDC:

> *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).*

8. Den Besten in the EPA (2010) RSC review stated at least 5 times the concept "that serum fluoride levels would be the most useful measurement, but these levels are not available."[403]

Den Besten makes a reasonable call. Repeated calls over many years have been made for more serum fluoride studies. However, enough serum fluoride evidence has been gained for EPA to make a more reasoned recommendation inclusive of serum fluoride concentrations.

Teotia, compared fluoride intake and plasma fluoride levels. One of the main differences in plasma and serum is fibrinogen and the ionic levels are reasonably comparable, although not exactly the same. Even at about 3 mg/day exposure, total

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[401] http://medind.nic.in/iaf/t04/i2/iaft04i2p100.pdf Accessed 2/3/2011

[402] As reported by Taves, either in Singer, L and Armstrong, W.D. J. App. Physiol., 15,508 (1960) or the same authors in Anal. Biochem., 10,495 (1965).

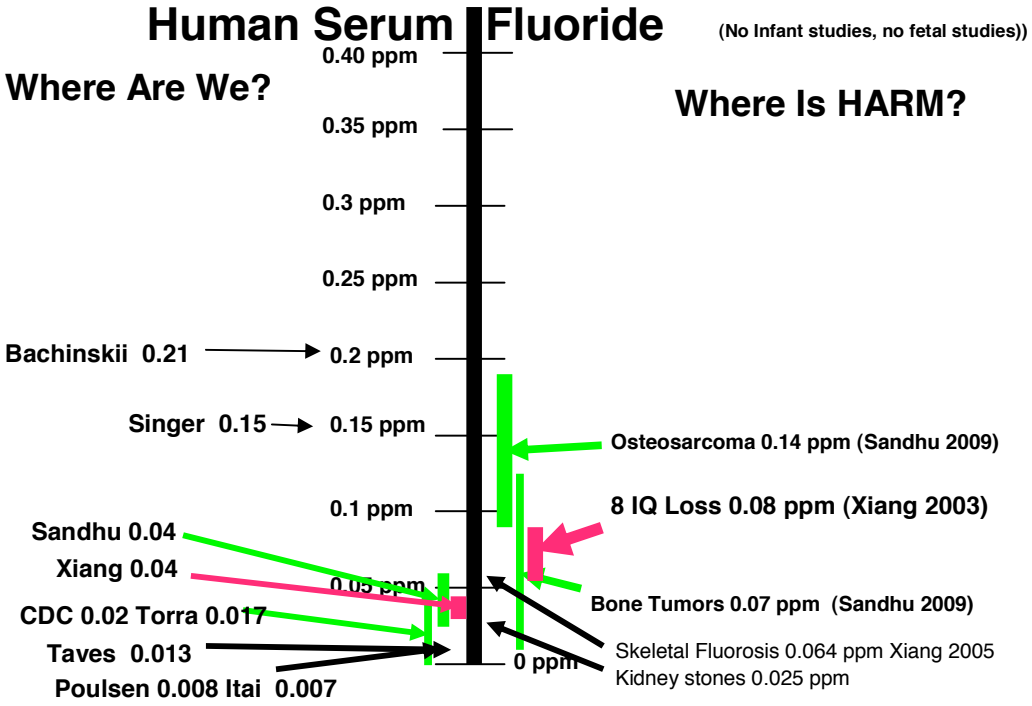
[403] Den Besten RSC 2010 report p 18, p 10, p 50, p 67, and again repeated on p 93.

fluoride plasma levels exceed 0.10 mg/L (ppm), above studies showing serum fluoride at that concentration with reduced IQ, tumors, cancer, fractures and fluorosis.

In vitro studies show hepatocellularcarcinoma at 0.06 ppm, neuroblastoma starting at 0.001 ppm. Liver, kidney and brain cells are damaged at very low concentrations. Our recommendations of <0.1 ppm urine, <0.001 ppm serum, and RfD of <0.01 mg F/kg/day for adults at this time are reasonable goals. The EPA's proposed 0.08 mg F/kg/day RfD will increase harm, disease, risk and is not protective.

At 0.02 ppm cell mitochondrial damage is seen and reduction in cellular antioxidant defenses are reported, Barabier (2010) The CDC's serum fluoride of <0.02 ppm is not protective at chronic levels and <0.01 ppm is a more reasonable goal.

The graph below is again provided for an overview of some serum fluoride studies. Based on the evidence available, the CDC's <0.02 ppm serum fluoride would be just below most Osteosarcoma, IQ loss, bone tumors, and skeletal fluorosis. The CDC's <0.02 ppm may not be protective for everyone and is without an adequate margin of safety. Our <0.01 ppm adds a reasonable margin of safety for chronic serum fluoride levels.



Looking closer at the CDC's <0.02 ppm safe serum fluoride levels indicates the focus was probably on an acute SF adult exposure of fluoride rather than chronic exposure. A normal chronic adult fluoride serum concentration of <0.01 ppm would be more reasonable and protective from cancer, brain damage, skeletal fluorosis and stones.

Extrapolating from the graphs by Gupta (2001) (NRC (2006 page 63) Figure 2-7 (below) for children and assuming a reasonable decline to zero (red dotted lines added to Gupta's chart), and with an intake at the EPA's proposed RfD of 0.08 mg/kg/day for a 40 kg child would be about 3.2 mg/day of fluoride and an estimated average of 0.4 ppm fluoride serum concentration. The proposed RfD is not protective of Osteosarcoma, IQ loss and increased mental retardation, bone tumors, skeletal fluorosis, kidney stones and dental fluorosis.

	Serum F Concentration
FDA RfD	0.4 ppm
Osteosarcoma	0.14 ppm
IQ loss	0.08 ppm
Bone Tumors	0.07 ppm
Skeletal Fluorosis	0.064 ppm
Kidney Stones	0.025 ppm

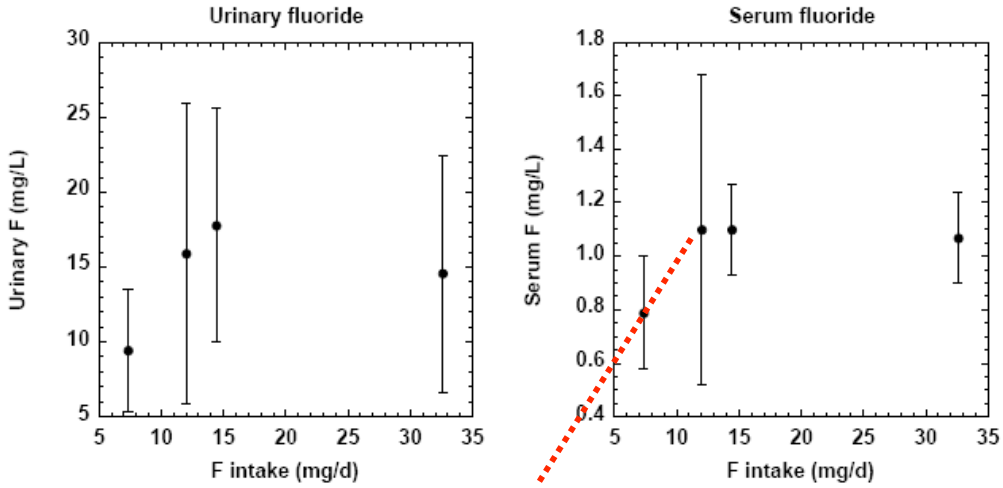


FIGURE 2-7 Urinary (left) and serum (right) fluoride concentrations as functions of estimated daily fluoride intake (data from Gupta et al. 2001). Dark circles indicate means of groups of 50 children (ages 6-12); vertical lines indicate 1 standard deviation from the mean.

Infant serum fluoride levels reflect mother's milk fluoride concentrations. It stands to reason, if an individual had no fluoride exposure they would have no fluoride in their serum. Therefore, the Gupta (2001) graphs of children mean serum levels would logically start from zero and at about 12 mg/day, serum fluoride appears to peak for children at about 1.1 ppm with the kidneys maxed out. Presumably kidneys would be most effective with very low concentrations.

Fluoride serum measurements have the advantage of not only evaluating fluoride water concentration but also fluoride intake from other sources. For example, if the

mean serum fluoride concentration in a community is 0.01 ppm and a child shows a measured 0.1 ppm serum fluoride concentration, the clinician and parent can work with the child to reduce fluoride intake such as swallowing toothpaste, diet, medications or other sources of excess exposure along with kidney function diagnosis.

Once again, Xiang compared serum fluoride levels in two villages, the control which had 0.04 ppm ionic fluoride serum (mean IQ 100) and the subject village with 0.08 ppm ionic fluoride serum (mean IQ 92) and provided the graph below left. Xiang's study compares favorably with the increase in mental retardation for the 50 states of the USA when ranked on the percentage of the whole population on fluoridated water, graph on the right. Remember, 0.08 ppm in serum is bad and 0.04 ppm is better but may not be protective for brain damage and 0.04 ppm is double CDC's <0.02 ppm normal.

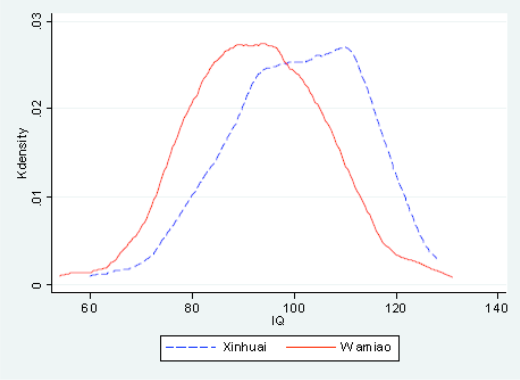
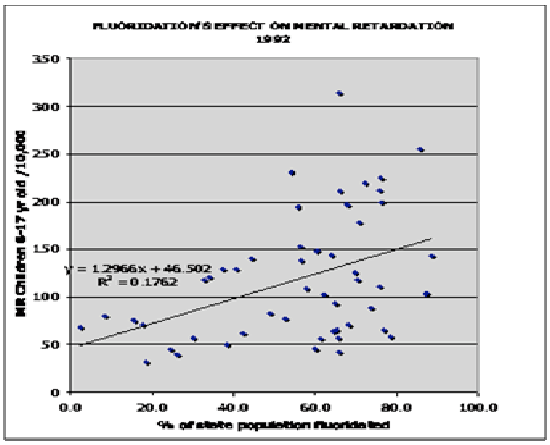
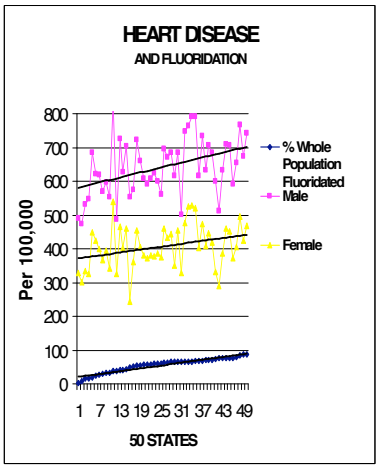


Figure 2 Kdensity distribution of children's IQ in Wamiao and Xinhuai village



"Hanhijärvi and Pentillä (1981) reported elevated serum fluoride in patients with cardiac failure." (NRC 2006, p 82)

The graph below ranking the 50 USA states on the percentage of each state's population on fluoridated water supports the work of Hanhijarvi (1981) finding about a 20% increase in CVD in fluoridated communities.



Hossney (2003)[404] reported, *"the fluoride levels in mothers' milk reflected the serum levels of their own infants."* The EPA must not increase the fluoride serum levels of infants higher than the fluoride serum levels of infants on mother's milk.

"The mean and median serum fluoride levels of 168 representative Danish adults were 470±270 and 400 nmol/L (0.0089±0.00513 and 0.0076 mg/L), respectively (Poulsen et al. 1994). Levels were significantly higher in urban inhabitants than rural inhabitants and increased significantly with age."[405] The Danes have reduced dental decay to similar levels as the USA and serum fluoride levels are very low, similar to the fluoride concentration in breast milk. Both mean and median serum fluoride levels are below our recommended 0.01 mg/L (ppm) and those above 0.01 mg/L should evaluate their intake of fluoride to lower their fluoride serum concentration.

The CDC less than 0.02 ppm serum fluoride would appear to be at the highest edge of risk with no margin of safety. Torra[406] at 0.017 and Taves[407] at 0.013 ppm serum fluoride are more protective and would include the majority of Paulsen's cohorts. A mean serum fluoride level at 0.013 ppm is close to reasonable and just below current studies of skeletal fluorosis, bone tumors, IQ loss, and osteosarcoma and is a reasonable goal for adults. Our recommended serum fluoride level, <0.01 ppm, is lower than the mean fluoride of Torra and Taves because mean is not protective and still does not provide an adequate margin of safety. However, <0.01 ppm serum fluoride is a reasonable compromise for adult serum fluoride concentration.

From <0.01 ppm adult serum fluoride concentration, 0.005 ppm children serum fluoride concentration and 0.000 ppm infant serum fluoride concentration, water fluoride concentration should have a MCLG of zero ppm.

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[404] Hossney E, Reda S, Marzouk S, Diab D, Fahmy H. Serum fluoride levels in a group of Egyptian infants and children from Cairo city. Arch Environ Health. 2003 May;58(5):306-15.
[405] ATSDR Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine. September 2003. p 228.
[406] Appendix 100 Torra
[407] Appendix 102 Taves

XXIII URINE: FLUORIDE CONCENTRATION

Urine fluoride concentration is another important measurement for general population trends and mean fluoride concentrations. If the kidneys are working well, the excretion of fluoride may reflect individual exposure. However, a low fluoride urine concentration may simply reflect kidney disablity. Fluoride serum levels are a better measurement of individual fluoride body burden and tooth fluoride concentration a better measurement of the target organ.

Table 9 from the NRC (2006) report indicates a ratio for a moderate 0.39 mg/L fluoride in water to fluoride urine concentration of 1.14 mg/L, almost three times more concentrated in urine. When fluoride exposure increases, the ratio decreases and reaches almost 1:1 at current MCLG levels of fluoride exposure. Remember, the amount of water ingested is more than excreted in the urine. A 1:1 ration of fluide in water to fluoride in urine means the tissues are retaining large amounts of fluoride.

Table 9. Fluoride in drinking water and in urine (Mean±SD)

No. samples	Drinking water F (mg/L)	Urinary fluoride (mg/L)	Urinary fluoride mg/mmol Cre
142	0.39±0.15	1.14±0.49	0.25±0.22
32	1.15±0.29	2.59±1.70	0.61±0.47
80	2.44±0.30	3.67±1.97	0.85±0.67
32	3.22±0.18	3.77±1.86	0.86±0.81
4	4.05±0.01	4.65±2.39	2.17±1.73

A. Jimenez-Farina (2011)[408] reported more than 60% of children 11-12 years old in their study had dental fluorosis with an estimated fluoride intake of 0.05 mg/kg/day, (proposed EPA RfD is 0.08 mg/kg/day) estimated 1.1 mg/day fluoride intake, fluoride concentration in home water and bottled water ranged from 0.18-0.44 ppm (about half of HHS recommendation and about 10% of EPA MCLG), and consistent with urine concentration of about 0.57 ppm (consistent with Table 9 of the NRC report).[409] The EPA's proposed 0.08 relative dose response would be expected to have even higher dental fluorosis rates.

B. Jimenez-Farina (2011) study had about half the concentration of fluoride in water proposed by HHS (0.7 ppm) and far more than the EPA's 4 ppm MCL/MCLG and with confidence found only 4.4% without dental fluorosis. In other words, cohorts

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[408] Jimenez-Faran M, et al. Fluoride Consumption and Its Impact on Oral Health, Int. J. Environ. Res. Public Health, 2011, 8, 148-160. Open access as of 2/25/11 http://www.mdpi.com/1660-4601/8/1/148/pdf

[409] Although 0.57 ppm fluoride concentration in the urine was considered within the normal range (0.2-3.2 ppm), the normal range is not protective. Li (2009)[409] reported 0.59 mgF/L urine with water concentration of 0.32 mgF/L drinking water. Jimenez-Farina (2011), Li (2009) and Oporowska-Moszyk (1997) are consistent at low levels of fluoride in water, urine fluoride concentrations should approach triple the water fluoride concentrations. A neutral balance of fluoride would expect about three times the concentration of fluoride in the urine.

did not have protection from excess total fluoride intake with about half the concentration of fluoride in water, as proposed by HHS and less than 10% EPA's MCLG. Urine fluoride concentrations were lower than the NRC table 9 would expect. The question, "Why?" must be answered.

Jimenez-Faran (2011) estimated cohorts had fluoride from other sources than just water and total fluoride intake of 0.05 mg/kg/day resulting in 0.57 ppm in their urine. Would our recommended <0.01 mg/kg/day total fluoride intake have been protective? Yes. Based on the ratio above of 0.05 : 0.57, if ingestion of fluoride had been reduced to 0.01 mg/kg/day instead of 0.05 mg/kg/day, fluoride urine would have been approximately 0.1 ppm. A goal for fluoride urine concentration is reasonable and should be <0.1 ppm.

C. Franco (2009)[410] in a smaller study, estimated children's fluoride intake of 0.07 and 0.08 mg/kg/day. Urinary fluoride concentrations were 0.8 to 0.9 mgL (compared to 0.57 mg/L in Jimenez-Faran above). 55% of fluoride ingested was from toothpaste. Total daily fluoride intake was considered above threshold. About 70% of fluoride ingested was retained.

D. The CDC's[411] suggestion of 0.2 to 3.2 mg/L normal range for fluoride urine appears too high and not protective of fluorosis, neurological disorders or cancer and tumors. Even the 0.2 mg/L would have a slim chance of achieving a 0.02 ppm fluoride serum concentration. HHS reduction of fluoride added to drinking water to 0.7 ppm is not protective and would not provide a "neutral balance" of fluoride in the body, see NRC (2006) Table 9 above. The EPA's recommended RfD is out of reason and not protective of the public.

HHS/CDC/EPA is regulating the concentration of fluoride in water with the correct assumption that increased fluoride in the water will increase fluoride concentration in the serum. To assume an increased serum fluoride concentration is safe and will result in an increased tooth fluoride concentration is not unreasonable. However, the resulting increase in fluoride dentin and enamel must show reduced dental caries, and to date, such evidence is lacking.

It should come as no surprise that one of the NRC (2006) recommendations to the EPA was:

> *"Additional studies on the relationship between individual fluoride exposures and measurements of fluoride in tissues (especially bone and nails) and bodily fluids (especially serum and urine) should be conducted. Such studies should determine both absolute intakes (mg/day) and body-weight normalized intakes (mg/kg/day)."* (NRC 2006, p. 72)

HHS/CDC/EPA has a flawed assumption by focusing on the concentration of fluoride in water. EPA has not found good studies on relative dose concentration

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[410] Appendix 5 Franco F Urine
[411] http://www.cdc.gov/niosh/docs/2003-154/pdfs/8308.pdf Accessed 2/9/11

because researchers are moving to measured evidence in human tissue and fluids.

The fluoride concentration in water is not the definitive health end point. Considering only dental fluorosis or dental caries is delayed by about six years and without individual specificity. All a parent, doctor or the HHS/CDC/EPA can do when the adult teeth erupt with fluorosis is say, “oops” too much fluoride several years ago. With fluoride serum measurements during routine blood or urine work, parents can detect excess fluoride years before it is too late.

Rather than focusing on fluoride concentration in “water”, the CDC/EPA/HHS/FDA need to focus on fluoride concentration in people.

A number of parameters affect the uptake, retention and excretion of fluoride and these are individually highly variable. Regulating the concentration of fluoride in water in order to regulate the concentration of fluoride in serum to finally regulate the fluoride concentration in teeth is problematic with multiple estimates and assumptions and not protecting the public.

Considering only dental fluorosis, the National Academy of Sciences (NAS), to avoid moderate fluorosis (yellow or brown teeth), recommended a daily intake of fluoride, from all sources, and should not exceed:

- -0.01 mg/day for 0 – 6-month-olds
-- 0.5 mg/day for 7 through 12 months
-- 0.7 mg/day for 1 – 3-year-olds.

The proposed EPA RfD of 0.08 mg F/kg/day would not be protective just for moderate dental fluorosis for any child over 9 kg.

XXIV. THE HHS RECOMMENDED REDUCTION OF FLUORIDE CONCENTRATION IN PUBLIC WATER TO 0.7 PPM AND EPA RfD DO NOT PROTECT THE PUBLIC FROM HARM.

HHS provided guidance to lower the concentration of fluoride based mainly on four considerations covered below:

A. "Scientific evidence related to effectiveness of water fluoridation on caries prevention and control across all age groups

B. Fluoride in drinking water as one of several available fluoride sources

C. Trends in the prevalence and severity of dental fluorosis

D. Current evidence on fluid intake in children across various ambient air temperatures."

A. HHS and EPA Overriding Premis is Flawed. A balanced review of the scientific evidence does not find fluoridation prevents caries across all age groups.

Effectiveness: HHS cherry picked the evidence and failed to include research finding no benefit, confounding factors, lack of economic benefit, lack of increased decay after cessation, and much more.[412] EPA scientists are correct, fluoridation no longer reduces tooth decay if it ever did. In contrast, HHS uses prevailing bias.

The history of medicine and dentistry is replete with flawed theories. Ioannidis (2005) reported, *"There is increasing concern that most current published research findings are false. . . Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research."*[413]

HHS/CDC/EPA must review science of fluoride exposure, risks, safety, and benefit not from a bias to prove the traditional position is correct, but always keeping in mind that most current published research findings are false. HHS/CDC/EPA must critically review all sides of the scientific controversy. Without inclusion of opposing views and a "third party" skilled in reviewing both sides of the literature for efficacy, HHS/CDC/EPA are putting the public in serious risk of harm without benefit. HHS/CDC/EPA have overriding blinders of prevailing bias preventing them from seriously looking critically at both sides of the scientific research[414] on fluoridation. A few samples from Appendix 91:

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[412] For example, see Appendix 116

[413] See Appendix 93 Ioannidis (2005) Why Most Published Research Findings Are False. PloS Medicine, August 2005, Vol 2, Issue 8, Accessed 2/23/11, Currently Chief of Standford University's Prevention Research Center. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1182327/pdf/pmed.0020124.pdf

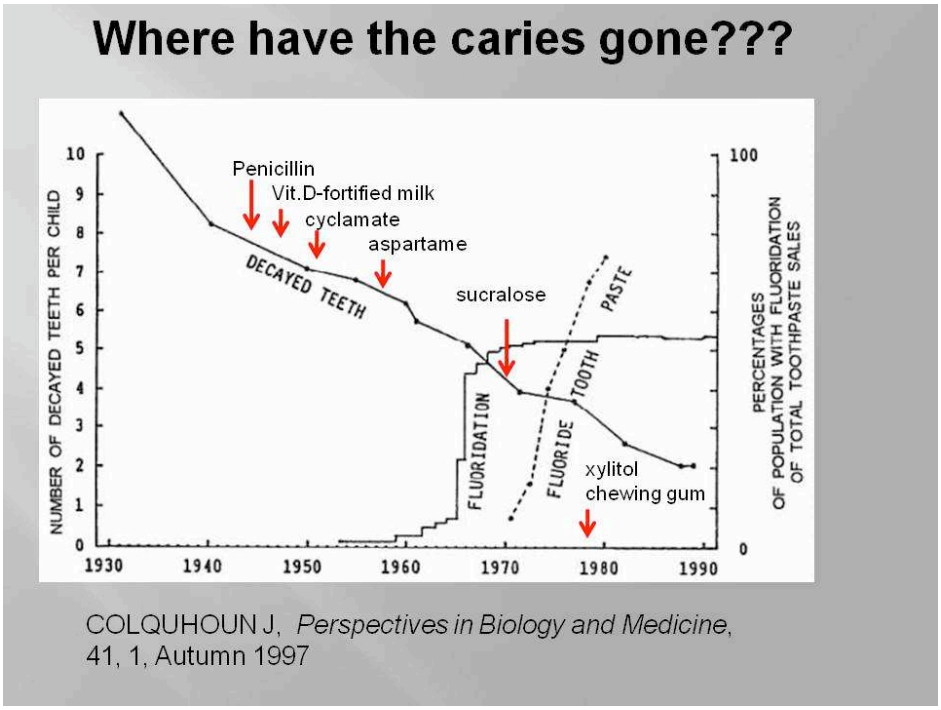
[414] See Appendix 91 Lack of Benefit

1. Komarek (2005) “Our analysis shows no convincing effect of fluoride-intake on caries development.”[415]

4. Colquhoun (1985) “In both areas the use of fluoride toothpastes and oral hygiene had been encouraged. When the socioeconomic variable is allowed for, child dental health appears to be better in the unfluoridated areas.”[416]

5. Yiamouyiannis, “Data from dental examinations of 39,207 school children, aged 5-17, in 84 areas throughout the United States are analyzed. . . No statistically significant differences were found in the decay rates of permanent teeth or the percentages of decay-free children.”[417]

6. One huge monster of unknown confounding factor distorting fluoride research is illustrated below. A significant decline in tooth decay from the 1930’s long before fluoridation was introduced is evident. Indeed, one or more unknown confounding factors has been decreasing dental caries starting long before fluoridation, fluoride toothpaste or fluoride dental products. We must repeat. Long before the theory of ingesting fluoride was introduced, most dental caries had been reduced. Carefully review the graph below.



The graph above (modified by Limeback with arrows and timelines for the introduction of other possible confounding factors) is probably the most important graph in the hundreds or thousands of pages presented to the HHS/CDC/EPA and should

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[415] See Appendix 92: Komarek A et al, A Bayesian analysis of multivariate doubly-interval-censored dental data. Biostatistics (2005), 6, 1, pp. 145-155.
[416] Appendix 95 Colquhoun (1985)
[417] Appendix 96 Yiamouiannis

send chills of concern through any dentist, physician, researcher, scientists, promoter of fluoridation and the HHS/CDC EPA. Dental caries levels have been reduced and scientists don't know why. Any claim for the efficacy of any method's efficacy is interesting speculation but not fact.

Clearly, one or more confounding factors caused decay to drop about in half from 1930 to 1960. No one has determined these confounding factors, researchers are puzzled. Some suggest socioeconomics, perhaps chemicals, drugs, access to year around fresh produce and/or other factors. Without knowing and controlling for those unknown confounding factors which have reduced dental caries by about 90%, any research evaluating dental caries and fluoridation may only be measuring far more powerful confounding factors or the prevailing bias.

Because the prevalence and incidence of dental decay has been a "moving target" decreasing by 90% over several decades from powerful unknown factors, any research using "before after studies" will have serious bias. This problem is noted in Donagh (2000)"P" below who found only three studies which were not "before after studies."

Researchers cannot assume all subpopulations or individuals were reducing dental caries at the same rates at the same time. The moving target is not moving in unison.

Reasonable minds should agree that before about 1960, the major national decay rates dropped without the help of fluoridation which had not even started and would not significantly be detected until measuring the 12 year olds having consumed fluoridated water. Any significant effect of fluoridation would not have been measured until the mid to late '60s perhaps '70s.

Do not forget the confounding factor of delayed tooth eruption in fluoridated communities of 6 months to 2 years. No research has corrected for the confounding factors which resulted in decay reduction nor the confounding factor of delayed tooth eruption. Put those two huge confounding factors together and current fluoride/dental caries research is seriously compromised.

Comparing predominantly fluoridated with nonfluoridated countries during the next 30 (1970 to 2000) years is a reasonable consideration to evaluate the possible coincidental effect of fluoridation. Both Neurath[418] and Chang[419] provide graphs below of WHO data during this later period. The reduction in dental caries to lower levels continued regardless of whether the country was fluoridated or not. The evidence does not support the theory that fluoridation was a significant contributing factor for the continued reduction in dental caries. Dental caries dropped by more than half before fluoridation and continued to drop at the same rate in all developed countries regardless of fluoridation.

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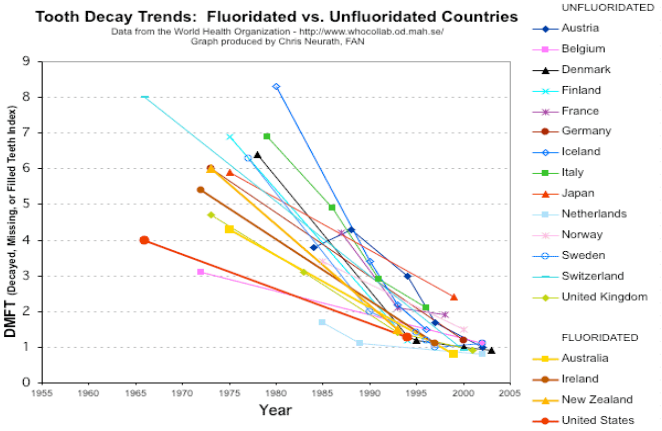
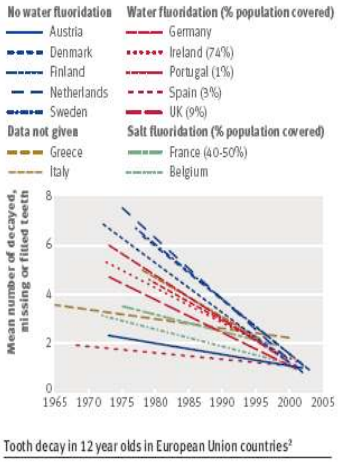
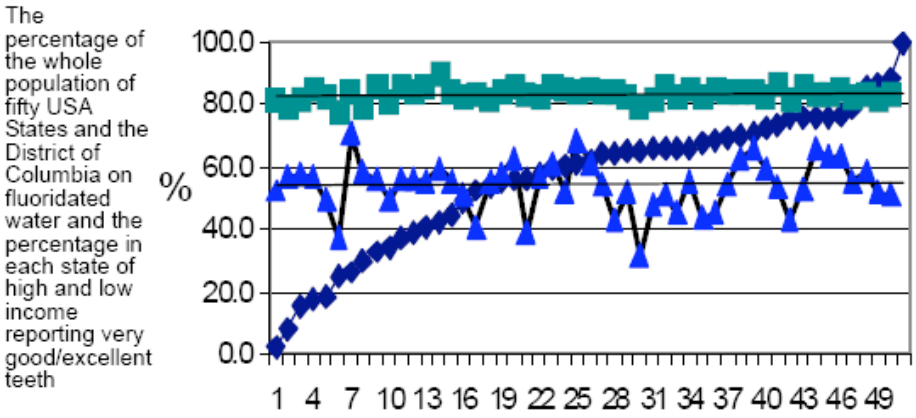
[418] http://www.fluoridealert.org/health/teeth/caries/who-dmft.html and http://www.fluorideresearch.org/384/files/384324-325.pdf Appendix 105

[419] Chen et al, BMJ 5 October 2007 Appendix 104





7. Osmunson (2007)[420] ranked the US states based on the percentage of the whole population in each country receiving fluoridated water. Something about socioeconomics is powerful. The rich are healthier. The percentage of the population on fluoridated water does not appear to have a common cause with dental health. A benefit from fluoridation is not detected. (See the graph below.)



EPA is flawed to put the public at risk with the assumption fluoridation is effective in reducing dental caries. Gathering a group of like minded biased individuals will not reduce the bias and repeatedly publishing the same bias does not reduce the bias. Good scientists must constantly fight the tendency to cherry pick the literature and the reviewers to prove and support a desired position. While the controversy over fluoridation rages, no one is looking for those elusive factors which have reduced the majority of caries.

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[420] http://www.fluorideresearch.org/404/files/FJ2007_v40_n4_p214-221.pdf Repeated from page 45 of first Comments to HHS/CDC.

B. "Fluoride in Drinking Water as One of Several Available Fluoride Sources"

Estimating fluoride exposure with numerous sources of fluoride and confounding factors is unreliable. Actual measured evidence of fluoride concentrations in serum and urine and urine excretion rate[421] is far more precise and the scientific standard for many years. Statistical estimates and assumptions based on historical studies is unreliable. Take "measurements" of the host and target organs rather than estimates based on assumptions.

C. "Trends in the Prevalence and Severity of Dental Fluorosis"

The EPA is horribly flawed to limit signs and symptoms of excess fluoride exposure only to dental fluorosis. Many people are being harmed from excess fluoride ingestion. These comments are full of examples of health risks.

The EPA should include stakeholders on both sides of the controversy. Cosmetic dentists treat the cosmetic damage from fluoride and should be included in any review of fluoridation. EPA internal reviews of fluoride exposure are simply a review of bias unless those opposed are included in the internatl reviews.

Academic freedom can be messy, but will provide greater safety than cherry picked research and researchers.

[421] Appendix 117 Extrand plasma urine

XXV. CRITICAL EVALUATION OF HHS/CDC REFERENCES

These comments are not a comprehensive review of all references provided by HHS/CDC as justification for lower concentrations of fluoride in public water. And HHS/CDC list of references is incomplete. For example, the list does not appear to even include the NRC (2006) review of fluoride in drinking water requested by the EPA which is the most comprehensive and definitive review to date. HHS/CDC needs to clearly state their jurisdiction and what their specific responsibilities encompass regarding fluoridation and total fluoride exposure. Does HHS/CDC have the same procedures as the FDA CDER for NDA? If not, what are the differences and on what Congressional authority does the HHS/CDC evaluate the safety and efficacy of substances used with the intent to prevent disease, drugs such as fluoride? These questions are critical because HHS/CDC promotes the ingestion of fluoride and state public health agencies and public water systems and the public assume HHS/CDC would not be promoting an unapproved illegal drug. The public assumes HHS/CDC has jurisdiction over the concentration of fluoridation.

(The HHS/CDC references are presumed to be in the possession of the HHS/CDC and not included here.)

1. HHS/CDC's bias has limited their review of health risks to dental fluorosis. Where are the references to empirical evidence proving the addition of hydrofluorosilicic acid to public water is safe for everyone and the scientific studies refuting the studies of health risks? The problem is both with the studies that are listed and those not listed. HHS/CDC is unwarranted in limiting the scientific review to only the risk of dental fluorosis.

2. Cost effectiveness has not been demonstrated with measured evidence. Estimates based on assumptions are incomplete and flawed. (Burt et al)

3. The CDC quotes them selves several times, simply repeating bias. Those opposed to fluoridation were excluded. As long as scientists and the studies are cherry picked for predetermined conclusion, the results can be predicted in advance.

4. Galagan (1953 and 1957) are historic and although interesting, do not include current measurement methods or additional sources of fluoride for total fluoride intake/exposure. Today scientists even in third world communities measure fluoride levels in serum and urine rather than guessing and estimating as the HHS/CDC/EPA have done.

5. Griffin (2007), a CDC report, may have done little more than measure bias. Of the 22 studies listed in Table 1, none are within the last 10 years. 5 studies are within the last 20 years. Griffing (2007) claims, "The combined results of the 9 studies examining the effectiveness of water fluoridation were significant." Griffin agrees there is a "paucity" of studies and states, "One limitation of this review is the quality and the quantity of studies on fluoride effectiveness among adults." Griffin avoided studies failing to find benefit.

Let us look closer at Griffin's chosen studies and the fluoride concentration compared in each study:

Burt compared 3.5 ppm vs. 0.7 ppm.
Englander (1962) compared 1.2 ppm vs. 0.1ppm,
Hunt (1989) 0.7 to 1.5 ppm vs. <0.5 ppm,
Morgan (1992) fluoride content NR,
Stamm (1990) 1.6 vs 0.2 ppm,
Thomas (1992) 0.9 vs. NR,
Wiktorsson (1992) fluoride content NR.
Murray (1971) 1.5-2.0 vs. 0.2 ppm
Grembowski (1992) community water system

Of those selected studies, only three come close to the proposed 0.7 ppm fluoride concentration in water. None compared the proposed 0.7 ppm (or even 1.0) public water with a low fluoride water such as 0.1 ppm, Englander (1962) was closest. In effect, only one study comes close to the 0.7 ppm proposed for fluoridation. Englander did not evaluate adding hyrdofluorosilicic or silicofluorides to hard water, but evaluated the "Effects of naturally fluoridated water on dental caries in adults." The author has published many articles on the benefits of fluoridation and was the examiner for all patients. No blinding was done, socioeconomics was not reported, health risks not considered, mineral content of the water not reported, and some confounding factors such as tooth brushing and diet were said to be the same in each city but specifics were not provided. Englander did take radiographs but compared to other studies of many thousands, this study had relatively fewer cohorts.

Griffin was unable to provide one study which reasonably applies to current fluoridation practices, the addition of silicofluorides to public water systems at 0.7 ppm. (See Appendix 72 Lack of Benefit)

F. Heller (1997) and Yiamouyiannis (1996)[422] reviewed 1986-1987NIDR survey of about 40,000 children. The HHS/CDC referenced Heller and both HHS/CDC and Heller avoided the earlier study of Yiamouyiannis. For 10 years the data was not released. Only with a possibility of suit was the public information disclosed.

Yiamouyiannis (1996) concluded: "No statistically significant differences were found in the decay rates of permanent teeth or the percentages of decay-free children in the F, NF and PF areas.

Such a conclusion could not stand, so Heller worked the data for a less formidable conclusion, but with careful understanding, Heller and Yiamouyiannis essentially agree. Heller concluded, Conclusions: A suitable trade-off between caries and fluorosis appears to occur around 0.7ppm F. Data from this study suggest that a reconsideration of the policies concerning the most appropriate concentrations for water fluoridation might be appropriate for the United States. [J Public Health Dent 1997;57(3): 136-431

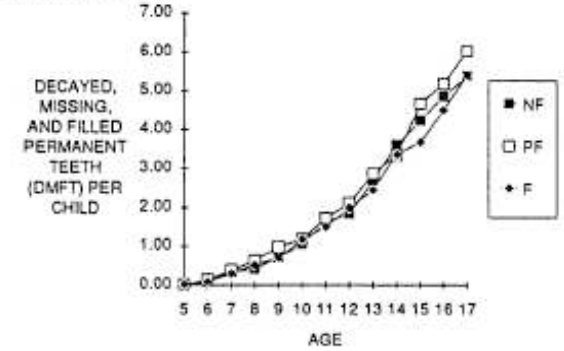
At first glance, the different conclusions of the same study seem to be

[422] Appendix 96 Yiamouyiannis (1996)

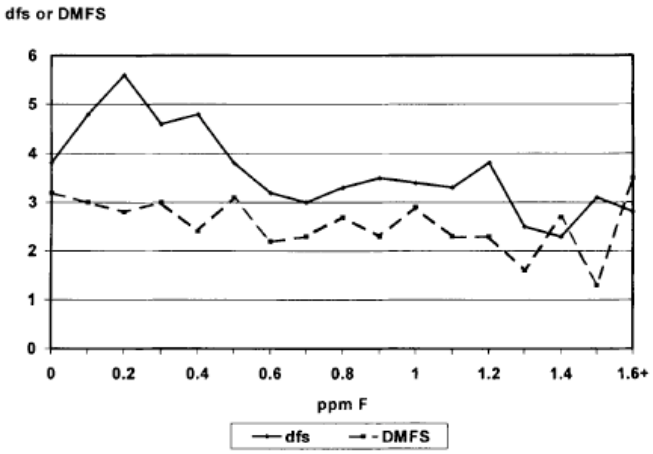
remarkable. Yiamouyiannis (1996) presented the graph below.

Figure 2A

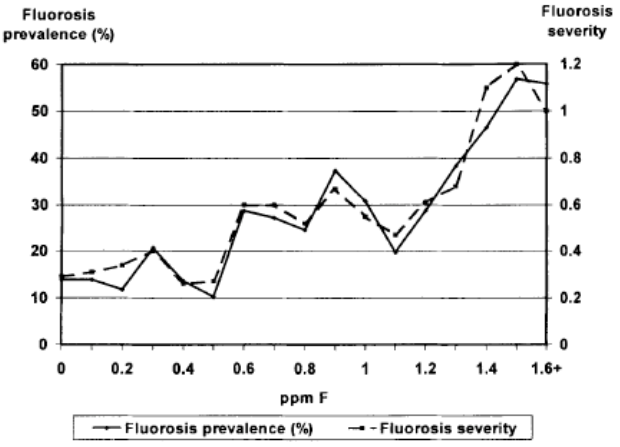
Tooth decay in residents of fluoridated (F), nonfluoridated (NF), and partially fluoridated (PF) areas who lived their entire life in the same household.



Heller divided children into two age groups, 5-10 dfs and 5-17 DMFS.



Heller also provided a graph of dental fluorosis, below.



Close to a doubling of dental fluorosis occurs from 0 to 0.7 ppm of fluoride in public water. HHS and CDC should note, a reduction from 1.2 ppm to 0.7 ppm F/public water actually increases dental fluorosis prevalence from about 20% to about 28%. However, below 0.5 ppm dental fluorosis is between 10-15%. 0.7 ppm is not protective and in this study doubles the rate of dental fluorosis. HHS/CDC must recommend lower fluoride concentrations than 0.7 ppm. We are not suggesting CDC increase the concentration of fluoride in water. We are simply demonstrating that 0.7 ppm is not protective.

At first glance, Heller made an apparent puzzling "opposite" conclusion of the same data. *"The major finding of this paper was that little decline in caries levels was observed between 0.7 and 1.2 ppm F, while considerable dental fluorosis was seen at this water fluoride level."*

However, on closer review, both Heller and Yiamouyiannis (1996) are saying the same thing in different ways. Heller simply chose two "random" numbers and said there was "little decline in caries levels." Heller could have used any two numbers or all the numbers because fluoride ingestion in the study with the largest number of cohorts did not find benefit from fluoridation.

Those with a bias of fluoride's efficacy, are not offended by Heller's conclusion because they assume other fluoride concentrations were not as "beneficial" and water could be adjusted within a range of 0.7 to 1.2 ppm and have relatively little change in caries levels. Heller did a careful wording on the data to support traditional bias even though the data showed no particular benefit between the 0.7 to 1.2 ppm. Heller essentially agreed with Yiamouyiannis's (1996) conclusion of no significant difference in caries regardless of fluoridation concentration. Heller chose 0.7 ppm to compare with 1.2 ppm, but could have used 0.0 ppm to compare with 0.7 ppm or any other concentration. HHS/CDC recommending 0.7 ppm is not supported by Heller's study.

Heller's statement that *"considerable dental fluorosis was seen at this water fluoride level"* is not clear. Is Heller referring to 1.2 ppm or 0.7 ppm or both? From the graphs of data, Heller was clearly referring to considerable dental fluorosis for both 0.7 and 1.2 ppm. Based on the data presented by both Yiamouyiannis and Heller, HHS/CDC will not reduce dental fluorosis by recommending 0.7 ppm fluoride in public water. Based on these studies and only considering dental fluorosis, fluoride concentration must by less than 0.5 ppm assuming no other fluoride sources have increased since this data was collected and assuming no other fluoride risks.

This data was collected in 1986 and 25 years later, HHS/CDC are just beginning to consider the lack of efficacy of fluoridation.

O. HHS/CDC failed to include the large USA survey by the Rand Corporation in 1977, which examined the tooth decay rate of 25,000 children, nonrandom selected

areas and reported no difference between fluoridated and nonfluoridated communities.[423]

P. HHS/CDC failed to include the large study by Jarvanin. Yiamouyiannis (1996) compared three areas of the Jarvanin study with his and compared tooth decay rates of 12 year olds finding no benefit. He reported, *"There was good agreement between this study and theirs with regard to tooth decay rate, after converting DMFS (decayed, missing and filled permanent tooth surfaces) to DMFT"*[424] In addition, the 36% decay rate decrease from the late '70s to the mid '80s should also be considered.[425]

Q. HHS/CDC failed to include the study by Hildebolt (1989)[426]. Hildebolt examined the tooth decay rates of over 6500 Missouri rural schoolchildren from grades 2 (average age 7.5) and 6 (average age 11.5). Among 6th graders living in the most intensively studied regions, the average DMFT+dft rate was 2.07 for those drinking nonfluoridated water and 2.17 for those drinking fluoridated water, compared to the MFT+dft rate of 2.00 reported for 11-year-olds living in Holcomb, Missouri in Yiamouyiannis (1996) study.

R. HHS/CDC failed to include Kumar (1986) who examined 1446 schoolchildren aged 7-14 from Newburg, New York (fluoridated in 1945) and cohorts from nonfluoridated Kingston, New York. The sample selection was nonrandom and had a response rate of only 50-65%. Nonetheless, the age-adjusted DMFT rates observed (1.5 for fluoridated Newburgh and 2.0 for nonfluoridated Kingston) were in line with the corresponding values obtained in Yiamouyiannis (1996) study for communities in the area (1.5 for nonfluoridated New Paltz, New York and 1.7 for fluoridated New York City). Based on this study, HHS and CDC should be shouting that fluoridation contributes to dental caries.

S. HHS/CDC failed to include other studies finding no significant difference in dental caries in fluoridated vs. non-fluoridated communities such as Colquhoun (1985[427] and 1987[428]), Gray (1987),[429] Diesendorf (1986)[430]

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T. HHS/CDC included three non peer reviewed internal statistical evaluations by Kelly from the 1970's. These may be persuasive documents, but do not rise to the level of published peer reviewed status. We are not opposed to HHS/CDC or anyone using unpublished non-peer reviewed evidence as long as the quality of study is good. However, HHS/CDC cannot reject unpublished high quality non-peer reviewed evidence which finds lack of efficacy or concern for risk. Each study must be reviewed.

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[423] Bell, R.M., Klein, S.P., Bohannan, H.M., Graves, R.C. and Dlsney, J.A.: Results of Basellne Dental Exams in the National Preventive Dentistry Demonstration Program. R-2862-RWJ. Rand Corporation, Santa Monica, CA, 1982.

[424] See Yiamouyiannis Appendix 96 and Jarvinen, S.: Epldemlologlc Characterlstlcs of Dental Caries: Relation of DhlFS to DMFT. Cornmunlty Dent. Oral Epidemiol., I1:363-366, 1983.

[425] Johnson, S. HHS **News (U.S.** Department of Health and Human Servlces: National Institutes of Health) June 21, 1988 in their references.

[426] Hlldebolt, C.F., Elvln-Lewis, M., Molnar, S., McKee, J.K., Perkins, h1.D. and Young, K.L.: Caries Prevalences Among Geochemical Regions of Missourl. Amer. J. Physical Anthropol., 78:79-92, 1989.

[427] Colquhoun, J.: Influence of Social Class and Fluoridation on Child Dental Health. Community Dent. Oral Epidemlol.. 13:37-41, 1985.

[428] Colquhoun, J.: Child Dental Health Differences in New Zealand. Community Health Studies, 11:85-90, 1987.

[429] Gray, AS.: Fluoridation: Time for a New Baseline? J. Canadian Dent. **ASSOC.,** 53:763-765, 1987.

[430] Dlesendorf, M.: The Mystery of Deciinlng Tooth Decay. Nature, **322:** 125-129, 1986.

U. HHS/CDC included a study from McClure (1943). This historical document is of a small group of individuals before significant fluoridation had taken place or the near universal fluoride medical and dental products were used. McClure determined dental fluorosis is "an example of the toxic effect of an excess intake of the element." There is no indication that McClure would have considered acceptable the toxic effect found in more than 40% of the public in 2002.

V. We were unable to locate the review by Koulourides (1990)[431] Perhaps this special issue has not been put on medline. The review does not appear to be a study and is mainly quoted by HHS/CDC and perhaps more of an internal document.

W. HHS/CDC references Lo (1990). It is unclear the reason for this reference. Lo confirms dental caries has decreased over 25 years but provides no measured evidence fluoridation was a contributing factor. Developed countries world wide have had the same dramatic decrease with or without fluoridation.

X. HHS/CDC references McDonagh (2000) but we are unable to locate in the list of HHS/CDC references the NRC (2006) report for the EPA. The 11 years since the McDonagh report has provided a good deal more research, so this study is historic. McDonagh could find no randomized controlled studies of water fluoridation and only 7 case-control studies. 26 level B studies were included, no level A studies. All but three were "before after studies." McDonagh (2000) Objectives:

"Objective 1: What are the effects of fluoridation of drinking water supplies on the incidence of caries?"

No confident answer was given.

Because fluoridation has been dropping in all developed countries measuring the moving target is problematic. In reality, measuring the DMFT over time in any developed community regardless of fluoridation will show a drop in dental caries. McDonagh repeatedly says, the studies reviewed were of moderate quality but limited quantity. "The estimates of effect could be biased due to poor adjustment for the effects of potential confounding factors."

"Objective 2: If water fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?"

The answer was similar to Objective 1. Again, no confident answer was given.

"Objective 3: Does water fluoridation result in a reduction of caries across social groups and between geographical locations, bringing equity?"

No "A" or "B" quality studies were available.

"Objective 4: Does water fluoridation have negative effects?"

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[431] Koulourides T. Summary of session II: fluoride and the caries process. J Dent Res 1990;69(Spec Iss):558

Each item will not be reviewed here again. McDonagh's response is incomplete, historic, and failed to include current assessment techniques. The NRC (2006) report included an additional six years of research and a new review should be done inclusive of all stake holders and all quality studies.

"Objective 5: Are there differences in the effects of natural and artificial water fluoridation?" More research is needed.

Y. The HHS/CDC references Levy (2010). Levy (2010) uses an historical approach of relating estimated intake of fluoride with dental fluorosis rather than measured fluoride serum levels.

1. Levy did not evaluate fluoride levels for the fetus with mothers on fluoridated water and fluoride products.
2. Levy did not evaluate children from birth to 3 months of age on formula with 0.7 ppm fluoridated water.
3. Levy did not evaluate serum or urine fluoride levels and relate them to dental fluorosis.
4. Exposure to fluoride was estimated.
5. Levy did not evaluate renal function as a factor for excess fluoride retention.
6. Levy assumed moderate dental fluorosis does not have a negative impact on oral health.
7. Levy did not consider any other adverse effect other than dental fluorosis.
8. Levy fully acknowledges study limitations and the need for more diverse populations.
9. Levy does not suggest a best fluoride concentration of water for use in making infant formula.

The references provided by HHS/CDC are not new. HHS/CDC has had the vast majority of these studies for decades and not protected the public by reducing exposure. Many more studies can be provided confirming probable harm to patients with fluoridation concentration of 0.7 ppm. The evidence is growing in one direction. The fluoridation experiment on the public without their individual consent is one of the biggest public health blunders of the 20th century.

HHS must support Congress and the President and designate one agency, the FDA CDER, to be responsible and no longer defer regulatory action and determine both efficacy and safety of fluoridation when marketed with the intent to prevent disease.

HHS/CDC do not have jurisdiction to approve or regulate drugs or foods. That role is with the FDA CDER. However, FDA CDER has abdicated their responsibility and HHS/CDC has assumed the FDA CDER role without legal authority to do so.

With the recommendation to lower fluoride concentration to 0.7 ppm, the public assumes that HHS/CDC is making the recommendation based on a complete thorough review of both sides of the efficacy issue and all health risks. If that assumption is incorrect, HHS/CDC must clearly specify what it does and does not include as the basis for their recommendation. If HHS/CDC is not including risks such as cancer, then other agencies, states and local water systems must understand the limited nature of their role.

XXV RECOMMENDATION:

A. The EPA AND HHS/CDC shall direct public water systems to seek FDA CDER approval for adjusting the concentration of fluoride in public water when the intent is to prevent dental caries. Unless FDA CDER approval is made, the EPA and HHS/CDC shall not promote fluoridation.

B. The EPA shall lower concentration of fluoride in public water until acute fluride serum levels drop below 0.02 ppm (as recommended by the CDC) and chronic serum fluoride levels are below 0.01 ppm for adults and 0.005 ppm for infants. Part of CDC currently recommends serum fluoride <0.02 ppm and part of CDC recommends fluoridation which frequently causes higher fluoride serum concentrations. The CDC is not consistent with itself. The EPA protects the pollutant in water rather than protecting people from excess pollutant.

C. Unless approved by the FDA CDER, HHS/CDC not set a minimum fluoridation concentration.

D. Unless approved by the FDA CDER, EPA set MCLG for fluoride at zero ppm, the same as arsenic and lead.

1. EPA must not protect pollutants assume efficacy for illicit drugs manufactured with public water.

2. The DRA must adhere to the SDWA and protect all. Providing a margin of safety, removing the overriding assumption of efficacy, and strictly evaluating all the evidence on safety and harm, protecting all, without an overriding influence of efficacy.

Sincerely ,

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Washington Action for Safe Water (WASW) is a nonprofit organization in Washington State dedicated to the protection of water from toxic substances, the freedom of water from drugs and the freedom of people to chose or refuse drugs. Several of the members of WASW are chemically sensitive and are experiencing harm from fluoride chemical.