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Is There More Fluoride In a Pea-Sized Amount of Toothpaste or a Liter of Water?

Posted by **Tom** • 20 April 2011 • Category: **Fluoride** • **Printer-friendly**

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Jake (whom I assume is a dentist) **left an interesting comment about fluoride on Sunday**. He said:

> *I had an anti-fluoride patient the other day that was saying he read somewhere that a pea-sized amount of toothpaste contains the same amount of fluoride in 1 liter of tap water (1 ppm). His argument was that the toothpaste labels says to call poison control if more than a pea-sized amount is swallowed (which it doesn't), and the same amount is in 1 liter of water. So he was wondering if he should call poison control every time he drinks more than a liter of water. It sounded ludicrous, but how much fluoride is actually in a pea-sized amount of toothpaste in comparison to 1 liter of water?*

Fluoride Warnings on Toothpaste (Click to enlarge)

I enjoy talking about water fluoridation. Looking back, I've actually written **15 different posts about fluoride**!

Jake's comment really got me wondering about how the fluoride levels compare between fluoridated water and toothpaste.

Do Toothpastes Contain a Warning Telling You to Call Poison Control?

First, let's take a look at the common anti-fluoride claim that fluoride is poison. I took a picture of the back of three different brands of toothpastes: Colgate, Aquafresh, and Crest. If you click on the picture, you can view a large size that will let you read the warning. Each tube has a similar warning. The back of the Colgate Total toothpaste box states:

If more than used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away.

But how much do people really use for brushing? There's the ultra-conservative pea size, and then there's the large stripe that toothpaste manufacturers want us to use so that we buy lots of toothpaste!

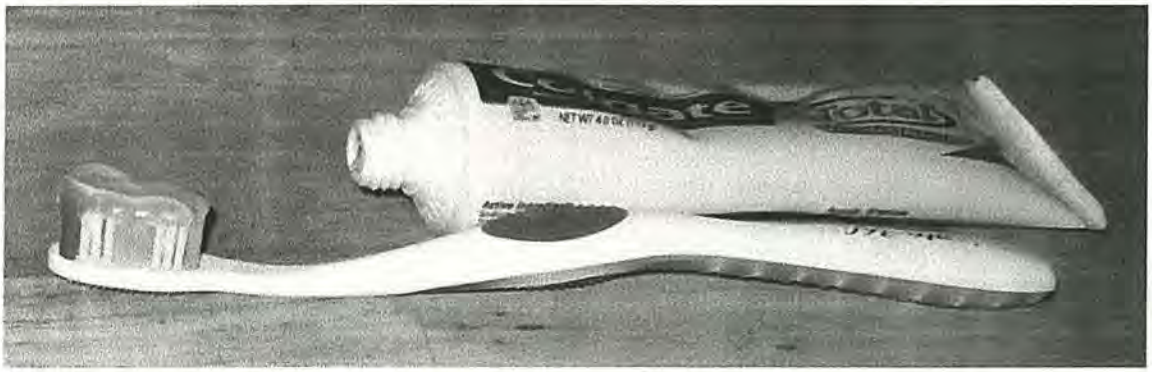
I decided to find out how much toothpaste is in a large stripe by conducting a two-part experiment.

My Toothpaste Experiment

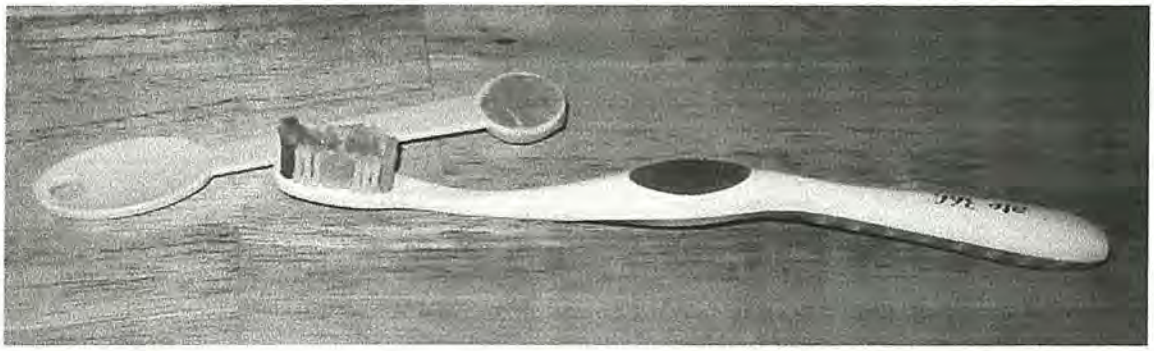
On the back of the toothpaste tube, it states that you should call the poison control center *if you swallow more than is used for brushing*. This is what the toothpaste manufacturers write. I took the liberty of assuming that a *normal* amount of toothpaste for them is a thick stripe on a manual toothbrush (like they show in their commercials).

I decided to find out exactly how much toothpaste is in a big stripe so that I could figure out how much fluoride it has. I got carried away and tried two different brands.

Here's the large stripe of Colgate Total that I put on my wife's toothbrush (are your toothbrush bristles as straight as hers? If not, it may be **time to get a new toothbrush**):



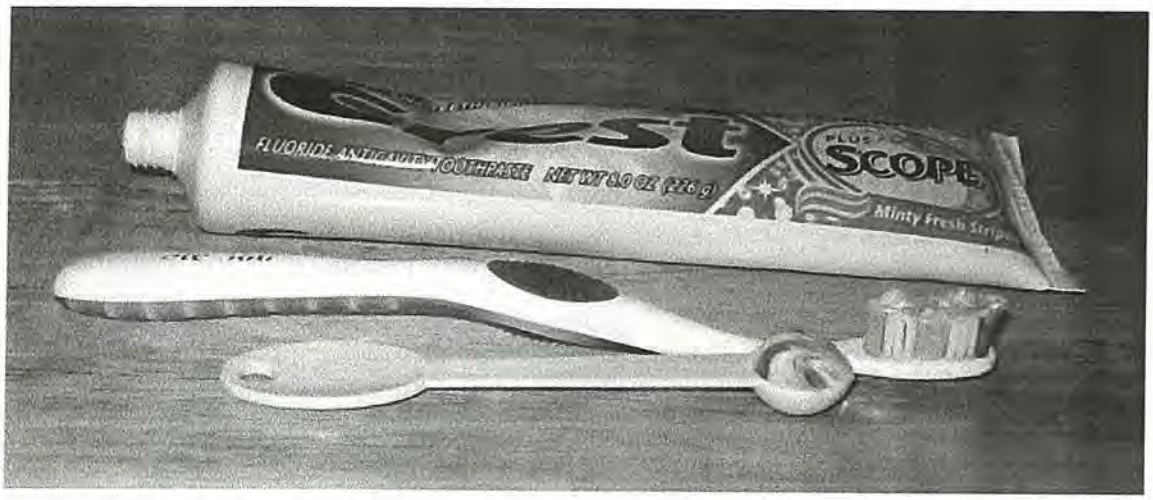
I measured the toothpaste and found that it filled the 1/4 teaspoon - giving us 1.25 ml of toothpaste:



Out of curiosity (and because it seemed like a fun idea after taking two finals over the past 36 hours), I measured the Crest Toothpaste as well. I was able to get a slightly bigger stripe on the brush this time. Unfortunately, the stripe I created just wasn't as good looking as it is on the toothpaste commercials!

However, if you want to practice making a beautiful stripe of toothpaste on your brush, I have to recommend the Crest since it is much thicker.

This large stripe of Crest ended up overflowing the 1/4 teaspoon, giving us about 1.75 ml of toothpaste:



I decided to take the average of my two "large stripes" to use as the baseline amount of toothpaste you can swallow and still be safe (according to the toothpaste manufacturers) - **which appears to be 1.5 ml from my unscientific experiment.**

Contrast this with a pea-size amount of toothpaste which is only 0.2 ml. Who would've guessed that the **average pea only takes up a volume of 0.2 ml**?

Now that we know how much toothpaste we use, we can figure out how much fluoride we would ingest if we swallowed a large stripe of toothpaste.

How Much Fluoride is in Toothpaste?

A majority of toothpastes on the market contain about 0.15% fluoride ion, which comes out to 1500 **ppm (parts per million.)**

In 1.5 ml of toothpaste (the large stripe pictured above) you would find **2.25 mg of fluoride.**

In a pea sized amount of toothpaste, you would only find **0.3 mg of fluoride.**

How Much Fluoride is in Fluoridated Water?

Most fluoridated water contains about 1.0 ppm. That means that in 1 liter of water, you would find about **1 mg of fluoride**.

Not sure how much fluoride is in your water? Then **find out how much fluoride is in your tap water!**

Comparing the Amount of Fluoride In Water with the Amount of Fluoride in Toothpaste

As you can see, you would have to drink over 2 liters of water to get the same amount of fluoride that you would get by swallowing a large stripe of toothpaste. You would only have to drink 300 ml of water (a little less than a 12 oz. can of soda) to get the same amount of fluoride you would get by swallowing a pea size amount of toothpaste.

You Don't Need to Call Poison Control When You Drink Fluoridated Water!

I'm sure Jake's patient was just trying to make a point. Point taken! However, according to the American Dental Association (**Page 31 in their Fluoridation Facts PDF**), it would take 5-10 grams of fluoride to cause fluoride toxicity in an average 155-pound man. That means that a 155-pound man would need to drink 5,000 liters of water (over 1300 gallons!) in order to get a toxic dose of fluoride.

The water would kill you (**as this tragic story illustrates**) long before the fluoride would have any toxic effect.

Conclusion

Interestingly, there is more fluoride in a liter of water than in a pea-sized amount of toothpaste, but more fluoride in a large stripe of toothpaste than in a liter of water. Here's what I found:

- In a pea size amount of toothpaste, there's 0.3 mg of fluoride.
- In a large stripe of toothpaste, there's 2.25 mg of fluoride.
- In one liter of fluoridated water, you'll find 1 mg of fluoride.

Although fluoride is great for your teeth, too much of it during development of the teeth can cause **dental fluorosis**.

Do you have any questions about toothpaste fluoride content or water fluoride content? I'd love to hear what you have to say in the comments section below. Thanks for reading!

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1.

Jake
21 April 2011 • 3:59 AM

Excellent response! Thank you. Yes, the patient did have a point. I told him that I was aware of the dangers of excess fluoride. It looks like we have differing definitions of excess fluoride, and his doesn't line up with the definition given by the ADA. He showed me and mentioned that he gets most of his information from fluoridealert.org. So, probably some anit-fluoride dentist on that website was making that argument, and it seems credible.

You mentioned that the lethal dose of fluoride is 5-10 grams. I was curious to know what an acute toxic dose was, so I did a little research. Oddly enough, I got my information from an anti-fluoride website. They mention research that shows an acute toxic dose around 5 mg/kg. So, in your 155 lb man, he would need at least 350 mg, or 350 liters of water, or over 1000 pea-sized amounts of toothpaste. They also used a case report that happened in Alaska where several hundred individuals got sick from a malfunction that put the fluoride levels at 150 ppm. The investigation concluded that the acute toxic dose was 0.3mg/kg. Much lower than 5mg, but still...do the math. Your 155 lb man would need 21mg, or 21 liters of water, or 70 pea-sized amounts of toothpaste. If you drank 21 liters of water (5.5 gallons) you'd die of hyponatremia before you even got sick from the fluoride.

Having said all of that, you still have to be safe, especially with kids in the house. A little 1-year old who's toddling all over and stumbles upon a tube of toothpaste could easily get sick if he ingests too much. However, the anti-fluoride hype is a bit irrational and over the top in my opinion.

Reply

Tom
21 April 2011 • 12:55 PM

Hi Jake - Thanks for running all the numbers above!

It seems like the ADA and anti-fluoride sites do end up disagreeing on the level of toxicity. When I was preparing a debate on the water fluoridation issue, I turned to a more neutral source, which is the book **Fluoride In Dentistry by Fejerskov**. The authors state, "Because there are several variables that can affect the outcome of acute fluoride poisoning, it is not surprising that the fatal dose is uncertain. In cases of human poisonings the uncertainty is amplified because, in most instances, the exact doses involved is not precisely known. **Dreisbach stated** that the acute lethal dose of fluoride for humans is 6-9 mg F/kg while **the data of Lidbeck suggested** that it is over 100 mg F/kg. The most frequently cited range for the certainly lethal dose of sodium fluoride was offered by Hodge & Smith (Hodge HC, Smith FA. Biological properties of inorganic fluorides. In: Fluorine chemistry. Simons HH, ed. New York: Academic Press;1965:1-42.) After reviewing case reports, they concluded that 5-10 g of sodium fluoride would certainly be fatal for a person with a body weight of 70 kg [which makes] the dose range for adults would be 32-64 mg F/kg."

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Original article

Neurodegenerative changes in different regions of brain, spinal cord and sciatic nerve of rats treated with sodium fluoride

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Abstract

Fluoride is known to cross the blood-brain barrier and alter the structure and function of neural tissue. There are few authoritative reports on neurodegenerative changes in hippocampus, neocortex, cerebellum, spinal cord and sciatic nerve in fluoride intoxication. We report the alterations in the structure of neuronal tissue after chronic administration of sodium fluoride (for 60days) to rats. Twelve male Wistar rats were divided equally into two groups: one group received 20 ppm of sodium fluoride (NaF) and the other group (which served as a control) received tap water for 60days.

The body weights and organic somatic index of brain in the sodium fluoride treated animals were significantly reduced, relative to the control group. Tissue fluoride levels of hippocampus, neocortex, cerebellum, spinal cord and sciatic nerve, all increased significantly in fluoride treated rats. Electron microscopy of the hippocampus, neocortex, cerebellum, spinal cord and sciatic nerve showed neurodegenerative changes in the NaF treated group compared to controls. Axon deterioration, myelin sheath degeneration and dark cells with scanty cytoplasm were observed in spinal cord and sciatic nerve in the treated group. Other distinctive morphological alterations observed were: vacuolated swollen mitochondria in neocortex, hippocampus and cerebellum; myelinated fibers with breaks in continuity (axon partly preserved and partly vacuolated) in hippocampus; myelin splitting and vacuolated schwann cell within the cerebellum and sciatic nerve respectively. Thus, neurodegeneration was clearly evident in the hippocampus, neocortex, cerebellum, spinal cord and sciatic nerve on fluoride exposure.

Key words: sciatic nerve, cerebellum, sodium fluoride, hippocampus, transmission electron microscope

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Fluorosis is a well-defined clinical entity characterized by the toxicity of elevated fluoride intake on teeth, bones and soft tissues[1,2]. Fluoride-exposed rat pups show mild degeneration of nerve cells[3]. Fluoride-induced morphological alterations in liver were reported with transmission

electron microscopy[4]. Cell lysis, mitochondria vacuolation, crenulations of nuclear membrane and cell shrinkage has been observed in renal cells of young pigs treated with fluoride[5]. The molecular basis of fluoride action is mainly concerned with cellular enzymes, especially antioxidant enzymes. High levels of fluoride in drinking water (1-12ppm) affect central nervous system directly without first causing the physical deformities of skeletal fluorosis[6,7]. According to Mullenix et al[8] hyperactivity and cognitive deficits can be correlated with hippocampus damage induced by sodium fluoride (NaF). Distinctive alterations in the brain have also been observed with the chronic administration of aluminium Fluoride (AlF_3) and NaF[9]. Histological changes in the brain of young, fluoride-intoxicated rats have been reported by Shivarajashankara[10]. However most of the studies have so far been confined to the whole brain. This study reports the neural changes with respect to the different regions of the brain with emphasis on hippocampus, neocortex and cerebellum of the brain, spinal cord and sciatic nerve by using transmission electron microscope (TEM), in rats administered with 20 ppm NaF for 60 days.

Materials and methods

Male Wistar rats weighing 180 ± 20gm were used in this experiment. They were housed in polycarbonated cages bedded with paddy husk; commercial pellet diet (Hindustan Lever Limited, Bangalore, India) and water were provided *ad libitum*. The animals were then divided into two groups, "control" and "fluoride" groups (n=6) respectively. The control group was given ordinary tap water, while the fluoride group received 20ppm concentration of fluoride through gavage feeding for two months. Following the treatment period the rats were euthanized and the brain (further dissected into cerebellum, neocortex and hippocampus) spinal cord and sciatic nerve were removed for TEM studies. Fluoride levels in the brain and spinal cord were determined with fluoride specific ionic electrode (Orion R 96-090).

For TEM studies, samples were transferred to vials and fixed in 2.5% glutaraldehyde in 0.5 M phosphate buffer pH 7.2 for 24 hrs at 4°C and post-fixed in 0.5% aqueous osmium tetroxide in the same buffer. After the post-fixation, the samples were dehydrated in a series of graded alcohol, infiltrated and embedded in spurs resin[11]. Both semi-thin and ultra-thin sections were cut with a glass knife on a leica ultra cut UCT-GA-D-E1-00 ultra microtome. Semi-thin sections of 200-300nm thickness were stained with toludine blue and ultra-thin section 50-70nm thickness were mounted on grids, stained with saturated aqueous uranyl acetate and counter stained with 4% lead citrate. sections were then examined at various magnifications under TEM (Hitachi, H-7500) at Ruska Laboratory, College of Veterinary Science, N.G Ranga Agricultural University, Hyderabad, India.

Results

The results revealed a significantly ($p<0.05$) higher mean value of fluoride in the neural tissue of the fluoride group compared to the control group. The mean body weight and relative organ body weight of brain was found to be relatively low in fluoride-treated group compared to control (Table I).

Neurodegenerative changes were observed in different regions of brain (neocortex, hippocampus, cerebellum), spinal cord and sciatic nerve of fluoride exposed group under different magnifications (Fig 1-16). The sciatic nerve showed normal microscopic features like oval nuclear membrane, normal electro-density and empty appearing axons in control group (Fig 1) while in fluoride group vacuolation of Schwann cells with enlarged axons and disrupted myelin sheaths were clearly observed within the sciatic nerve (Fig 2). As seen in Fig 3 normal nuclei and nucleoli were observed in the spinal cord in the control group, while the fluoride group (Fig 4, 5 & 6) showed irregular nuclei with normal nucleoli, vacuolated cytosol and axons with split myelin. In the cerebellar tissue of the control group normal nuclei and myelinated fibers with empty appearing axons, were seen (Fig 7).

Table I. The body weight, somatic index of brain and accumulation of fluoride in brain of rat after sodium fluoride treatment

Group	Fluoride levels (μg/gram tissue)	Body weight (grams)	Organ somatic index
Control	0.2452 ± 0.013	111.2 ± 2.662	2.072 ± 0.04
Fluoride	0.864 ± 0.014	92.888 ± 2.621	1.3464 ± 0.137

Values represent mean ± standard deviation. The values are significant at $p<0.05$

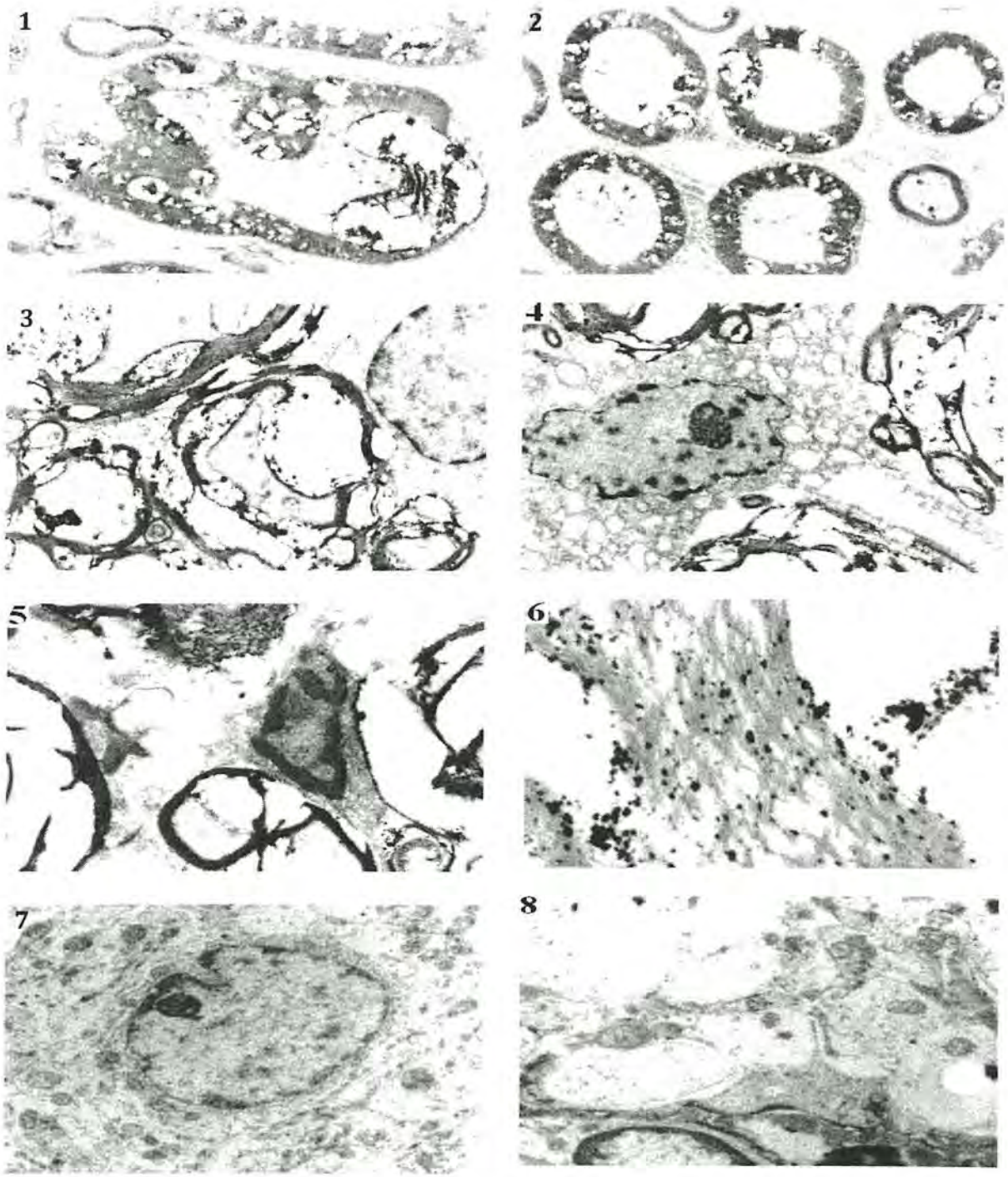

Fig 1. Sciatic nerve in control rat (magnification 3k). Electro density normal, myelin, debris cytoplasm, empty appearing axons (EA); **Fig 2.** Sciatic nerve in fluoride treated rat (magnification 3k). Vacuolation of schwann cells (VS)-cytoplasm appearing enlarged axons (CAE), disrupted myelin sheaths (DMS), fiber density normal; **Fig 3.** Spinal cord in control rat (magnification 7k). Normal dense myelin in cross section (NDM), normal nucleus with nucleolus, organelle contents normal; **Fig 4, 5 & 6.** Spinal cord in fluoride treated rat (magnification 3.5k, 4k and 3k respectively). Irregular nucleus (IN) with normal nucleolus, vacuolated cytosol, myelinated axons normal, disrupted myelin sheath (DMS); **Fig 7.** Cerebellum in control rat (magnification 3k). Normal oval mitochondria (NOM), neuropile normal, nuclei appear normal, myelinated fibers noted, empty appearing axons, organelle contents normal, nucleus normal (NN); **Fig 8 & 9.** Cerebellum in fluoride treated rat (magnification 3k). Predominantly blood vessels (PBV) appear normal, astrocytes normal, swollen mitochondria (SM), crenulated nuclear membrane (CNM), dumbbell shaped mitochondria.

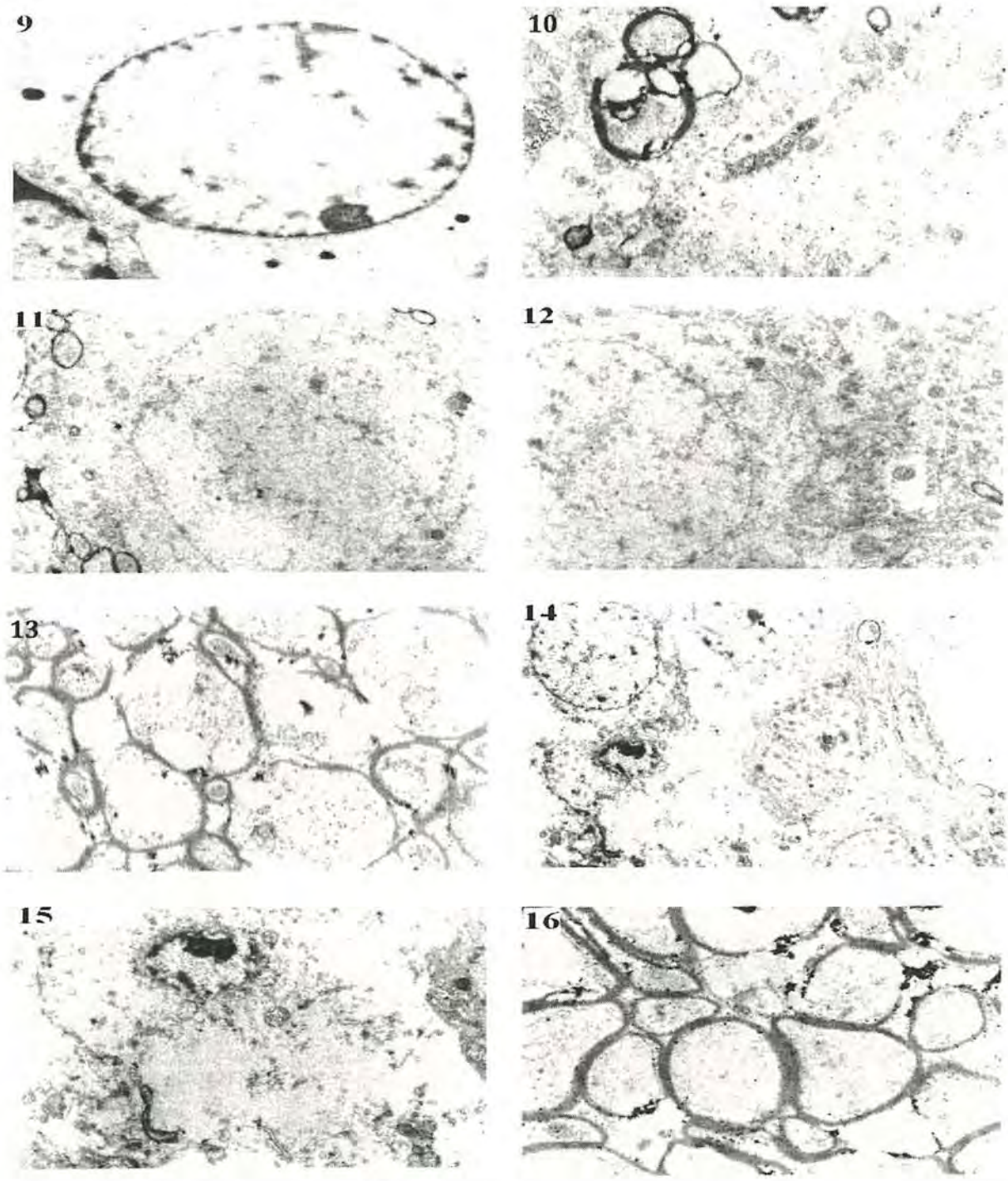

Fig 10. Neocortex in control rat (magnification 3.5k). Oligodendrocyte nucleus appears normal. Few myelinated fibers noted, few mitochondria appear normal (MA), few show vacuolated changes; **Fig 11 & 12.** Neocortex in fluoride treated rat (magnification 4k and 7k respectively). Oligodendrocyte nucleus (ON) normal, myelinated fibers shows myelin splitting (MS). Few axons shows thin myelin (TM), axon preserved, stain precipitate; **Fig 13.** Hippocampus in control rat (magnification 8k). Myelinated fibers (MF) empty axons, stain precipitates; **Fig 14, 15 & 16.** Hippocampus in fluoride treated rat (magnification 8k, 2k and 4k respectively). Disrupted myelin fibers (DMF), rough endoplasmic reticulum strands, organellae preserved, mitochondria show vacuolation. Cell loss more vascular inclusion (CMV), compressed golgi cisternae (CGC), granulated mitochondria (GM).

The cerebellar tissue of the fluoride treated rats (Fig 8 & 9) has shown predominantly normal blood vessels and normal astrocytes, however the mitochondrial morphology became dumbbell shaped and nuclear membrane crenulated. The neocortex of brain in control animals (Fig 10) showed normal oligodendrocytes with normal-appearing nuclei, axons that showed thin myelin and normal-appearing mitochondria. Significant changes in the cell pattern were observed in the neocortex of the brain on fluoride treatment; myelinated fibers with myelin splitting, vacuolated mitochondria, normal oligodendrocyte with slight indentation of nucleus and few axons with thin myelin (Fig 11 & 12). The cytoarchitecture of hippocampus of brain in the fluoride group revealed degrees of alteration in structure which included degenerated cell bodies, granulated mitochondria, vacuolation in cytosol, compressed golgi cisternae and scattered rough endoplasmic reticulum (Fig 14, 15 & 16). Thin broken myelinated fibers, axon partly preserved and partly vacuolated, in hippocampus were observed in the fluoride exposed group (Fig 13). This contrasts with the normal microscopic features like myelinated fibers, empty axons and unchanged nuclear morphology in control animals.

Discussion

In previous reports neurological changes associated with skeletal fluoride have been attributed to compression radiculomyelopathy[12]. The central and peripheral nerve damage has been ascribed to a direct toxic effect of fluoride whereas the loss of function in the motor neuron was attributed to osteoproliferation of vertebrae. Many reports have revealed that excessive fluoride treatment induces extensive damage to the nervous system[8,13].

In our earlier laboratory studies[14] we demonstrated the suppression of both antioxidant enzymes and energy-generating enzymes in female mice treated with 20 mg/kg body weight of NaF for 14 days. The Fluoride induced changes within neuronal cells included scattered and low RER, swollen mitochondria, compressed golgi cisternae in the previous studies[5,15]. It appears that fluoride in a concentration of 20 ppm extensively damages neurons in the brain, spinal cord and sciatic nerve of rats leading to paralysis and brain dysfunction. Varner et al[16] reported that the chronic administration of drinking water containing aluminium fluoride and sodium fluoride to rats resulted in distinctive morphological alteration in specific regions of the brain. In our experiment we found the vacuolation of schwann cell with enlarged and disrupted myelin sheath in the sciatic nerve of the fluoride group. Beside these changes we have also observed the significant changes like crenulated nucleus, vacuolated cytosol at different magnification in the spinal cord of fluoride group compared to control group.

Free radicals and lipid peroxidation products generated by excitotoxicity have been shown to damage dendrites and synaptic connection and, if unrelieved can lead to neuronal destruction[17]. Fluoride is known to accumulate within various parts of rat brain especially in hippocampus[13,18]. Fluoride intoxication decreases the synthesis of cholesterol, free fatty acid, proteins amino acids and RNA in the brain of rabbits[19]. The possible mechanisms for the neurodegenerative effects of fluoride are likely related to excitotoxicity by free radical and lipid peroxidation which impairs the glutamate removal and by activating microglia which contain abundant stores of glutamate[18,20,21]. It has been shown that one of the lipid peroxidation products, 4-hydeoxynonenal (4-HNE), specifically impairs synaptic functions and inhibits glutamate removal by the glutamate transport protein[22]. It was also observed that NaF increased nitric oxide synthase activity plays a major role in all neurodegenerative diseases, primarily by damaging mitochondrial energy production, Inhibiting glutamate reuptake and stimulating lipid peroxidation[23,24,25].

In conclusion, electron microscopic observations comprehensively defined the structural alteration in the specific regions of the brain like the neocortex, hippocampus, cerebellum, spinal cord and sciatic nerve, secondary to fluoride exposure in rats. Further studies are required to unravel the molecular and cellular mechanisms responsible for neurodegenerative changes in cytoarchitecture of the specific structures of the nervous system. This is the first report on ultrastructural changes in the neuronal cells in fluoride-treated rats using TEM.

Conflict of interest: None

Acknowledgments

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HEALTH RELATED RESEARCH STUDIES

Excerpts from:

Fluoride: The Aging Factor (2nd Edition)
Author: Dr. John Yiamouyiannis
Published: Health Action Press
Year: 1986 (first edition 1983, third edition 1993)
ISBN: 0-913571-01-6

About the Author: Dr. John Yiamouyiannis was, until his death in the fall of 2000, the world's leading authority on the biological effects of fluoride. His formal education included a B.S. in biochemistry from the University of Chicago and a Ph.D in biochemistry from the University of Rhode Island. After a year of postdoctoral research at Western Reserve University Medical School, Yiamouyiannis went on to become biochemical editor at Chemical Abstracts Service, the world's largest chemical information center. It was at Chemical Abstracts Service, where Yiamouyiannis became interested in the damaging effects of fluoride.

Chapter 4 - Breaking Down the Body's Glue

All animals, including humans, are made up of cells. The cell, the basic unit of life, can be identified under a microscope by its outer membrane and a nucleus within the membrane.

Some cells are able to produce a protein called collagen. In this book, the term "collagen" refers to collagen as well as collagen-like proteins. This process occurs inside the cell. Little globules called vesicles carry the collagen from the inside of the cell to the cell membrane where it is released to the outside of the cell. There, the collagen thickens into fibers.

The five different types of cells capable of producing and releasing collagen in this way are:

- fibroblasts, which produce collagen for the structural support of skin, tendons, ligaments and muscle;
- chondroblasts, which produce collagen for the structual support of cartilage;
- osteoblasts, which produce collagen for the structual foundation and framework upon which calcium and phosphate are deposited, giving rise to bone;
- ameloblasts, which produce collagen for the structural foundation and framework upon which calcium and phosphate are deposited, giving rise to tooth enamel.
- odontoblasts, which produce collagen for the structual foundation and framework upon which calcium and phosphate are deposited, giving rise to the inner part of the tooth. This material is called dentin.

Like other proteins, collagen is composed of amino acids linked together in a chain. However, collagen contains two additional amino acids, hydroxyproline and hydroxylysine, not found in other proteins. Thus when collagen breaks down, the hydroxyproline and hydroxylysine levels in the blood and urine increase.

Researchers from Harvard University and the National Institutes of Health knew in the 1960s that fluoride disrupted collagen synthesis. It was not until 1979-1981, however, that a new flurry of

research activity in this area began.

In 1981, Dr. Kakuya Ishida of the Kanagawa Dental University in Japan reported the results of studies in which he fed laboratory animals 1 part per million fluoride in their drinking water and analyzed the urine for hydroxyproline. He found that urinary hydroxyproline levels increased in those animals. This indicates that as little as 1 part per million fluoride interferes with collagen metabolism and leads to its breakdown.

Dr. Marian Drozdz and co-workers from the Institute of Bioanalytical and Environmental Studies in Katowice, Poland found increased hydroxyproline and hydroxylysine levels in the blood and urine as well as a decrease in skin and lung collagen levels in rats fed 1 part per million fluoride in their drinking water.

Dr. Anna Put and co-workers from the Department of Pharmacology of the Pomorska Akademy of Medicine in Szczecin, Poland also found that fluoride increased hydroxyproline levels in urine.

Drs. A.K. Susheela, Y.D. Sharma and co-workers from the All-India Institute of Medical Sciences found that fluoride exposure disrupts the synthesis of collagen and leads to the breakdown of collagen in bone, tendon, muscle, skin, cartilage, lung, kidney, and trachea.

As already noted, small vesicles transport collagen from the inside of the cell to the outside of the cell. Drs. Harold Fleming and Val Greenfield of Yale University School of Medicine found a larger number of these vesicles in collagen forming cells (ameloblasts) in animals exposed to fluoride. This work was recently confirmed by S. Chen and D. Eisenmann of the University of Illinois, who also found a fluoride-induced increase of these granules in ameloblasts.

It appears that fluoride disruption of collagen synthesis in cells responsible for laying down collagen leads these cells to try to compensate for their inability to put out intact collagen by producing larger quantities of imperfect collagen and/or noncollagenous protein.

In 1983, Dr. John R. Farley and co-workers from Loma Linda University showed that treatment of bone cells with less than 1 part per million fluoride increased collagen formation by 50 percent. One year later, Dr. J.R. Smid and co-workers from the Department of Oral Biology at the University of Queensland in Australia found that fluoride ingestion led to an increase of noncollagen proteins as well as collagen proteins.

This is supported by the works of Drs. J.H. Bowes and M.M. Murray, Dr. Kh.A. Abishev and co-workers, and Dr. B.R. Bhussry who report a vastly higher protein content in teeth and bone damaged by fluoride. Clinical findings also show that new irregular bone growth is stimulated by fluoride.

The drawings below illustrate the effect of fluoride on collagen metabolism.

While collagen is made by many different types of cells and, under normal circumstances, is only mineralized in teeth and bones, the body obviously has some mechanism to mineralize the collagen of some tissues while leaving the collagen of other tissues, such as skin, ligaments, tendons, etc., unmineralized.

During the aging process, the body loses its ability to discriminate between which tissues should be mineralized and which tissues should not. As will be shown, consumption of fluoride results in the same loss of the body's ability to discriminate. In other words, mineralization of tissue, such as bone, which should be mineralized, is disrupted, and tendons, ligaments, muscles, and other soft tissue which should not be mineralized start to become mineralized as a result of fluoride exposure.

By interfering with collagen production, fluoride leads to the production of larger quantites of imperfect collagen and/or other types of protein and thus interferes with the body's normal regulation of collagen mineralization.

The type and array of collagen and collagen-related proteins made by the various collagen-producing cells determine whether or not the collagen framework will be mineralized. During the aging process, cumulative damage to these cells leads to the diseases attributed to "old age" - arthritis, arteriosclerosis, brittle bones, wrinkled skin, etc. Consumption of fluoride produces the same effects and results in the same diseases.

Fluoride probably acts by interfering with enzymes essential for setting up the proper conditions for producing intact collagen. Thus, as has already been indicated, larger amounts of imperfect or deformed collagen fibers are formed and the body's ability to regulate collagen formation and mineralization is hindered...

Chapter 6 - Aging the Bone: The Degenerative Effects of Skeletal Fluorosis

Now let's look at the bone. Unlike the ameloblasts, and odontoblasts of teeth whose regenerative activity stops after tooth development, osteoblasts continue to actively lay down collagen, and new bone formation continues to take place.

If a tooth breaks or fractures, you're out of luck. The damage cannot be repaired. However, if a bone breaks or fractures, osteoblasts lay down collagen to produce a framework for new bone formation to repair the damage.

Bone also has the ability to rejuvenate itself. As older bone is removed by bone scavenger cells called osteoclasts, osteoblasts lay down collagen to produce a framework for new bone formation to renew the skeletal structure.

Thus, damage to collagen production in bone can interfere with the normal processes of bone rejuvenation and repair throughout life.

Cartilage

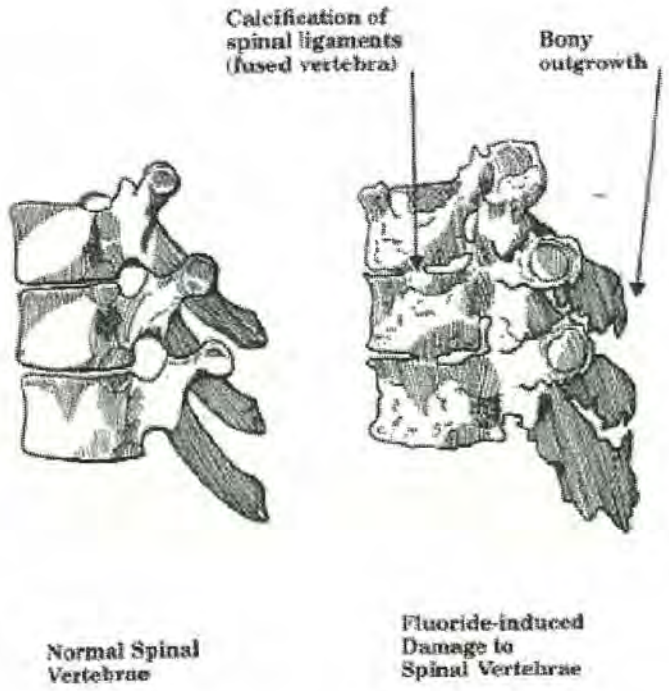
The balls and sockets of bones are lined with a smooth, tough elastic substance called cartilage. Maintaining the integrity of cartilage depends largely upon the ability of cells called chondroblasts to lay down noncalcified collagen which is the major structural component of cartilage.

The Effect of Fluoride on Bone and Cartilage

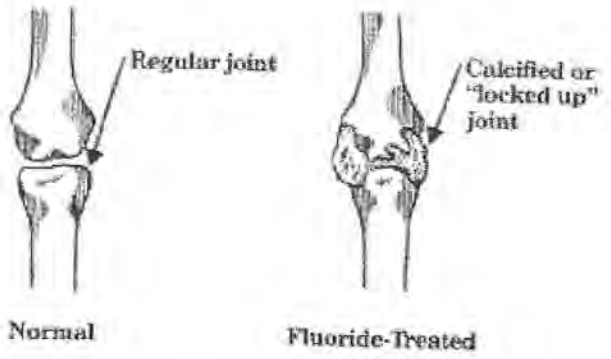
Fluoride has been shown to interfere with collagen formation in osteoblasts and chondroblasts. If, as pointed out, increased production of imperfect collagen or collagen-like protein results in mineralization of tissues which should not be mineralized, and vice versa, one would expect a calcification of ligaments, cartilage, and tendons as well as the formation of poorly and overly mineralized bone. This is exactly what happens after exposure to fluoride.

In discussing their examination of tissues from patients exposed to fluoride, Drs. A. Singh and S.S. Jolly, world-renowned experts on the clinical effects of fluoride on bone, point out that:

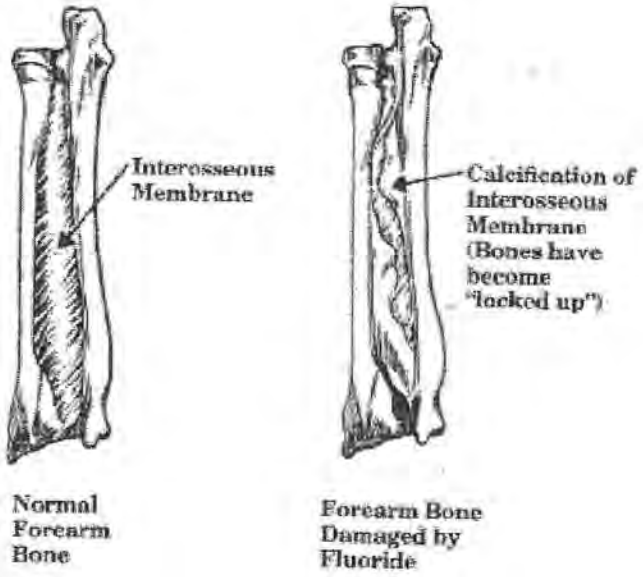
- The most noticeable changes are detected in the spine with calcification of various spinal ligaments, resulting in pronounced bony outgrowths. The other bones show numerous spiky outgrowths especially in tendons (collagen-rich fibrous tissue which attach muscles to bone) and ligaments (collagen rich fibrous tissue which holds bones together). Under careful inspection, the bony outgrowths are found to consist of coarse, woven fibers which are largely uncalcified.



- Irregular bone is also laid down in joint sockets...



and interosseous membranes (membranes between bones in arms and legs).



- In more advanced cases of fluoride exposure, bones become held together by masses of new bone laid down in the joint socket, ligaments and tendons. This results in the locking up of joints and permanent inability of victims to move or flex their joints. Vertebrae become fused at many places. This results in the characteristic "hunch back" symptom of skeletal fluorosis.

- There is a low degree of remineralization of the bone itself, which is partly due to a wide seam of uncalcified osteoid (collagen).

In 1973, Dr. Jolly and co-workers presented radiological evidence of skeletal fluorosis which results in these bone deformities in parts of India where the drinking water contained as little as 0.7 parts per million fluoride, with the occurrence and severity increasing with increasing levels of fluoride in the drinking water.

RADIOLOGICAL EVIDENCE OF SKELETAL FLUOROSIS IN MALES 21 YEARS OF AGE AND OLDER

Village	Water Fluoride (ppm)	Percentage
Mandi Baretta	.7	2.8
Kooriwara	2.3	40.0
Gurnay Kalan	2.4	19.6
Ganza Dhanaula	4.2	26.3
Bajakhana	5.1	46.9
Rajia	5.2	52.2
Village Baretta	5.5	29.6
Rorki	7.0	52.5
Saideke	8.2	52.6
Khara	9.4	80.1

In 1985, Dr. I. Arnala and co-workers of Kuopio University in Finland reported that: *"The upper limit for fluoride concentration in drinking water that does not increase the amount of unmineralized bone is roughly 1.5 parts per million. ...We should however, recognize that it is difficult to give a strict value for a safe concentration in drinking water because individual susceptibility to fluoride varies."*

In addition to fluoride-induced bone irregularities, one could expect that the fluoride-induced irregularities of the joint cartilage (which is normally smooth) would result in the irritation and inflammation commonly referred to as arthritis. One could also expect fluoride to cause an increase in the incidence of fractures and a decrease in the body's ability to heal bone breaks and bone fractures.

Clinical observations show that this is exactly what happens.

Arthritic Changes

Drs. Singh and Jolly point out that early symptoms of fluoride-induced damage to bones and cartilage start with *"vague pains noted most frequently in the small joints of the spine. These cases are frequent in the endemic* [local] *areas and may be misdiagnosed as rheumatoid or osteoarthritis.*

"In later stages, there is an obvious stiffness of the spine with limitation of movements, and still later, the development of kyphosis [hunch back].

"There is difficulty in walking, due partly to stiffness and limitation of the movements of various joints....

"Some patients complain of dyspnea, [difficulty in breathing] *on exertion because of the rigidity of the thoracic cage."*

Dr. Jolly and co-workers reported these symptoms in parts of India where the drinking water contains as little as 0.7 parts per million fluoride, the occurrence and severity increasing as the

fluoride content in the drinking water increased.

In the United States, Dr. George Waldbott also diagnosed some of the early symptoms listed above, including arthritis and joint pains, as being due to the consumption of water fluoridated at 1 part per million. He was able to bring about a reversal in these symptoms by eliminating fluoridated water from the patients'diets. However, if left unattended, the degeneration leads to the advanced stages of arthritis and "old age."

Similar arthritic symptoms have been reported among people exposed to air-borne fluoride in Switzerland, Germany, Britain, United States, Canada, and North Africa. Dr. Yiamouyiannis was contacted by an independent British broadcasting company who consulted him concerning a problem they had found in a brick manufacturing area about 50 miles outside of London where they reported that over 90% of the population was suffering from arthritis induced by air-borne fluoride.

Dr.Waldbott noted the possibility of the age-accelerating effects of fluoride with respect to arthritis and stated:

"Among the elderly, arthritis of the spine is an especially common ailment that is customarily attributed to 'aging.' Since fluoride retention in bones increases as a person grows older, how can we disregard the possibility that this 'old age' disease might be linked with fluoride intake? For example ... [others have] described in detail X-ray changes encountered in skeletal fluorosis in North Africa, that are in every respect identical to those present in the arthritic spine of the elderly."

Breaks and Fractures

In 1978, Dr. J.A. Albright and co-workers from Yale University reported at the Annual Meeting of the Orthopedics Research Society that as little as 1 part per million fluoride decreases bone strength and elasticity.

In 1983, Dr. B. Uslu from Anadelu University School of Medicine in Eskisehir, Turkey reported that addition of fluoride to the drinking water of rats with fractured bones resulted in defective healing of the fracture due to disruption of collagen synthesis.

In 1978, the ***Journal of the American Medical Association*** published an editorial pointing out that *"in several short-term studies, fluoride has been administered for treatment of involutional osteoporosis, alone or with supplemental calcium, vitamin D or both. No studies have demonstrated alleviation of fracture[s]. ... However, studies in humans have shown an increased incidence of... fractures. When high doses of fluorides have been given to animals receiving a diet that was otherwise unchanged, most studies have shown no change or a decrease in the strength of the bone."* They also pointed out that administration of fluoride resulted in nonmineralized seams in bones, resulting in the disease called osteomalacia. These nonmineralized seams imply that breaks and fractures in the patients' bones would tend to heal more slowly.

It is ironic that anyone would ever think of treating osteoporosis (a disease in which the bones lose calcium) with fluoride, a substance which leads to decalcification of bone. In 1977, Dr. Jennifer Jowsey, one of the originators of fluoride therapy for osteoporosis, admitted that fluoride was

leading to a greater degree of osteoporosis (demineralization) in some bones while leading to osteosclerosis (overmineralization) in others. In other words, fluoride treatment of osteoporosis "robs Peter to pay Paul" and leads to a general weakening of the bones.

In 1980, Dr. J.C. Robin and co-workers from the Roswell Park Memorial Institute confirmed the foolishness of using fluoride for the treatment of osteoporosis by publishing their results in the ***Journal of Medicine***. According to the authors, *"fluoride had no preventive effect. In some experiments there was even a deleterious effect of fluoride."* They found fluoride accelerated the process of osteoporosis leading to a loss of calcium from the bone.

Claims that the amount of fluoride found in fluoridated water would help prevent osteoporosis have been studied epidemiologically. Researchers from the U.S. National Center for Health Statistics claimed to find no preventive effect, while researchers from the National Board of Health in Finland claim to find a preventive effect. However, the number of people examined in these two studies was far too small to yield statistically meaningful results. The studies of Drs. Singh and Jolly as well as the studies of Dr. I. Arnala and co-workers who report increases in unmineralized bone, are consistent with the finding of Dr. Robin that fluoride accelerates the process of osteoporosis.

In 1973, a report from the National Institute of Arthritis and Metabolic Diseases found 50 to 100% increases in the incidence of a disease called osteitis fibrosa among patients whose artificial kidney machines were run on fluoridated water. Osteitis fibrosa is a disease characterized by fibrous degeneration of the bone; it results in bone deformities and sometimes in fracture...

Hardening of the Arteries

In a number of areas where people consume water containing 3 parts per million fluoride or more, calcification of the arteries has been clinically correlated with the fluoride-induced bone disorders described in Chapter 6. The indication again is that fibroblasts in the arterial cell walls are producing larger amounts of an imperfect collagen or collagen-like protein, resulting in hardening of the arteries or arteriosclerosis, the leading cause of death in the United States.

During aging, hardening of the arteries is probably due to disruption of collagen production, according to Dr. John Negalesko, director of the first year medical program at the Ohio State University Medical School and an expert in the field. Thus, fluoride, by disrupting the production of collagen and by stimulating the calcification of arteries, has speeded up another phase of the aging process...

Chapter 8: **Fluoride & Genetic Damage**

As pointed out in Chapter 4, all animals, including humans, are made up of cells. Each cell contains a nucleus, which is separated from the remainder of the cell by a nuclear membrane. Within the nucleus exist chromosomes, which contain DNA and protein. DNA is the body's master blueprint material. It is the genetic material that determines how the body is built. DNA specifies traits such as height, hair texture and color, number of fingers on each hand, blood type, and by means of its control of protein and enzyme synthesis, the susceptibility of the individual to

various diseases.

Since maintaining the integrity of this master blueprint is so vital, the cell makes a "photocopy" of the DNA called RNA, so that the risk of damaging the DNA is minimized. This photocopy blueprint is taken to "construction sites" in the cell. These construction sites are called ribosomes. On these ribosomes, the RNA blueprint is used to direct the manufacture of proteins and enzymes, which, in turn, directly determine the structure, traits, and limiting capabilities of the body.

To further insure the integrity of DNA, the cell provides a group of enzymes called the DNA repair enzyme system which repairs DNA when damage is done to it. As people age, their DNA repair enzyme system slows down. This results in DNA damage which goes unrepaired and leads to cell damage or death. Damaged or dead cells may then put out products which in turn damage other cells, leading eventually to massive cell death and the degenerative loss of various tissues and organs in a snowballing cycle of aging > damage > aging ....

Serious consequences can also arise if the unrepaired DNA damage occurs in a cell which gives rise to a sperm or egg cell. In these cases, DNA damage in the defective egg or sperm cell will be replicated in every cell of the offspring's body and will lead to a birth defect. If the child with this birth defect survives to maturity and reproduces, this genetic deformity will be passed on from generation to generation. A decline in DNA repair activity with "age" is one of the reasons why the number of birth defects increases as maternal age increases.

Unrepaired damage of a segment of the DNA responsible for control of cell growth (brought about by a deficient DNA repair enzyme system) can lead to uncontrolled cell growth or tumors. Many tumors stop growing when they are contained by the cells around them. However, in some cases, tumor cells may release an enzyme, or may be induced by additional genetic damage to release an enzyme, which digests the surrounding cells. The result is an invasive or malignant tumor and is more commonly referred to as cancer.

An excellent example of a defective DNA repair enzyme system leading to cancer is provided by victims of a disease called xeroderma pigmentosum. These people suffer from an inherited deficiency of DNA repair enzyme activity and are known to succumb to cancer early in life as a result.

A decline in DNA repair activity with "age" is one of the primary reasons why the incidence of cancer among older people is so much higher than the cancer incidence among younger people. The defective DNA repair enzyme in patients with xeroderma pigmentosum accelerates the aging process to the extent that xeroderma pigmentosum patients in their 20's have the same cancer risk as "normal" people in their 80's.

Dr. Wolfgang Klein and co-workers at the Seibersdorf Research Center in Austria reported that 1 part per million fluoride inhibits DNA repair enzyme activity by 50%. Since fluoride inhibits DNA repair enzyme activity, fluoride should also be expected to lead to an increase in genetic or chromosome damage.

This has indeed been found to occur in numerous studies showing that fluoride in water, even at the concentration of 1 part per million, can cause chromosome damage.

The following table outlines the results of laboratory studies regarding the effect of fluoride on genetic damage in mammals.

Year	Institution	Animal	Findings
1973	Russian Research Institute of Industrial Health & Occupational Diseases (USSR)	rat	fluoride causes genetic damage
1974	Columbia University College of Physicians & Surgeons (USA)	mouse/sheep/cow	fluoride causes genetic damage
1978	Pomeranian Medical Academy (Poland)	human WBCs	fluoride causes genetic damage
1979	National Institute of Dental Research (USA)*	mouse	fluoride does not cause genetic damage*
1981	Institute of Botany, Baku (USSR)	rat 3 studies	fluoride causes genetic damage
1982	University of Missouri, Kansas City (USA)	mouse	fluoride causes genetic damage
1983	Kunming Institute of Zoology, Kunming (Peop. Rep. China)	deer	fluoride causes genetic damage
1983	Kunming Institute of Zoology, Kunming (Peop. Rep. China)	human WBCs	fluoride causes genetic damage
1984	Nippon Dental University, Tokyo (Japan)	hamster embryo cell	fluoride causes genetic damage
1984	Nippon Dental University, Tokyo (Japan)	human cell culture	fluoride causes genetic damage
1985	Medical Research Council, Edinburgh (UK)	human WBCs	fluoride causes genetic damage

**A prepublication copy of this paper was submitted as an exhibit in a court case in Pittsburgh (USA). During trial, it was brought out that the results showed that increasing fluoride contents in drinking water increased genetic damage in mouse testes cells. Before the paper was published these figures were altered so as to destroy the original figures showing a relation between fluoride and genetic damage (see Chapter 16).*

One of the most relevant of these studies are those of Dr. Aly Mohamed, a geneticist at the University of Missouri. They show that one part per million fluoride in the drinking water of mice causes chromosomal damage. These studies also show that as the fluoride content of the water increases the degree of chromosomal damage increases in both testes and bone marrow. The results are presented in the following table:

1973	Texas A&M University (USA)	Barley (2)	fluoride causes genetic damage
1982	Institute of Botany, Baku (USSR)	Onion	fluoride causes genetic damage
1983	Institute of Botany, Baku (USSR)	Onion	fluoride causes genetic damage

Drs. R.N. Mukherjee and F.H. Sobels from the University of Leiden in Holland found that fluoride increased the frequency of genetic damage in sperm cells which were produced by laboratory animals exposed to X-rays. It is evident, from their studies, that fluoride inhibited the repair of DNA damaged X-rays. The authors themselves concluded: *"sodium fluoride resulted in a consistent and highly significant increase of the mutation* [i.e. genetic damage] *frequency. This effect is thought to result from interference with a repair process."*

In agreement with Drs. Mukheijee and Sobels were Dr. S.I. Voroshilin and co-workers from the Russian Research Institute of Industrial Health and Occupational Diseases. From their studies they concluded: *"It would seem to us that fluoride could cause some kind of disturbance in the enzymes that are related to the mechanisms of DNA repair and synthesis."*

In 1981, Dr. A. Iarez and co-workers from the Department of Toxicology from Central University ofVenezuela in Caracas, reported that fluoride added to the drinking water of female rats produced birth defects in their offspring. Just one year later Drs. Rhuitao Zhang and Shunguang Zhang of the Changjian Institute of Marine Products found that fluoride caused birth defects in fish.

According to the June 16, 1976 issue of the San Diego Union, an experiment showed that 10% of the litters of female mice drinking tap water from Durham, North Carolina (fluoridated in 1962) contained at least one malformed baby. No birth defects were observed in mice drinking purified water. While this study in itself does not prove that fluoride was the cause, the effects of fluoride as determined by the investigators mentioned above certainly make fluoride a prime suspect.

Fluoride-Induced Cancer

The ability of fluoride to cause genetic damage is so well recognized that investigators are now trying to find ways to counteract its genetic damaging effects.

Substances like fluoride which cause genetic damage are called mutagenic substances and it is a well-accepted fact that substances which are mutagenic also tend to be carcinogenic, or cancer producing. In fact, this is exactly what has been found with regard to fluoride.

Dr. Takeki Tsutsui and co-workers of the Nippon Dental College in Japan showed that fluoride not only caused genetic damage but was also capable of transforming normal cells into cancer cells. The levels of fluoride used in this study were the same levels of fluoride that the U.S. National Cancer Institute suggested should be used to determine whether or not fluoridation of public water supplies causes cancer.

They found that cells treated with 34 and 45 parts per million fluoride produced cancer (fibrosarcoma) when injected under the skin of otherwise healthy adult hamsters. In contrast, they

CHROMOSOME DAMAGE CAUSED BY FLUORIDE

Fluoride (parts per million)	PERCENT OF CELLS WITH CHROMOSOMAL DAMAGE			
	Bone Marrow		Testes	
	3 weeks	6 weeks	3 weeks	6 weeks
0	18.4	19.3	16.0	15.8
1	25.7	32.1	21.4	21.1
5	29.9	41.3	23.2	22.8
10	35.5	46.0	30.5	29.7
50	44.6	47.1	34.3	41.3
100	47.5	47.9	40.3	48.2
200	45.6	49.2	42.5	50.3

(Click to enlarge table)

Chromosomes (and thus any chromosomal abnormalities that may occur) are only visible while the cell is dividing. Therefore, Dr. Mohamed studied bone marrow and testes cells since these cells divide rapidly.

Since the testes cells observed by Dr. Mohamed give rise to sperm cells which are passed on to future generations, genetic damage to these testes cells can lead to birth defects and other metabolic disorders which can be passed on from generation to generation.

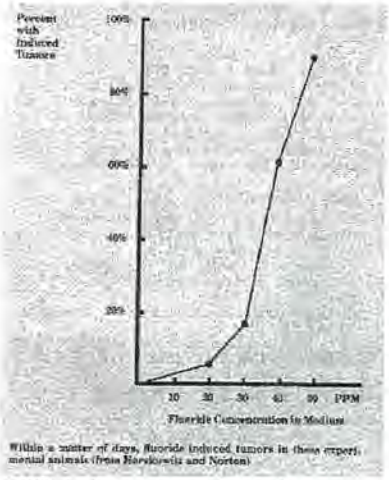
Early studies regarding the ability of fluoride to cause chromosome damage were done on plants and insects and as a result drew little attention. However, since the basic structure, function, and repair of chromosomes is similar in plants, insects, and animals, substances like fluoride which cause genetic damage in plants and insects, will most likely cause genetic damage in animals-including man.

The following table outlines the results of laboratory studies regarding the effect of fluoride on genetic damage in plants and insects.

Year	Institution	Plant or Insect Used	Findings
1966	Texas A&M University (USA)	Onion	fluoride causes genetic damage
1966	Texas A&M University (USA)	Tomato	fluoride causes genetic damage
1968	University of Missouri, Kansas City (USA)	Tomato	fluoride causes genetic damage
1970	University of Missouri, Kansas City (USA)	Maize	fluoride causes genetic damage
1970	University of Missouri, Kansas City (USA)	Fruit Fly	fluoride causes genetic damage
1971	Texas A&M University (USA)	Fruit Fly	fluoride causes genetic damage
1973	Texas A&M University (USA)	Fruit Fly	fluoride causes genetic damage
1973	Central Laboratory for Mutagen Testing (W. Germany)	Fruit Fly	fluoride causes genetic damage

found that cells that were not treated with fluoride did not produce cancer.

This confirms the earlier U.S. National Cancer Institute sponsored studies done by Drs. Irwin Herskowitz and Isabel Norton. In 1963, these St. Louis University scientists showed that low levels of fluoride increased the incidence of melanotic tumors in fruit flies by 12 to 100% (see the following figure).



(Click here to enlarge)

Similar types of transformations of normal cells to potentially cancerous cells have been observed in humans.

Dr. Danuta Jachimczak and co-workers from the Pomeranian Medical Academy in Poland reported that as little as 0.6 part per million fluoride produces chromosomal damage in human white blood cells. This study has received support from two other studies by Dr. R. Lin and co-workers from the Kumming Institute of Zoology and Dr. E.J. Thomson and co-workers from the Medical Research Council in Edinburgh, Scotland, who showed a 2-fold to 15-fold increase in chromosomal aberration rates at levels of 1.5 to 60 parts per million fluoride. The Thomson study suffers from the fact that the investigators administered another mutagenic substance to all the cells tested to measure other indexes of chromosomal activity.

Dr. Stephen Greenberg from the Chicago Medical School observed a disturbance of the DNA in white blood cells of animals treated with 5-10 ppm fluoride and observed other changes which he maintained were characteristic of cancer cells. In humans, Dr. Paul H. Duffey and co-workers from the Tucson Medical Center also found that fluoride transforms certain white blood cells into cells which appeared to be cancerous.

It is quite clear that fluoride causes genetic damage. The mechanism of action of fluoride cannot be exactly pinpointed because fluoride interferes with a number of physiological processes. Most evidence indicates that fluoride acts on the DNA repair enzyme system. This does not rule out the possibility that fluoride also interferes with DNA synthesis or that it may even act directly on the DNA itself. DNA is composed of two molecular strands held together by hydrogen bonds and fluoride is capable of disrupting these bonds. Such disruption would be expected to result in genetic damage directly and/or interference with DNA synthesis and DNA repair.

Furthermore, fluoride-induced genetic damage may also result from the general metabolic imbalance caused by fluoride selectively inhibiting certain enzymes.

The fact that fluoride has also been shown to cause cancer should not be surprising since it is almost universally accepted that cancer results from genetic damage.

In any event, the fact that fluoride disrupts DNA repair enzyme activity, the fact that fluoride causes genetic damage, and the fact that fluoride causes cancer shows again that fluoride is directly accelerating the aging process.

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ORIGINAL PAPER

Age-specific fluoride exposure in drinking water and osteosarcoma (United States)

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Abstract

Objective We explored age-specific and gender-specific effects of fluoride level in drinking water and the incidence of osteosarcoma.

Methods We used data from a matched case–control study conducted through 11 hospitals in the United States that included a complete residential history for each patient and type of drinking water (public, private well, bottled) used at each address. Our analysis was limited to cases less than 20 years old. We standardized fluoride exposure estimates based on CDC-recommended target levels that take climate into account. We categorized exposure into three groups (<30%, 30–99%, >99% of target) and used conditional logistic regression to estimate odds ratios.

Results Analysis is based on 103 cases under the age of 20 and 215 matched controls. For males, the unadjusted odds ratios for higher exposures were greater than 1.0 at each exposure age, reaching a peak of 4.07 (95% CI 1.43, 11.56) at age 7 years for the highest exposure. Adjusting for potential confounders produced similar results with an adjusted odds ratio for males of 5.46 (95% CI 1.50, 19.90) at age 7 years. This association was not apparent among females.

Conclusions Our exploratory analysis found an association between fluoride exposure in drinking water during childhood and the incidence of osteosarcoma among males but not consistently among females. Further research is required to confirm or refute this observation.

Keywords Osteosarcoma · Fluoride · Fluoridation · Case–control

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Introduction

Osteosarcoma is a very rare primary malignant tumor of bone. Although uncommon, primary malignant bone tumors comprise the sixth most common group of malignant tumors in children and the third most common malignant tumor for adolescents, with an annual incidence rate of 5.6 per million for Caucasian children under 15 years old [1]. Osteosarcoma is the most common tumor of bone and for patients less than 20 years old more than 80% of these tumors tend to occur in the long bones of the appendicular skeleton which are undergoing rapid growth [2]. The incidence of osteosarcoma is slightly higher in males than females with an annual incidence rate of approximately 3.5 per million for males and 2.9 per million for females under the age of 24 years [3].

The etiology of osteosarcoma is largely unknown [1, 4]. In humans, ionizing radiation is the only environmental agent known to cause bone cancer and is thought to have an effect in approximately 3% of cases from either external high-dose irradiation used in cancer therapy or internal bone-seeking radioisotopes from occupational or medical use [1, 5, 6]. Alkylating agents used in chemotherapy are thought to increase the risk for osteosarcoma and evidence for other etiologic factors including viruses, antecedent trauma, or radium in drinking water has been suggested but inconclusive [1, 5, 7, 8]. Certain pre-existing bone defects including Paget's disease have been found more frequently in patients who subsequently developed bone cancers [1, 4, 5]. Also, a genetic predisposition for osteosarcoma has been described, specifically for patients with a hereditary form of retinoblastoma or those with familial Li-Fraumeni cancer syndrome [1, 5, 6].

The age-incidence distribution of osteosarcoma is bimodal, raising the possibility of different risk factors contributing to the incidence of osteosarcoma at different ages. The first and larger peak in incidence occurs in the second decade of life and a subsequent peak occurs in males in the eighth decade of life [2, 4, 5, 9]. Evidence suggests that osteosarcoma is associated with skeletal growth, particularly for patients diagnosed during adolescence [1, 9–11]. Since fluoride may act as a mitogen (increasing the proliferation of osteoblasts) and its uptake in bone increases when skeletal growth is more rapid [12, 13], it is biologically plausible that fluoride exposure during growth is associated with the subsequent development of osteosarcoma, and fluoride could either increase or decrease the rate of osteosarcoma.

There are conflicting data regarding the association between fluoride exposure and the incidence of osteosarcoma. Several animal studies have been conducted, but only one found evidence that fluoride exposure may increase osteosarcoma formation, specifically in male rats [14]. Human studies also show conflicting results. The majority of epidemiologic studies found no association between fluoride and osteosarcoma [15–21]. However, two studies found evidence of an association in males under age 20, but not in females [22, 23]. Furthermore, prior studies have primarily evaluated fluoride exposure at the time of diagnosis or as an average lifetime exposure and have not evaluated exposure at specific ages during growth and development when cell division is occurring rapidly.

Therefore, we use data from the Harvard Fluoride Osteosarcoma Study [24] to explore age-specific and sex-specific effects and evaluate exposure to fluoride in drinking water from birth through early adolescence. Specifically, based on prior studies suggesting an effect of fluoride limited to males under age 20, we limited our analysis to the first two decades of life and evaluated effects in males and females separately.

Materials and methods

We used data from a hospital-based, matched case–control study which evaluated lifetime exposure to fluoride from drinking water and self-administered fluoride products [24]. Subjects were identified through the orthopedic departments at 11 teaching hospitals across the United States. Cases had histologically confirmed osteosarcoma diagnosed between November 1989 and November 1992. Exclusion criteria were: age 40 years or older, any history of radiation therapy or a history of renal dialysis. Controls were patients of the same hospital's orthopedics department, seen within ±6 months of the case's diagnosis and matched with cases on age (±5 years), gender, distance from hospital, with the same exclusion criteria applied to cases. Telephone interviews were conducted between January 1992 and January 1995 with the parent or subject (over 18 years old) or with a proxy if subjects were deceased or incapacitated. Interviewers collected information which included a complete residential history, use of fluoride supplements and mouth rinses. Study procedures were approved by the Harvard Medical School Committee on Human Studies and each of the participating institutions. Data on a total of 419 subjects, 139 cases and their 280 matched controls, were available based on eligibility criteria, matching criteria and a completed interview. However, we limit the current analysis to 103 cases less than 20 years old and 215 controls matched to these cases.

Fluoride level in drinking water was the primary exposure of interest. The interview obtained the usual type of the subject's drinking water (municipal, private well, bottled) and the subject's age(s) while at each address. From these data, we estimated the level of fluoride in drinking water for each subject at each age, and explored the effects of fluoride during their growth and development. To estimate fluoride concentration for public water supplies, we obtained preliminary data from the 1985 CDC Fluoridation Census [25] and the 1992 CDC Fluoridation Census [26]. We then contacted state agencies (State Dental Director's Office, State EPA Office of Drinking Water, Water Administrators Office) and local sources (county health departments, the town or city clerk's office and specific water systems) to confirm and supplement the CDC data [27]. For subjects who drank well water, a sample was obtained from current or former residents for the specific appropriate addresses. Fluoride concentrations were measured at Harvard School of Dental Medicine using a Colorimeter (Model 41100-21, Hach Company, Ames, IA). Subjects who used bottled water as their usual source of drinking water were identified, but information about specific brand was not collected. We estimated fluoride

levels to be 0.1 parts per million (ppm) in bottled water based on the weighted average of fluoride concentration in leading brands [28]. Since subjects who used bottled water were also likely to consume fluoride from tap water in food and beverage preparation and use outside the home (e.g., school), we used the mean of fluoride estimates for bottled water (i.e., 0.1 ppm) and municipal water for these residences. Since water consumption may vary based on climate, we standardized fluoride exposure estimates based on CDC recommendations for optimal target levels of fluoride [29]. For example, for locations in warmer climates where the target fluoride level is 0.7 ppm, we divided fluoride levels by 0.7, while for locations in colder climates where the target fluoride level is 1.2 ppm we divided by 1.2. The standardization of fluoride exposure was done for all three types of drinking water.

We created a proxy measure for socioeconomic status (SES) by linking zip code at the time of diagnosis with data from the Census Bureau that provide 1989 median family income for each zip code. Median family income was categorized into quartiles based on the distribution for controls. We also used data from the Census Bureau to determine the 1990 population of the county where subjects resided at the time of diagnosis, categorized by approximate tertiles. We examined type of drinking water by including indicators for use of bottled water or well water at any time up to the exposure age. Since age matching allowed for a difference as large as 5 years, we included age (at diagnosis for cases and at time of hospital treatment for controls) as a covariate. Lastly, since information was collected for use of self-administered fluoride products at home or in school-based programs, we included an indicator for any use of these products as an additional covariate.

We used conditional logistic regression to estimate the odds ratio for the association between fluoride exposure and osteosarcoma, taking into account the matching between cases and controls. The dependent variable was an indicator identifying cases and the primary independent variables were measures of fluoride exposure. We fit two basic models. The first model included only the exposure measures as independent variables. The second model also included age, a proxy for SES, county population, use of private well water or bottled water, and any use of fluoride supplements or mouth rinses as covariates. In this analysis, our a priori hypothesis was that fluoride exposure may have sex-specific differential effects on osteosarcoma risk based on age at exposure. The models we employed therefore do not assess the question of average induction time or latency.

We report the mean and standard deviation of fluoride levels in ppm and percent of target for each specific age. To examine the association between osteosarcoma and fluoride exposure at specific ages, we fit separate models for each exposure age up to the age of diagnosis for each case and the same age for the matched controls. Each model included the age-specific fluoride level and a sex–fluoride interaction term. In this analysis we expect substantial correlation in exposure to fluoride in drinking water from year to year, limiting our ability to identify age-specific effects precisely. For our primary analysis we categorized climate-standardized fluoride exposure into three categories (<30%, 30–99%, >99% of target fluoride content) corresponding to approximate tertiles based on the distribution among controls. We plot sex-specific estimates of the odds ratio and 95% confidence intervals as a function of exposure age. We also fit a model using fluoride exposure categorized without standardization by climate into three groups (<0.3, 0.3–0.69, and ≥0.7 ppm).

We performed a sensitivity analysis on our assumption that the fluoride content of bottled water is 0.1 ppm by fitting models using values as high as 0.5 ppm for bottled water (assuming that bottled water and municipal water each contributed half of the consumption for subjects who used bottled water). In addition, we conducted a sensitivity analysis evaluating the age-specific and sex-specific effects of fluoride in drinking water among subjects who reported never having used any fluoride supplements or fluoride mouth rinses.

Results

A total of 157 cases diagnosed before age 20 were identified at the participating hospitals. No interviews were completed for 13 of the cases (did not attempt to contact, could not contact, or respondent refused). Eleven cases used well water for which no sample was obtained and 12 cases lived outside the United States for more than 6 months. An additional 18 cases with interview data were excluded due to lack of appropriately matched controls (nine had no eligible matches identified or successfully interviewed, seven whose only matches used well water for which no sample was obtained and two whose matches lived outside the United States >6 months). Characteristics of the remaining 103 cases and their 215 matched controls are presented in Table 1. Cases were diagnosed at a median age of 14 years (range 6–19, interquartile range 11–17). Residential histories for six participants, five cases and one control, were provided by proxies (grandparents, stepparent, sibling, aunt, neighbor). The 1989 median family income for zip code of residence was lower for cases than controls (P=0.01, Student's t-test) and a larger proportion of controls used bottled water (P=0.002, chi-square test). Table 2 shows the average fluoride level and percent of climate-specific target level in drinking water at each age for cases and controls.

Table 1 Characteristics of study population[a]

	Cases	Controls
Number	103	215
Age (years)	13.7 ± 3.5	14.5 ± 3.9
Gender		
Male	60 (58%)	122 (57%)
Female	43 (42%)	93 (43%)
Self-reported race[b]		
White	81 (79%)	180 (84%)
Black	16 (16%)	23 (11%)
Asian	3 (3%)	2 (1%)
Other	3 (3%)	9 (4%)
Number of residences	2.5 ± 1.7	2.6 ± 1.7
1989 Median family income[c]	$41,458 ± 15,146	$46,841 ± 19,319
County population[c]		
<250,000	37 (37%)	69 (32%)
250,000–999,999	44 (44%)	86 (40%)
1,000,000+	19 (19%)	60 (28%)
Hospital		
MGH	17 (17%)	27 (13%)
CH, Boston	15 (15%)	45 (21%)
Creighton	5 (5%)	11 (5%)
CH, DC	11 (11%)	20 (9%)
MSKCC	7 (7%)	14 (7%)
U Chicago	8 (8%)	16 (7%)
Rush	3 (3%)	6 (3%)
U Florida	12 (12%)	19 (9%)
UCLA	14 (14%)	32 (15%)
Cleveland clinic	8 (8%)	19 (9%)
CWRU	3 (3%)	6 (3%)
Ever well water use	29 (28%)	44 (20%)
Ever bottled water use	8 (8%)	46 (21%)
Fluoride Products		
Rinses	3 (3%)	19 (9%)
School program	17 (17%)	30 (14%)
Tablets	10 (10%)	28 (13%)
Drops	9 (9%)	19 (9%)
Any of above	27 (26%)	77 (36%)

[a] Values reported are mean ± standard deviation or *n* (%)

[b] Race not available for one control

[c] 1989 Median family income and county population data not available for three cases

Figure 1 shows the odds ratio, relative to the lowest exposure group, of osteosarcoma for the climate-standardized fluoride level at each exposure age from 0 to 14 years, estimated using the conditional logistic regression models unadjusted for other covariates. Among males, exposure to fluoride at or above the target level was associated with an increased risk of developing osteosarcoma (Fig. 1a). The association was most apparent between ages 4 and 12 with a peak at 6–8 years of age. The odds ratio for the high exposure group was 4.07 at 7 years of age with a 95% confidence interval of 1.43–11.56. Among females less than 20 years old, no association between fluoride in drinking water and osteosarcoma was apparent at any age (Fig. 1b).

Next we fit models with all the covariates. As an example, Table 3 shows the model for subjects at 7 years

Table 2 Fluoride level for drinking water[a]

	F level in ppm		Percent of target	
	Cases	Controls	Cases	Controls
Age (years)				
0	0.63 ± 0.40	0.60 ± 0.41	66% ± 41%	62% ± 41%
1	0.63 ± 0.40	0.60 ± 0.40	65% ± 41%	61% ± 40%
2	0.64 ± 0.40	0.61 ± 0.40	67% ± 41%	63% ± 40%
3	0.67 ± 0.39	0.63 ± 0.39	69% ± 40%	64% ± 39%
4	0.70 ± 0.40	0.62 ± 0.39	73% ± 41%	63% ± 39%
5	0.69 ± 0.40	0.63 ± 0.39	72% ± 41%	65% ± 38%
6	0.70 ± 0.40	0.62 ± 0.39	74% ± 41%	63% ± 39%
7	0.70 ± 0.38	0.61 ± 0.39	75% ± 40%	63% ± 39%
8	0.69 ± 0.38	0.61 ± 0.39	73% ± 40%	63% ± 38%
9	0.68 ± 0.39	0.63 ± 0.38	73% ± 41%	65% ± 38%
10	0.67 ± 0.39	0.61 ± 0.39	71% ± 41%	63% ± 39%
11	0.70 ± 0.56	0.60 ± 0.39	74% ± 65%	62% ± 39%
12	0.69 ± 0.56	0.59 ± 0.39	75% ± 66%	61% ± 39%
13	0.68 ± 0.39	0.61 ± 0.39	71% ± 41%	62% ± 38%
14	0.65 ± 0.41	0.59 ± 0.39	69% ± 43%	61% ± 38%

[a] When bottled water was used, the estimate was 0.1 ppm for bottled water and it was assumed that bottled water and municipal supply each accounted for 50% of consumption

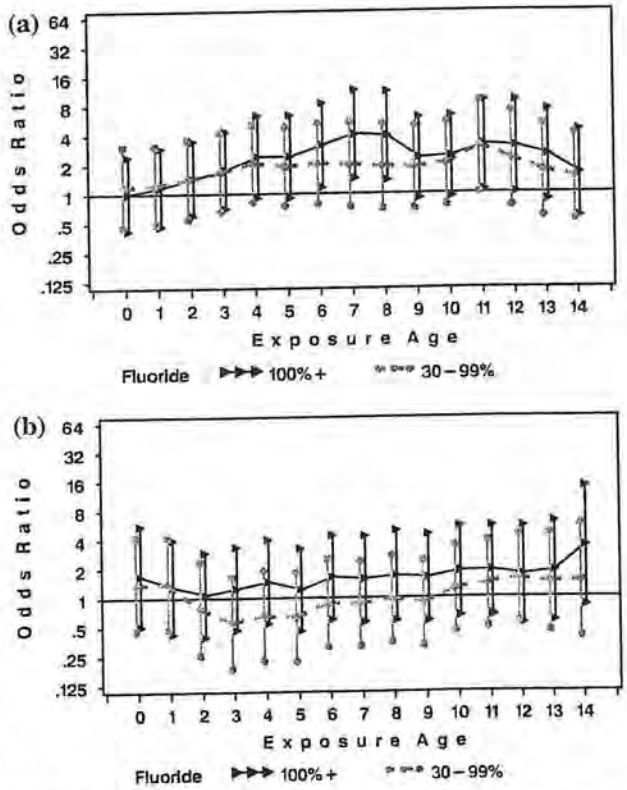

Fig. 1 Odds ratios and 95% confidence intervals relative to fluoride levels less than 30% of target are shown for males (panel a) and for females (panel b). The dashed line shows the odds ratios for the intermediate exposure category (30–99% of target fluoride level) and the solid line shows the odds ratios for the high exposure category (100% of target or greater)

Table 3 Sex-specific associations between fluoride exposure at age 7 years and osteosarcoma, estimated by conditional logistic regression

Fluoride exposure at age 7 years	Odds ratio (95% C.I.)[a]
Males	
Less than 30% of target	1.00
30–99% of target	3.36 (0.99, 11.42)
At least 100% of target	5.46 (1.50, 19.90)
Females	
Less than 30% of target	1.00
30–99% of target	1.39 (0.41, 4.76)
At least 100% of target	1.75 (0.48, 6.35)

[a] Adjusted for age, zip code median income, county population, use of well water by age 7, use of bottled water by age 7, any use of fluoride supplements

of age. Figure 2 shows a similar effect of fluoride level in drinking water after adjusting for income by zip code, county population, ever use of bottled or well water, age, and any use of self-administered fluoride products. For males, the odds ratio for the high exposure group was 5.46 at 7 years of age with a 95% confidence interval of 1.50–19.90. Sensitivity analyses, which assumed that the fluoride content of bottled was as low as 0.1 ppm or as high as 0.5 ppm, yielded essentially identical results. A sensitivity analysis that categorized fluoride exposure based on the absolute fluoride concentration, without standardizing for climate-specific target fluoride level, also showed essentially the same results (unadjusted OR=3.77; 95% CI 1.41, 10.05, and adjusted OR=5.55; 95% CI 1.60, 19.24 for 0.7 ppm or greater relative to less than 0.3 ppm). To avoid potential confounding by fluoride supplementation or fluoride rinses, we conducted a sensitivity analysis restricting our population to subjects who reported that they did not use supplements or rinses. This substantially reduced the sample size limiting us to unadjusted analyses for males. The results were consistent (Fig. 3).

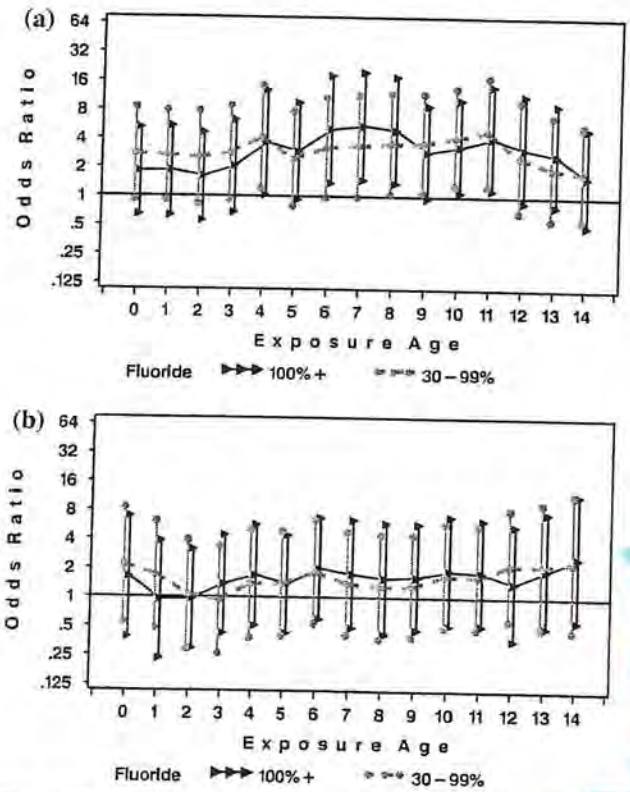

Fig. 2 Odds ratios and 95% confidence intervals relative to fluoride levels less than 30% of target are shown for males (panel a) and for females (panel b). The dashed line shows the odds ratios for the intermediate exposure category (30–99% of target fluoride level) and the solid line shows the odds ratios for the high exposure category (100% of target or greater). Estimates are adjusted for age, zip code median income, county population, prior use of well water, prior use of bottled water, and any use of fluoride supplements

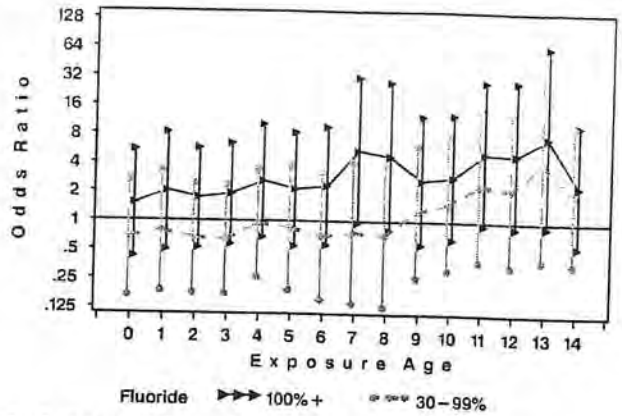

Fig. 3 Odds ratios and 95% confidence intervals relative to fluoride levels less than 30% of target are shown for the subset of male participants who never used fluoride supplements or rinses. The dashed line shows the odds ratios for the intermediate exposure category (30–99% of target fluoride level) and the solid line shows the odds ratios for the high exposure category (100% of target or greater)

Discussion

Our exploratory analysis described the association of fluoride level in drinking water at specific ages and the incidence of osteosarcoma. 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 [30–33]. For females, no clear association between fluoride in drinking water during growth and osteosarcoma emerged.

We found similar effect magnitudes in the intermediate and high exposure levels, as opposed to a dose–response gradient. This may be due to misclassification of the primary exposure for some artificially fluoridated systems.

Reeves [34] reported that only 65% of fluoridated water systems routinely have target levels of fluoride maintained in the drinking water, which may result in our misclassifying up to 35% of the adjusted water systems, categorizing them in the highest group (100% of target or greater) when some truly belong in the middle group (30–99% of target). While non-differential misclassification of exposure results in bias towards the null for a dichotomous exposure, Birkett [35] has shown that with three levels of exposure, the estimated odds ratio for the highest exposure level is biased towards the null, but for the intermediate category the estimate can be biased in either direction. Hence, in our study the misclassification might mask an effect that increases with dose.

Our results are consistent with a pattern seen in the National Toxicology Program (NTP) animal study and two ecological studies. The NTP animal study, which reported "equivocal evidence" for an association between fluoride and osteosarcoma, found a positive association for male rats, but no association for female rats or mice of either gender [14]. Using data from the Surveillance, Epidemiology and End Results (SEER), Hoover et al. found an unexplained increase in osteosarcoma in males less than 20 years of age in fluoridated versus non-fluoridated areas. However, a time-trend analysis which took into account the duration of fluoride exposure failed to demonstrate a higher incidence among males exposed to fluoridated water their entire lives than among those exposed less than half their lives [22]. A similar, but smaller study examining osteosarcoma in New Jersey also showed an increase in incidence rates for males less than 20 years old who lived in fluoridated areas compared to those living in non-fluoridated areas [23].

A number of other case–control studies did not find an association between fluoride in drinking water and osteosarcoma [18–21]. In addition, preliminary analyses of an ongoing case–control study of the determinants of osteosarcoma conducted at the same network of hospitals that participated in the present study and recruited cases during their initial hospitalization, found no overall association between lifetime exposure to fluoride or fluoride content in bone biopsies, a marker of cumulative exposure, and osteosarcoma (personal communication, Chester Douglass, D.M.D., Ph.D.). This lack of agreement may be related to the bimodal age-incidence distribution of osteosarcoma [2, 4, 5, 9]. When there are two distinct peaks in an age-incidence distribution, two distinct sets of component causes should be considered [36]. McGuire et al. [19] and Moss et al. [20] included cases up to age 40 years and 84 years, respectively, and if fluoride exhibits a different effect according to the age-specific distribution, detecting an effect would be unlikely. Operskalski et al. [18] selected friends and neighbors of the cases as controls, which might have been optimal for some exposures of interest, but resulted in inadvertently matching on drinking water fluoride level. The evaluation of age-specific effects distinguishes our study from the other investigations. Rothman [37] has warned that failure to identify the appropriate time window for exposure may result in misclassification which can adversely affect the ability to detect an association. This might explain why the study by Gelberg et al. [21] did not find an association between fluoride in drinking water and osteosarcoma since age-specific effects were not evaluated.

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) [13]. Second, fluoride acts as a mitogen, increasing the proliferation of osteoblasts [12, 38] and its uptake in bone increases during periods of rapid skeletal growth [13]. 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 [39, 13]. Also, osteosarcoma, for the ages we considered, generally originates in the metaphyseal areas of long bones [2] and the pattern of the blood supply to the metaphyses and epiphyses, where growth of long bones takes place, differs from that of the diaphyses because of the special circulation to the epiphyseal growth plate in the young which in turn disappears when growth is complete [40, 41]. Lastly, the amount of fluoride present in bone depends on gender and intake [39] and intake, on average, is greater for males than females for all ages over 1 year [42].

There are several limitations to our study. First, our estimates of fluoride in drinking water at each residence do not reflect actual consumption by subjects and the study did not obtain biologic markers for fluoride uptake in bone. However, dietary sources of fluoride comprise the majority of human exposure [13], and for individuals living in fluoridated communities, the fluoride in drinking water is estimated to contribute two-thirds of the total dietary intake [39]. Also, when we added use of self-administered (home- or school-based) products as a covariate in the model, there was no substantial change in results. The *halo* or *diffusion* effect, described in the dental literature, refers to people in non-fluoridated communities receiving fluoride from food and beverages processed in fluoridated communities and vice versa [43]. We would expect this type of measurement error to result in a bias towards underestimating any true effect that might exist.

Because cases and controls moved rarely up to the age at diagnosis (an average of 1.5 times) leading to essentially

collinear exposure from year to year, we were unable to apply statistical models that assess the effect of age-specific exposure while simultaneously adjusting for exposure at other ages such as distributed lag models. Residential histories were obtained from proxies more often among cases than controls, however the absolute number was small and the proxies were generally close relatives.

The estimation of fluoride concentration at each residence is subject to several sources of measurement error. Monitoring guidelines for fluoridated water systems permit actual fluoride levels to vary. For example, if the target fluoride concentration for a specific water system is 1.0 ppm, guidelines may consider values between 0.8 and 1.3 ppm acceptable. Also, natural fluoride levels may vary over time, but they are unlikely to do so for the length of time subjects lived at their respective address unless the water source changed. For bottled-water users, we did not know the specific brands consumed and a small proportion of brands on the market do have substantial levels of fluoride. However, analysis of the leading national brands makes a value of 0.1 ppm a reasonable estimate [28]. Further, we demonstrated that our findings were not sensitive to this assumption.

The lack of data available for other potential confounders is also a limitation. Fluoride may not be the causative agent; instead there may be another factor in drinking water correlated with the presence of fluoride. Data to assess fluoride exposure in diet, industrial fluoride exposure or other fluoride exposures (e.g., pesticides) were not available. Instead, by including type of drinking water subjects used (ever well, ever bottled) as a covariate, we may have partially controlled for some of the "other unknown factors" such as contaminants or carcinogens subjects might have been exposed to irrespective of fluoride concentration in these natural sources or products.

Another limitation is the possibility of selection bias. In our case–control study, the secondary study base is defined by the cases and in order for the results to be valid the exposure distribution for controls must represent the exposure distribution in this theoretical population. Referral patterns to the participating hospitals may differ for cases and controls because the participating hospitals were primary referral centers for osteosarcoma for large regions but the controls likely represented a more proximate population. Further, for some of the hospitals the referral base for controls could represent different socioeconomic populations than for cases. Distance from hospitals was used as a matching factor, to limit selection bias. This matching factor could also result in some overmatching on exposure, resulting in possible underestimation of the effect. Additionally, we included the 1989 median family income and county population as covariates.

For this study, cases of osteosarcoma that were diagnosed at participating hospitals between November 1989 and November 1992 were identified. However, case and control interviews took place later, between January 1992 and January 1995. Although efforts were made to interview a parent or proxy respondent if the subject was deceased or incapacitated, it is possible that cases with more favorable prognosis may have been over-sampled. If this occurred, an alternative explanation for our observation is that boys exposed to higher levels of fluoride who subsequently develop osteosarcoma have a better prognosis than boys exposed to lower levels. While we cannot rule out this possibility, the magnitude of the protective effect that would be required to explain the observed association is unlikely.

Differential recall of exposure information between cases and controls is unlikely in the current study because respondents did not provide information about the fluoride level in their drinking water but rather a complete residential history. For other covariates, such as date of birth, sex, or zip code at time of diagnosis, information was obtained by medical record review. Reporting of the type of water used or the use of self-administered fluoride products could be affected by recall bias.

In summary, this exploratory analysis found an association between exposure to fluoride in drinking water and the incidence of osteosarcoma, demonstrating a peak in the odds ratio for exposure at ages 6–8 years among males diagnosed less than 20 years old, but no consistent association among females. Future studies would benefit from the inclusion of biomarkers of fluoride exposure and assessment of potential gene–environment interactions. Such studies with larger numbers of osteosarcoma patients, with incidence under age 20, that examine age-specific and sex-specific associations are required to confirm or refute the findings of the current study.

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Fluoride Exposure and Childhood Osteosarcoma: A Case–Control Study

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ABSTRACT

Objectives. This study tests the hypothesis that fluoride exposure in a nonoccupational setting is a risk factor for childhood osteosarcoma.

Methods. A population-based case–control study was conducted among residents of New York State, excluding New York City. Case subjects (n = 130) were diagnosed with osteosarcoma between 1978 and 1988, at age 24 years or younger. Control subjects were matched to case subjects on year of birth and sex. Exposure information was obtained by a telephone interview with the subject, parent, or both.

Results. Based on the parents' responses, total lifetime fluoride exposure was not significantly associated with osteosarcoma among all subjects combined or among females. However, a significant protective trend was observed among males. Protective trends were observed for fluoridated toothpaste, fluoride tablets, and dental fluoride treatments among all subjects and among males. Based on the subjects' responses, no significant associations between fluoride exposure and osteosarcoma were observed.

Conclusions. Fluoride exposure does not increase the risk of osteosarcoma and may be protective in males. The protective effect may not be directly due to fluoride exposure but to other factors associated with good dental hygiene. There is also biologic plausibility for a protective effect. (*Am J Public Health.* 1995;85:1678–1683)

Introduction

Although the benefit to dental health of fluoride exposure has been clearly established, the release of the National Toxicology Program study in which a dose–response relationship for osteosarcoma was indicated for exposure to sodium fluoride among male rats has provoked criticism of water fluoridation programs.[1] In response, the Department of Health and Human Services conducted a review of fluoride's benefits and risks and recommended that analytical epidemiologic studies of osteosarcoma be conducted to determine the risk factors associated with its development.[2]

Osteosarcoma is the fourth most common cancer in persons under 25 years of age[3] occurring most often around puberty.[4] The only known etiological agent is radiation[5]; other suggested risk factors include a rapid rate of bone growth, previous bone trauma, and viruses.[6–8] Persons with the hereditary form of retinoblastoma or with the Li–Fraumeni cancer family syndrome are at high risk for osteosarcoma.[9,10]

Fluoride is deposited directly into the bone, with about 99% of fluoride in the body contained in the skeleton.[1,2] Children, who are actively forming bone, have a higher amount of uptake of fluoride into the bone matrix than adults.[1,2] Fluoride uptake into bone results in an increased rate of osteoblast proliferation and bone formation.[11] Bone in the areas of the knees, ankles, shoulders, and wrists, where childhood osteosarcomas most often occur, shows a high response to fluoride.[12]

Toxicological studies of sodium fluoride have yielded mixed results.[1,13–15] In in vitro studies fluoride appears to be mutagenic and can induce chromosome aberrations, sister chromatid exchanges, cytotoxicity, and neoplastic transformation in cultured mammalian cells.[1,13,14] The recent study conducted by the National Toxicology Program found equivocal evidence for a carcinogenic effect among male F344/N rats, but there was no evidence for carcinogenicity in female F344/N rats, nor in male or female mice.[1] Another study sponsored by the Procter and Gamble company found no carcinogenic evidence in Sprague–Dawley rats.[16]

Ecological studies generally have found no relationship between fluoride levels in drinking water and osteosarcoma and bone cancer incidence or mortality rates.[17–23] Individual exposures were examined in only two small studies.[24,25] One study based on only 20 males found that males under age 20 years who resided in communities with fluoridated water at the time of diagnosis had a higher osteosarcoma rate than those who resided in communities with nonfluoridated water.[24] The other study had only 22 matched case–control pairs and found no associa-

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Note. The views expressed here are the authors' and do not necessarily represent those of the National Cancer Institute.

tion between osteosarcoma and lifetime fluoride exposure from drinking water.[25]

Within New York State, average annual osteosarcoma incidence rates from 1976 to 1987 in fluoridated areas were found not to differ from rates in nonfluoridated areas.[23] To further investigate the potential association of fluoride exposure with childhood osteosarcoma in New York State, excluding New York City, we conducted a population-based case–control study. All sources of fluoride except dietary sources were examined separately and were combined to estimate total lifetime fluoride exposure. Because deleterious effects were limited to male rats in the National Toxicology Program study, additional analyses were conducted by gender.

Methods

Study Population

Cases of osteosarcoma newly diagnosed from January 1978 through December 1988 were identified from the New York State Cancer Registry. Case subjects who were 24 years of age or younger and residing in New York State, excluding New York City, at the time of diagnosis were eligible for inclusion in the study. Case subjects with preexisting cancers were excluded, resulting in a case population of 171.

Control subjects were pair-matched one-to-one to case subjects by year of birth and sex. Potential control subjects were randomly selected from live birth records maintained by the New York State Department of Health. All children born in New York City were excluded. Control subjects were assigned the same age at diagnosis as the corresponding case subjects as a reference date to provide equal time periods at risk. Control subjects had to survive until their matched case subject's age at diagnosis.

Case and control subjects and their parents were traced to determine their vital status and to locate their current address and telephone number. Although it was easier to trace the case subjects than the control subjects because more current information was available, an exhaustive search was made for each potential control subject before another one was selected as a replacement. An average of 2.10 birth certificates were searched before an adequate control subject was located and interviewed.

TABLE 1—Number of Case and Control Subjects, Odds Ratios (ORs), and 95% Confidence Intervals (CIs) for Lifetime Fluoride Exposure Variables (Parents' Data Set)

	No. Subjects				
	Case	Control	OR	95% CI	*P*
Tablets, mg					.03
0	110	104	1.00	...	
1–250	3	4	0.81	0.18, 3.66	
251–550	7	4	1.72	0.50, 5.91	
551–3500	2	10	0.11	0.01, 0.88	
Mouth rinses, mg					.43
0	110	111	1.00	...	
1–7	5	2	4.02	0.44, 36.75	
8–50	4	4	1.03	0.23, 4.57	
51–1005	3	5	0.60	0.14, 2.65	
Toothpaste, mg					.06
0–433	38	23	1.00	...	
434–862	26	35	0.43	0.20, 0.92	
863–1425	30	31	0.54	0.25, 1.19	
1426–2235	28	33	0.49	0.23, 1.06	
Dental treatments, mg					.06
0	88	91	1.00	...	
15	25	17	1.52	0.75, 3.08	
30–60	4	6	0.75	0.21, 2.72	
75–390	5	8	0.64	0.18, 2.21	
Water, mg					.61
0	40	57	1.00	...	
1–1850	32	16	4.13	1.65, 10.35	
1851–3385	26	23	1.84	0.81, 4.20	
3386–6100	24	26	1.40	0.60, 3.29	
Total fluoride, mg					.24
0–1235	31	31	1.00	...	
1236–2161	31	29	1.04	0.50, 2.14	
2162–4101	34	27	1.20	0.56, 2.57	
4102–8433	26	35	0.67	0.29, 1.54	

Note. Odds ratios were estimated from conditional logistic models.

Interviews

A telephone interview was requested from all living study subjects who were at least 18 years of age. Permission to interview the subject's parent was requested during the interview. If a case subject refused the interview, permission was requested to interview the case subject's parent. If permission was not granted, the parent was not interviewed. If the subjects were deceased or too young for an interview (<18 years old), the contact letters were sent directly to the parents. If a control subject did not allow us to contact his or her parents (n = 3), or if the parents refused to be interviewed after the control subject was interviewed (n = 6), the control subject was replaced.

The interview focused on the subjects' sociodemographic, medical, and exposure histories before the date of diagnosis or reference date. Fluoride exposure information was obtained from questions about the use of fluoridated products (toothpastes and mouth rinses) and fluoride supplements (drops, tablets, vitamins, and dental treatments). In addition, a complete residential history from birth until the age of diagnosis or reference age was taken. This history included complete addresses, the years of residence at each address, the water source (public supply or private well) at each address, and whether the water at each address was fluoridated.

There were a total of 130 case–control pairs for which the subject or the parent or both were interviewed for both members of the pair. Sixty-four (49%) interviews were completed for the case subjects, 126 (97%) for the case parents, 119 (92%) for the control subjects, and 126 (97%) for the control parents. Ninety percent of the parents who were interviewed were biologic mothers. The primary reasons for not obtaining interviews

TABLE 2—Number of Case and Control Subjects, Odds Ratios (ORs), and 95% Confidence Intervals (CIs) for Lifetime Fluoride Exposure Variables for Males (Parents' Data Set)

	No. Subjects				
	Case	Control	OR	95% CI	*P*
Tablets, mg					.08
0	73	67	1.00	...	
1–250	2	2	1.00	0.14, 7.10	
251–550	1	3	0.33	0.03, 3.21	
551–3500	2	6	0.20	0.02, 1.71	
Mouth rinses, mg					.99
0	73	72	1.00	...	
1–7	2	2	0.90	0.05, 17.89	
8–50	2	2	0.81	0.09, 7.52	
51–1005	1	2	0.46	0.04, 5.81	
Toothpaste, mg					.01
0–433	12	27	1.00	...	
434–862	23	15	0.23	0.08, 0.70	
863–1425	19	21	0.41	0.14, 1.18	
1426–2235	24	15	0.25	0.09, 0.70	
Dental treatments, mg					.04
0	60	56	1.00	...	
15	14	11	1.00	0.39, 2.55	
30–60	1	5	0.20	0.02, 1.80	
75–390	3	6	0.50	0.12, 2.07	
Water, mg					.62
0	27	34	1.00	...	
1–1850	20	11	2.81	0.97, 8.09	
1851–3385	15	12	1.67	0.58, 4.77	
3386–6100	16	21	0.93	0.31, 2.83	
Total fluoride, mg					.02
0–1235	17	19	1.00	...	
1236–2161	17	23	1.14	0.46, 2.84	
2162–4101	17	19	0.78	0.27, 2.22	
4102–8433	27	17	0.41	0.14, 1.22	

Note. Odds ratios were estimated from conditional logistic models.

were the subject being deceased (42% of the case subjects), inability to locate the subject or parent (8% of the case subjects, 42% of the control subjects), and refusal by the subject or parent to participate in the study. Approximately 6% of the case subjects, control subjects, and control parents refused, and 12% of the case parents refused. Eleven case subjects and their matched control subjects were too young for interviews.

Fluoride Exposure Index

To analyze the relationship between fluoride exposure and osteosarcoma, the lifetime exposure to each source of fluoride was determined, and these were summed into a total lifetime fluoride exposure index. These sources included fluoride drops, tablets, and vitamins, fluoridated mouth rinses and toothpastes, dental fluoride treatments, and fluoride from drinking water and breast milk. It was not possible to measure fluoride from food, which ranges from 6% to 32% of total fluoride intake.[26]

For more than 96% of the addresses identified, the respondent indicated knowledge of whether the water supply was public or private. These data were validated by geocoding all addresses and matching them to census data. There was 96% agreement between the water source according to the 1990 census and the water source reported by interview.

The subjects or parents indicated knowledge of the fluoridation status of their water for only 40% of the addresses. Therefore, instead of relying on the interview information, all of the addresses were further investigated to determine fluoridation status. Natural fluoride levels are relatively low in New York State, so the water was considered not fluoridated for all addresses with private wells in New York. Because fluoridation often follows town boundaries, addresses identified to be within city limits were then compared with a fluoridation census.[27] Telephone calls were made to appropriate agencies to determine the fluoridation status of addresses that could not be classified with the aforementioned method.

The average amount of fluoride ingested by age for each fluoride source was determined from the literature. For example, the dose recommended by the American Dental Association for fluoride drops, tablets, and vitamins was 0.25 mg per day for an infant newborn to 2 years old, 0.50 mg for a 2- to 3-year-old, and 1.0 mg for a child 3 to 13 years of age for the time period of this study.[28–30]

Population-based estimates of tap water intake were used to determine the amount of water ingested by age and sex categories. The estimates were derived from the 1977 and 1978 US Department of Agriculture Nationwide Food Consumption Survey, and the mean estimates for the northeast geographic region (all seasons) were used.[31] The fluoride level in water was assumed to be 1.0 mg/liter for fluoridated areas and 0 mg/liter for nonfluoridated regions.

Cumulative lifetime exposure for each fluoride source was estimated in milligrams by multiplying the amount ingested per exposure by the number of times per day exposed by the total number of days exposed. The lifetime exposures for each fluoride source were then summed to create a total lifetime fluoride exposure index.

Apart from dental fluoride treatments, for which there was a large amount of missing data (approximately 23% of the parents and 8% of the subjects), fewer than 5% of the parents' responses and fewer than 2% of the subjects' responses were missing. The percentage of missing responses did not differ between case and control subjects. A standard set of rules was established to impute values for missing data.

To measure intensity of exposure, each lifetime fluoride exposure variable was divided by the age at diagnosis or reference age to get an average annual exposure. Although matched pairs would still have the same within-pair association because of the matching by age, the relationship among pairs would change with this measure.

Analysis

Because recall could be different between the subjects and parents, separate data sets were created for each of these data sources, maintaining the matching. Sixty-four matched pairs were in-

cluded in the subjects' data set and 122 matched pairs were included in the parents' data set.

EGRET was used to analyze matched observations of each variable against disease status.[32] Odds ratios, 95% confidence intervals, and *P* values were computed by creating conditional logistic models. *P* values for trend were calculated by including the variables in models in their original, noncategorized continuous form. The *P* value for the likelihood ratio statistic reflecting the difference between the model with and the model without the continuous variable was interpreted as the *P* value for trend, which indicated whether the linear component of the trend was statistically significant. The *P* values do not necessarily appear to correspond to the trends of the categorical variables as presented because of the creation of arbitrary cutpoints in the continuous variables for presentation purposes. Extensive subgroup analyses were not conducted due to limitations presented by the relatively small number of subjects in the sample.

Results

Case subjects who were final study subjects (case subject and/or parent was interviewed) were not significantly different from case subjects for whom no interview was obtained (neither case subject nor parent was interviewed) with respect to race, vital status, age at diagnosis, year of diagnosis, stage of tumor, and anatomic location of tumor. However, a statistically significant higher percentage of case subjects not interviewed were male (61% vs 32%). Of the 130 case subjects who were final study subjects, 42 (32%) were male, 51 (39%) were deceased, and 96 (74%) were between ages 10 and 19 years. Eighteen case subjects (14%) but only 4 control subjects (3%) were non-White. This difference was statistically significant ($P = .002$).

The bivariate relationships between osteosarcoma and lifetime exposure to fluoride from tablets, mouth rinses, toothpaste, dental treatments, and drinking water, along with the total lifetime fluoride exposure index, are shown in Table 1 for the parents' data set. Because of the small number of affirmative responses, the fluoride from drops and the fluoride from vitamins were not analyzed separately. Fluoride from toothpaste and total lifetime fluoride exposure were categorized into quartiles. However, because so many individuals did not have exposure to the other fluoride sources, the lowest-level category for these variables included only those individuals with no exposure. Tables 2 and 3 present results for the same lifetime fluoride variables for males and females, respectively.

TABLE 3—Number of Case and Control Subjects, Odds Ratios (ORs), and 95% Confidence Intervals (CIs) for Lifetime Fluoride Exposure Variables for Females (Parents' Data Set)

	No. Subjects				
	Case	Control	OR	95% CI	*P*
Tablets, mg					.20
0	37	37	No convergence		
1–250	1	2			
251–550	6	1			
551–3500	0	4			
Mouth rinses, mg					.30
0	37	39	No convergence		
1–7	3	0			
8–50	2	2			
51–1005	2	3			
Toothpaste, mg					.85
0–433	11	11	1.00	...	
434–862	12	11	0.93	0.31, 2.80	
863–1425	12	9	0.65	0.17, 2.47	
1426–2235	9	13	1.80	0.45, 7.18	
Dental treatments, mg					.70
0	28	35	1.00	...	
15	11	6	2.25	0.69, 7.61	
30–60	3	1	3.00	0.31, 28.84	
75–390	2	2	1.00	0.06, 15.99	
Water, mg					.12
0	13	23	1.00	...	
1–1850	12	5	10.55	1.22, 91.04	
1851–3385	11	11	1.65	0.41, 6.59	
3386–6100	8	5	2.81	0.62, 12.69	
Total fluoride, mg					.24
0–1235	14	12	1.00	...	
1236–2161	12	8	0.74	0.20, 2.69	
2162–4101	10	15	1.81	0.56, 5.82	
4102–8433	8	9	1.34	0.32, 5.57	

Note. Odds ratios were estimated from conditional logistic models.

Total lifetime fluoride exposure was not significantly associated with osteosarcoma among all subjects combined or among females. However, a significant protective trend was observed among males ($P = .02$). With respect to the individual sources of fluoride, a significant trend of decreasing risk with higher exposure was observed among all subjects for tablets ($P = .03$). The trends for toothpaste ($P = .06$) and for dental treatments ($P = .06$) were borderline significant and were also protective. The lowest exposure level for toothpaste was significantly protective for all subjects and for females; and the highest exposure level was significantly protective for tablets, further emphasizing the protective effect. Significant or borderline significant protective trends were also observed for each of these variables among males. The lowest exposure level for water had a significantly elevated odds ratio for all subjects and for females; however, trends were not significant.

The relationships between osteosarcoma and lifetime exposure to fluoride from the various sources, along with the total lifetime fluoride exposure index, are shown in Table 4 for the subjects' data set. Because of the small number of affirmative responses, fluoride from tablets was not analyzed separately. Although there appears to be an increasing risk with exposure, especially for the total fluoride intake, no significant trends were observed and all confidence intervals included 1.0. Models could not be run separately for each sex because of the small number of individuals in this data set.

For both the parents' and subjects' data sets, results of analyses controlling

TABLE 4—Number of Case and Control Subjects, Odds Ratios (ORs), and 95% Confidence Intervals (CIs) for Lifetime Fluoride Exposure Variables (Subjects' Data Set)

	No. Subjects				
	Case	Control	OR	95% CI	P
Mouth rinses, mg					.14
0	55	56	1.00	...	
1–35	3	2	1.50	0.25, 8.98	
36–150	2	4	0.55	0.10, 3.06	
151–950	4	2	1.83	0.33, 10.21	
Toothpaste, mg					.22
0–615	15	17	1.00	...	
616–1149	14	18	0.89	0.31, 2.61	
1150–1444	15	16	1.03	0.36, 2.97	
1445–3411	20	13	1.93	0.64, 5.84	
Dental treatments, mg					.52
0	45	45	1.00	...	
15	8	12	0.77	0.31, 1.96	
30–45	7	2	3.21	0.63, 16.50	
60–300	4	5	0.98	0.25, 3.93	
Water, mg					.48
0	21	29	1.00	...	
1–1950	15	11	2.31	0.74, 7.20	
1951–3350	14	12	2.07	0.53, 8.02	
3351–5650	14	12	1.76	0.59, 5.21	
Total fluoride, mg					.25
0–1250	14	18	1.00	...	
1251–2338	15	17	1.16	0.44, 3.04	
2339–3987	17	15	1.72	0.55, 5.39	
3988–9291	18	14	1.88	0.64, 5.55	

Note. Odds ratios were estimated from conditional logistic models.

for race and maternal age (which was found to be negatively associated with osteosarcoma in these data) were similar to the bivariate analyses. The results of the analyses for the average annual fluoride exposure variables were essentially the same as the lifetime exposure analyses in both data sets.

Discussion

The total lifetime fluoride exposure index is the most important indicator of whether fluoride is significantly associated with osteosarcoma. In the parents' data set, a significant association was not observed among all subjects, but a significant protective trend was observed among males. Borderline significant or significant protective trends were also observed for lifetime fluoride exposure from tablets, toothpaste, and dental treatments among all subjects and among males only. In the subjects' data set, however, a protective trend was not observed for the total lifetime fluoride exposure index, nor for any of the individual lifetime fluoride exposure variables. Importantly, there was no statistically significant finding from either data set that fluoride exposure increases the risk of childhood osteosarcoma. This result is consistent with previous studies that found no association between fluoride exposure and osteosarcoma.[17–23,25]

The protective effects observed in the parents' data set may be due to concern for personal health and hygiene and not to fluoride exposure. Those individuals who use fluoride tablets, who brush their teeth more often with fluoridated toothpaste, and who receive dental fluoride treatments are possibly more involved with good health practices. The observed protective effects could be the result of healthy behavior practices or of correlates of health behaviors that protect against osteosarcoma, rather than a consequence of fluoride exposure, although it is unusual to find these practices more among boys. The fact that the protective effect was not observed for fluoridated water supports this argument. However, because fluoride is directly deposited into the bone and directly affects the bone structure, it is biologically plausible that the protective effect observed from fluoride exposure could, in fact, be real.

The only demographic variables significantly associated with osteosarcoma in this study were race and maternal age. In general, race is not considered a risk factor for osteosarcoma.[3,33–36] The procedure used to randomly select the control birth certificates did not produce the same percentage of non-White certificates as the percentage from the total live births for upstate New York (7.6% vs 12.8%). Of those certificates obtained for non-White control subjects, a substantially higher proportion did not contain the father's name compared with certificates obtained for White control subjects (33.3% among non-Whites vs 3.9% among Whites), making the non-White control subjects more difficult to trace. Neither race nor maternal age was observed to confound the osteosarcoma–fluoride relationship.

One major limitation in this study was that cases were identified retrospectively for the period 1978 to 1988. Problems with recall became exacerbated because of the long period of time that may have passed since the childhood exposures. Also, only 64 case subjects were directly interviewed because of deaths occurring after diagnosis. Despite this limitation, the case subjects, control subjects, and their parents were equally able to report on the fluoride-related exposures, with a low percentage of missing responses. Because neither the case nor the control group appeared to be more accurate in their reporting of exposures, any misclassification that occurred should be nondifferential and would therefore bias the results toward the null value.

The extent of nondifferential misclassification of fluoride exposure and resultant bias toward the null value are difficult to evaluate. We are confident that the water fluoridation information is accurate. There is no reason to suspect that residential histories were reported inaccurately, the water source information was validated by geocoding, and fluoridation status was objectively determined. However, subjects' and parents' accuracy in reporting exposure to other sources of fluoride could not be assessed.

The low response rate of 48% among control subjects (mainly due to an inability to trace them) was a concern. However, among study subjects, individuals who moved more than two times did not have significantly different total lifetime fluoride exposures than individuals who maintained one or two addresses up to the

diagnosis or reference age. This suggests that the nonparticipant control subjects who could not be traced because they moved often would not have differed from the participant control subjects with respect to total lifetime fluoride exposure.

A strength of this study was the relatively large sample size (122 case–control pairs for the parents' data set and 64 case–control pairs for the subjects' data set) compared with prior studies that examined individual fluoride exposures from drinking water.[27,28] Another advantage of this study was the inclusion of exposures to fluoride from sources other than drinking water.

The differences in results between the parents' and subjects' data sets are probably a reflection of differences in knowledge and recall. Parents were probably more aware of exposures that occurred at young ages, including use of fluoridated drops, tablets, vitamins, and toothpastes and exposure to dental treatments. Subjects probably provided more accurate information for exposures that occurred when they were older, particularly the use of fluoridated toothpastes and mouth rinses. Overall, the parents' data set is probably the more accurate one because of better knowledge of more types of fluoride exposure and when those exposures began.

Conclusion

In conclusion, this study provides no support for the hypothesis that fluoride exposure increases the risk for osteosarcoma. It contributes to the body of evidence that indicates that the public can continue to enjoy the dental health benefits of fluoride with no associated major risks. □

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The Effects Of Fluoride On The Thyroid Gland

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9-9-4

There is a daunting amount of research studies showing that the widely acclaimed benefits on fluoride dental health are more imagined than real. My main concern however, is the effect of sustained fluoride intake on general health. Again, there is a huge body of research literature on this subject, freely available and in the public domain.

But this body of work was not considered by the York Review when their remit was changed from "Studies of the effects of fluoride on health" to "Studies on the effects of fluoridated water on health." It is clearly evident that it was not considered by the BMA (Britsh Medical Association), British Dental Association (BDA), BFS (British Fluoridation Society) and FPHM, (Faculty for Public Health and Medicine) since they all insist, as in the briefing paper to Members of Parliament - that fluoridation is safe and non-injurious to health.

This is a public disgrace, I will now show by reviewing the damaging effects of fluoridation, with special reference to thyroid illness.

It has been known since the latter part of the 19th century that certain communities, notably in Argentina, India and Turkey were chronically ill, with premature ageing, arthritis, mental retardation, and infertility; and high levels of natural fluorides in the water were responsible. Not only was it clear that the fluoride was having a general effect on the health of the community, but in the early 1920s Goldemberg, working in Argentina showed that fluoride was displacing iodine; thus compounding the damage and rendering the community also hypothyroid from iodine deficiency.

Highly damaging to the thyroid gland

This was the basis of the research in the 1930s of May, Litzka, Gorlitzer von Mundy, who used fluoride preparations to treat over-active thyroid illness. Their patients

either drank fluoridated water, swallowed fluoride pills or were bathed in fluoridated bath water; and their thyroid function was as a result, greatly depressed. The use in 1937 of fluorotyrosine for this purpose showed how effective this treatment was; but the effectiveness was difficult to predict and many patients suffered total thyroid loss. So it was given a new role and received a new name, Pardinon. It was marketed not for over-active thyroid disease but as a pesticide. (Note the manufacturer of fluorotyrosine was IG Farben who also made sarin, a gas used in World War II).

This bit of history illustrates the fact that fluorides are dangerous in general and in particular highly damaging to the thyroid gland, a matter to which I shall return shortly. While it is unlikely that it will be disputed that fluorides are toxic - let us be reminded that they are Schedule 2 Poisons under the Poisons Act 1972, the matter in dispute is the level of toxicity attributable to given amounts; in today's context the degree of damage caused by given concentrations in the water supply. While admitting its toxicity, proponents rely on the fact that it is diluted and therefore, it is claimed, unlikely to have deleterious effects.

They could not be more mistaken

It seems to me that we must be aware of how fluoride does its damage. It is an enzyme poison. Enzymes are complex protein compounds that vastly speed up biological chemical reactions while themselves remaining unchanged. As we speak, there occurs in all of us a vast multitude of these reactions to maintain life and produce the energy to sustain it. The chains of amino acids that make up these complex proteins are linked by simple compounds called amides; and it is with these that fluorine molecules react, splitting and distorting them, thus damaging the enzymes and their activity. Let it be said at once, this effect can occur at extraordinary low concentrations; even lower than the one part per million which is the dilution proposed for fluoridation in our water supply.

The body can only eliminate half

Moreover, fluorides are cumulative and build up steadily with ingestion of fluoride from all sources, which include not just water but the air we breathe and the food we eat. The use of fluoride toothpaste in dental hygiene and the coating of teeth are further sources of substantial levels of fluoride intake. The body can only eliminate half of the total intake, which means that the older you are the more fluoride will have accumulated in your body. Inevitably this means the ageing population is particularly targeted. And even worse for the very young there is a major element of risk in baby formula made with fluoridated water. The extreme sensitivity of the very young to fluoride toxicity makes this unacceptable. Since there are so many sources

of fluoride in our everyday living, it will prove impossible to maintain an average level of 1ppm as is suggested.

What is the result of these toxic effects?

First the immune system. The distortion of protein structure causes the immune proteins to fail to recognise body proteins, and so instigate an attack on them, which is Autoimmune Disease. Autoimmune diseases constitute a body of disease processes troubling many thousands of people: Rheumatoid Arthritis, Systemic Lupus Erythematosis, Asthma and Systemic Sclerosis are examples; but in my particular context today, thyroid antibodies will be produced which will cause Thyroiditis resulting in the common hypothyroid disease, Hashimoto's Disease and the hyperthyroidism of Graves' Disease.

Musculo Skeletal damage results further from the enzyme toxic effect; the collagen tissue of which muscles, tendons, ligaments and bones are made, is damaged. Rheumatoid illness, osteoporosis and deformation of bones inevitably follow. This toxic effect extends to the ameloblasts making tooth enamel, which is consequently weakened and then made brittle; and its visible appearance is, of course, dental fluorosis.

The enzyme poison effect extends to our genes; DNA cannot repair itself, and chromosomes are damaged. Work at the University of Missouri showed genital damage, targeting ovaries and testes. Also affected is inter uterine growth and development of the foetus, especially the nervous system. Increased incidence of Down's Syndrome has been documented.
Fluorides are mutagenic. That is, they can cause the uncontrolled proliferation of cells we call cancer. This applies to cancer anywhere in the body; but bones are particularly picked out. The incidence of osteosarcoma in a study reporting in 1991 showed an unbelievable 50% increase. A report in 1955 in the New England Journal of Medicine showed a 400% increase in cancer of the thyroid in San Francisco during the period their water was fluoridated.

My particular concern is the effect of fluorides on the thyroid gland

Perhaps I may remind you about thyroid disease. The thyroid gland produces hormones which control our metabolism - the rate at which we burn our fuel. Deficiency is relatively common, much more than is generally accepted by many medical authorities: a figure of 1:4 or 1:3 by mid life is more likely. The illness is insidious in its onset and progression. People become tired, cold, overweight, depressed, constipated; they suffer arthritis, hair loss, infertility, atherosclerosis and chronic illness. Sadly, it is poorly diagnosed and poorly managed by very many

doctors in this country.
What concerns me so deeply is that in concentrations as low as 1ppm, fluorides damage the thyroid system on 4 levels.

1. The enzyme manufacture of thyroid hormones within the thyroid gland itself. The process by which iodine is attached to the amino acid tyrosine and converted to the two significant thyroid hormones, thyroxine (T4) and liothyronine (T3), is slowed.

2. The stimulation of certain G proteins from the toxic effect of fluoride (whose function is to govern uptake of substances into each of the cells of the body), has the effect of switching off the uptake into the cell of the active thyroid hormone.

3. The thyroid control mechanism is compromised. The thyroid stimulating hormone output from the pituitary gland is inhibited by fluoride, thus reducing thyroid output of thyroid hormones.

4. Fluoride competes for the receptor sites on the thyroid gland which respond to the thyroid stimulating hormone; so that less of this hormone reaches the thyroid gland and so less thyroid hormone is manufactured.
These damaging effects, all of which occur with small concentrations of fluoride, have obvious and easily identifiable effects on thyroid status. The running down of thyroid hormone means a slow slide into hypothyroidism. Already the incidence of hypothyroidism is increasing as a result of other environmental toxins and pollutions together with wide spread nutritional deficiencies.

141 million Europeans are at risk

One further factor should give us deep anxiety. Professor Hume of Dundee, in his paper given earlier this year to the Novartis Foundation, pointed out that iodine deficiency is growing worldwide. There are 141 million Europeans are at risk; only 5 European countries are iodine sufficient. UK now falls into the marginal and focal category. Professor Hume recently produced figures to show that 40% of pregnant women in the Tayside region of Scotland were deficient by at least half of the iodine required for a normal pregnancy. A relatively high level of missing, decayed, filled teeth was noted in this non-fluoridated area, suggesting that the iodine deficiency was causing early hypothyroidism which interferes with the health of teeth. Dare one speculate on the result of now fluoridating the water?

Displaces iodine in the body

These figures would be worrying enough, since they mean that iodine deficiency, which results in hypothyroidism (thyroid hormone cannot be manufactured without

iodine) is likely to affect huge numbers of people. What makes it infinitely worse, is that fluorine, being a halogen (chemically related to iodine), but very much more active, displaces iodine. So that the uptake of iodine is compromised by the ejection, as it were, of the iodine by fluorine. To condemn the entire population, already having marginal levels of iodine, to inevitable progressive failure of their thyroid system by fluoridating the water, borders on criminal lunacy.
I would like to place a scenario in front of those colleagues who favour fluoridation. A new pill is marketed. Some trials not all together satisfactory, nevertheless, show a striking improvement in dental caries. Unfortunately, it has been found to be thyrotoxic, mutagenic, immunosuppressive, cause arthritis and infertility in comparatively small doses over a relatively short period of time.

Do you think it should be marketed?
Fluoridation of the nation's water supply will do little for our dental health; but will have catastrophic effects on our general health. We cannot, must not, dare not, subject our nation to this appalling risk.

Dr Barry Durrant-Peatfield
obtained his Medical degrees in 1960 at Guy's Hospital London. He left the NHS in 1980 to specialise in thyroid illnesses drawing inspiration from the work of infamous Dr Broda Barnes, at the Foundation that bears his name, Connecticut, USA. He has been a medical practitioner for over forty years specialising in metabolic disorders during which time he became a leading authority in the UK for thyroid and adrenal management. For over twenty years he also ran a successful private clinic and became a nation-wide leading authority on thyroid and adrenal dysfunction, but clashed with establishment medicine in the management of thyroid illness. He is the author of The Great Thyroid Scandal (see opposite page), he currently lectures at nutritional colleges in London as well as conducting his own teaching seminars. Barry will shortly be opening a diagnostic clinic in the UK for thyroid and adrenal disorders where he will provide advice on diagnosis and treatment with special interests in nutritional aspects. For further information contact: Dr B Durrant-Peatfield 36A High St, Mersham, Redhill Surrey, RH1 3EA.
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Sarin: (GB: isopropyl methylphosono-fluoridate) is a colorless, odorless volatile liquid, soluble in water, first synthesized at IG Farben in 1938. It kills mainly through inhalation.

Cyclosarin (GF) and Thiosarin are variants. Pennsylvania Department of Health http://www.dsf.health.state.pa.us/health/cwp/view.asp?a=171&q=233740

Sarin: (GB: CH3-P(=O)(-F)(-OCH(CH3)2)
Source: A FOA Briefing Book on Chemical Weapons
http://www.opcw.org/resp/html/nerve.html Gerhard Schrader, a chemist at IG Farben, was given the task of developing a pesticide. Two years later a phosphorus compound with extremely high toxicity was produced for the first time.
IG Farben: "...the board of American IG Farben had three directors from the Federal Reserve Bank of New York, the most influential of the various Federal Reserve Banks. American IG Farben. also had interlocks with Standard Oil of New Jersey, Ford Motor Company, Bank of Manhattan (later to become the Chase Manhattan Bank), and AEG. (German General Electric) Source: Moody's Manual of Investments; 1930, page 2149."

http://reformed-theology.org/html/books/wall_street/chapter_02.htm

At a later date, Namaste will be publishing a more in-depth article outlining the devastating affects that fluoride, aspartame and MSG have on the endocrine system. Dr Durrant-Peatfield wiill be answering frequently asked questions on thyroid illness in Namaste's next issue. Send your questions to us preferably by email to: info@namastepublishing.co.uk

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Nucl Med Commun. 2012 Jan;33(1):14-20.

Association of vascular fluoride uptake with vascular calcification and coronary artery disease.

Li Y, Berenji GR, Shaba WF, Tafti B, Yevdayev E, Dadparvar S.
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Abstract

OBJECTIVE: The feasibility of a fluoride positron emission tomography/computed tomography (PET/CT) scan for imaging atherosclerosis has not been well documented. The purpose of this study was to assess fluoride uptake of vascular calcification in various major arteries, including coronary arteries.

METHODS: We retrospectively reviewed the imaging data and cardiovascular history of 61 patients who received whole-body sodium [^{18}F]fluoride PET/CT studies at our institution from 2009 to 2010. Fluoride uptake and calcification in major arteries, including coronary arteries, were analyzed by both visual assessment and standardized uptake value measurement.

RESULTS: Fluoride uptake in vascular walls was demonstrated in 361 sites of 54 (96%) patients, whereas calcification was observed in 317 sites of 49 (88%) patients. Significant correlation between fluoride uptake and calcification was observed in most of the arterial walls, except in those of the abdominal aorta. Fluoride uptake in coronary arteries was demonstrated in 28 (46%) patients and coronary calcifications were observed in 34 (56%) patients. There was significant correlation between history of cardiovascular events and presence of fluoride uptake in coronary arteries. The coronary fluoride uptake value in patients with cardiovascular events was significantly higher than in patients without cardiovascular events.

CONCLUSION: sodium [^{18}F]fluoride PET/CT might be useful in the evaluation of the atherosclerotic process in major arteries, including coronary arteries. An increased fluoride uptake in coronary arteries may be associated with an increased cardiovascular risk.

PMID:21946616[PubMed - in process]

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ORIGINAL ARTICLE

Acute Fluoride Poisoning from a Public Water System

Bradford D. Gessner, Michael Beller, John P. Middaugh and Gary M. Whitford

N Engl J Med 1994; 330:95-99 January 13, 1994

Abstract Article References Citing Articles (17)

Since the late 1940s, many communities in the United States have adjusted the fluoride concentration in their water systems to prevent dental caries[1]. Numerous studies attest to the effectiveness and safety of maintaining fluoride concentrations in the range recommended by the Public Health Service -- 0.7 to 1.2 mg per liter[2,3]. As of 1989, a total of 9411 public water systems in the United States provided fluoridated drinking water to 135 million people,[4] yet only six outbreaks of acute fluoride poisoning related to overfluoridation have been reported[5-10]. Acute fluoride poisoning caused the death of one patient in Maryland[8] and, recently, of three patients in Illinois (Flanders R, Illinois Department of Public Health: personal communication), all of whom were undergoing dialysis therapy. In this paper we describe an outbreak of acute fluoride poisoning resulting from overfluoridation of a public water system.

METHODS

Background

Hooper Bay, Alaska, is a small village on the Bering Sea populated predominantly by Alaska Natives. The village has two geographically distinct sections with separate wells and water systems: sections 1 (population, 470) and 2 (population, 375). Neither water system provided running water to individual homes; residents carried water from holding tanks to their homes, where it was stored for domestic use. On May 26, 1992, the Alaska Division of Public Health was notified of an outbreak of acute gastrointestinal illness in the village. The water system in section 1 had been turned off on May 23 after staff members at the Hooper Bay health clinic noted that many residents had become ill shortly after drinking water from that system. Since acute fluoride poisoning produces a clinical syndrome characterized by nausea, vomiting, diarrhea, abdominal pain, and paresthesias and because tests conducted during the six weeks before the outbreak had shown fluoride concentrations in water system 1 of 6.5 and 20.0 mg per liter, acute fluoride poisoning was suspected.

The outbreak resulted in one serious illness and one death. On May 23, a 37-year-old woman with a two-day history of vomiting and diarrhea was evacuated by air to a regional hospital. Her serum calcium concentration was 5.2 mg per deciliter (1.3 mmol per liter), and her serum fluoride concentration was 9.1 mg per liter (480 µmol per liter) (the normal fasting serum fluoride concentration in persons using drinking water containing 1 mg of fluoride per liter is 0.01 to 0.03 mg per liter [0.5 to 1.6 µmol per liter]). She recovered without apparent sequelae. On May 23, after 24 hours of intractable vomiting, a 41-year-old man was found dead at home. He had attempted to remain hydrated by drinking an estimated 10 liters of water from water system 1 on May 21 and 22. His only known medical problem was peptic ulcer disease, for which he took cimetidine. The postmortem serum calcium concentration was 4.9 mg per deciliter (1.22 mmol per liter), and the urinary fluoride concentration (not corrected for creatinine content) was 55 mg per liter (2900 µmol per liter).

Epidemiologic Study

To determine the duration of the outbreak, we reviewed the health clinic records of all patients seen from May 1 to May 25 with nausea, vomiting, diarrhea, or abdominal pain. Of 31 patients with these

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symptoms, 22 were seen on May 21, 22, or 23. We therefore defined a case patient with fluoride poisoning as a resident who had at least one of the following symptoms on May 21, 22, or 23: nausea, vomiting, diarrhea, abdominal pain, or numbness or tingling of the face or extremities.

On May 27 we went to the clinic and asked patients who were seen there on May 21, 22, or 23 to come to the clinic with any available family members. These persons, as well as patients being seen at the clinic for any reason on May 27, were interviewed as described below. On May 28 we identified case patients (and control subjects) through a household survey conducted by starting at one randomly selected household in each section of the village and walking door to door until residents of 15 households in section 1 and 17 households in section 2 had been interviewed. We collected information on all residents of each household, and adult residents were asked to provide information about anyone not at home. Since case patients identified at the clinic and through the household survey were similar with respect to age and onset, duration, and type of symptoms, we considered all case patients together.

All residents interviewed on May 27 or 28 responded to a questionnaire that included questions about symptoms and water consumption. Information about persons under 18 years of age was obtained from a parent or guardian. Some residents had difficulty recalling the details of their illness or their water consumption; results are given only for those able to recall the details.

To evaluate risk factors and calculate attack rates, we conducted a case-control study and a retrospective cohort study. The case-control study analyzed the case patients and control subjects who were interviewed at the clinic on May 27; it compared the characteristics of persons meeting the definition of a case patient with those of persons who did not. All persons interviewed on May 27 who did not meet the case-patient definition were considered controls for this analysis. The retrospective cohort study analyzed the case patients and control subjects identified during the household survey. Since almost all the acutely ill persons lived in section 1, we used the cohort study to estimate the total number with fluoride poisoning.

Biochemical Measurements

On May 27 and 28, we collected blood and spot urine specimens from 20 case patients and blood or urine alone from 7 case patients. Urine specimens were also collected from 15 control subjects, 3 of whom also provided a blood sample. Urine was analyzed for fluoride and creatinine. Serum was analyzed for fluoride and, in most cases, aspartate aminotransferase, calcium, creatine kinase, lactate dehydrogenase, magnesium, and phosphorus.

Follow-up urine specimens were collected from case patients with the highest initial urinary fluoride concentrations. Six case patients provided a specimen on June 5 or June 9, and three provided specimens on both dates. On June 9 follow-up blood specimens were collected from 11 case patients who had an abnormal result on serum-chemistry testing or an elevated serum fluoride concentration.

Urinary fluoride was measured by direct ion-specific electrode potentiometry and corrected for the creatinine content by dividing the measured fluoride concentration (in milligrams per liter) by the urinary creatinine concentration (in milligrams per deciliter) and then multiplying the value by 100 mg per deciliter. Serum fluoride was measured in the same manner after overnight diffusion by the hexamethyldisiloxane-facilitated technique[11].

Environmental Investigation

We reviewed the records of routine fluoride determinations for the Hooper Bay water systems and collected water samples from the two systems and from residents who still had water from system 1 in their homes. The Alaska Department of Environmental Conservation inspected both water systems and had water samples analyzed for fluoride using protocols approved by the Environmental Protection Agency.

Dose Estimates

To estimate the dose of fluoride ingested, we asked each case patient to recall how much water he or she had consumed that had been obtained from system 1 from May 21 to 23. Beverages made with water were included in the calculation, but water consumed in food was not. The estimated dose was calculated as the volume of water consumed (in liters) multiplied by the presumed fluoride concentration of the water (in milligrams per liter) divided by body weight (in kilograms). The presumed fluoride concentration was based on the results of the environmental investigation.

Statistical Analysis

Odds ratios, relative risks, and 95 percent confidence intervals were calculated with the Epi Info program[12]. Pearson's correlation coefficients were determined by the least-squares method[13]; we report corresponding two-tailed P values. The confidence interval for the estimated number of section 1 residents with fluoride poisoning was calculated according to the method of Levy and Lemeshow[14].

RESULTS

Epidemiologic Study

Overall we identified 91 case patients; all were Alaska Natives, ranging in age from 6 months to 73 years (median, 21 years), and 51 percent were female. The most common symptoms were nausea, vomiting, and abdominal pain (Table 1). All case patients had stopped drinking water from system 1 by May 23. Most case patients began to have symptoms on May 22 (Figure 1). The median interval between the consumption of water and the onset of symptoms was 7 minutes (range, <1 to 150), and the median duration of symptoms was 24 hours (range, 1 to 132).

There were 42 case patients and 54 control subjects in the case-control study. As compared with the controls, the case patients were 7 times more likely to live in section 1, 18.5 times more likely to consume water from water system 1, and 76 times more likely to have consumed water obtained from water system 1 on May 21, 22, or 23 (Table 2).

There were 175 persons in the retrospective cohort study. The attack rates among residents of sections 1 and 2 were 63 percent and 2 percent, respectively (Table 3). Among residents of section 1, the attack rate among those who usually drank water from system 1 was 71 percent, whereas among those who drank water obtained from system 1 from May 21 to 23, the attack rate was 91 percent (Table 3). Six residents of section 1 who were sick but who had not drunk water collected from system 1 on May 21, 22, or 23 recalled drinking water obtained on May 20. The attack rate among the residents of section 1 implies that 296 of the 470 residents (63 percent) had acute fluoride poisoning (95 percent confidence interval, 249 to 343).

Biochemical Measurements

For specimens collected on May 27 or 28, the median urinary fluoride concentrations in case patients and control subjects were 3.4 mg per liter (180 µmol per liter) and 1.7 mg per liter (89 µmol per liter), respectively. Ten case patients and no control subjects had elevated urinary fluoride concentrations (>5.0 mg per liter [>260 µmol per liter]). The median serum fluoride concentrations were 0.067 mg per liter (3.5 µmol per liter) in the case patients and 0.029 mg per liter (1.5 µmol per liter) in the control subjects. The serum fluoride concentrations in the case patients correlated strongly with the duration of illness ($r = 0.84$, $P<0.001$).

The median urinary fluoride concentrations in case patients retested on June 5 and 9 were 6.4 mg per liter (340 µmol per liter) and 4.4 mg per liter (230 µmol per liter), respectively. The urinary fluoride concentrations decreased consistently from May 27 or 28 to June 9; for the persons retested on both June 5 and 9, the decrease was nonlinear.

All 14 case patients tested on May 27 or 28 had an elevated serum lactate dehydrogenase concentration (median, 152 U per liter). Eleven case patients had elevated serum aspartate aminotransferase concentrations, eight had hypomagnesemia, three had hyperphosphatemia, and one had an elevated creatine kinase concentration. All serum calcium values were normal. Serum lactate dehydrogenase concentrations correlated with the urinary ($r = 0.74$, $P = 0.002$) and serum ($r = 0.57$, $P = 0.004$) fluoride concentrations obtained on May 27 or 28. Among 11 case patients retested on June 9, 6 had hypomagnesemia, 3 had hyperphosphatemia, and 1 had an elevated serum lactate dehydrogenase concentration; the median serum fluoride concentration was 0.086 mg per liter (4.5 µmol per liter).

Environmental Investigation

Water system 1 included a 6340-liter (1675 gal) holding tank, two 95-liter (25 gal) chemical vats (for chlorine and fluoride concentrates), a water pump and two chemical feed pumps, high and low floats connected to an electrical control system to regulate the volume of water in the holding tank, and a public watering point outside the well house (Figure 2). Regulations requiring that results of monthly fluoride measurements be submitted to the state had been unmet for almost two years. The operator lacked formal training and could not correctly perform fluoride tests. High fluoride concentrations were documented in January 1991 (7.3 mg per liter) and again six and three weeks before the outbreak (6.5 and 20 mg per liter, respectively). After the third report of an elevated fluoride concentration, local health officials asked the water-system operator to drain the holding tank and unplug the fluoride pump. On May 26, 1992, however, the fluoride pump was still operating. Water obtained from water system 1 by residents on May 20 and 21 had fluoride concentrations of 2

TABLE 1

Symptoms of 91 Case Patients with Acute Fluoride Poisoning in Hooper Bay, Alaska, in May 1992.

FIGURE 1

Onset of Symptoms of Acute Fluoride Poisoning in 89 Case Patients and Onset of Gastrointestinal Symptoms in 15 Other Residents of Hooper Bay, Alaska, in May 1992.

TABLE 2

Odds Ratios for Various Types of Exposure in a Case-Control Study of Acute Fluoride Poisoning.

TABLE 3

Attack Rates and Relative Risks for Various Types of Exposure in a Retrospective Cohort Study of Acute Fluoride Poisoning.

FIGURE 2

Diagram of Water System 1.

and 150 mg per liter, respectively; water obtained on May 27 had a fluoride concentration of 58 mg per liter. Water obtained from system 2 on May 27 had a fluoride concentration of 1.1 mg per liter.

Major electrical and mechanical defects of water system 1 were identified. The control system was unreliable and did not activate the water pump consistently. The fluoride pump performed four times faster than expected and, because of improper electrical wiring, could be activated independently of the water pump. Because of these defects, the fluoride concentration of a full holding tank could be increased from 0 to 150 mg per liter in 26 hours. Finally, under certain operating conditions, the fluoride concentrate (18,000 mg per liter) could be siphoned into the well if the hose was kept connected to the drop pipe (Figure 2) and its free end was placed in the fluoride vat. After the outbreak, tests demonstrated that siphonage could have led to the elevated fluoride concentration by emptying a full fluoride vat in several minutes.

Dose Estimates

Among 62 case patients able to remember how much water they had consumed from water system 1 from May 21 to 23, reports ranged from 2 to 140 ml per kilogram of body weight (median, 27). Assuming that the fluoride concentration of all water collected from May 21 to 23 was 150 mg per liter, the fluoride doses ranged from 0.3 to 21.0 mg per kilogram; 21 persons received an estimated dose of less than 2.0 mg per kilogram, and 10 received doses below 1.0 mg per kilogram. The man who died received an estimated dose of 17.9 mg per kilogram. The estimated fluoride dose strongly correlated with the urinary ($r = 0.78$, $P<0.001$) and serum ($r = 0.71$, $P<0.001$) fluoride concentrations obtained on May 27 or 28 and with the duration of illness ($r = 0.58$, $P<0.001$).

DISCUSSION

These results indicate that excess fluoride entered a community water system in a rural Alaska village, causing 1 death and almost 300 nonfatal cases of fluoride intoxication. The symptoms can be explained by well-described mechanisms[15]. Fluoride and hydrogen ions combine in the stomach to form hydrofluoric acid, which causes nausea, vomiting, diarrhea, and abdominal pain. Fluoride has a direct toxic effect on intracellular metabolism that includes the inhibition of glycolytic enzymes and cholinesterases. Profound hyperkalemia may result. Finally, fluoride forms a complex with calcium in extracellular fluid that causes hypocalcemia; the fate of the complex is not known. Our findings suggest that serum magnesium concentrations may also be reduced; the mechanism for this reduction is unknown. Death from fluoride poisoning is believed to occur from cardiac dysrhythmias due to hyperkalemia or hypocalcemia[16-18].

Although the interval between water consumption and the onset of symptoms was consistent with that in other reports,[7,19,20] the median duration of symptoms – 24 hours – was longer than the previously reported range of less than 1 hour to 5.5 hours[9,10,19]. The prolonged elevation of serum and urinary fluoride concentrations was also unexpected; more than two weeks after the outbreak, the median serum fluoride concentration among the case patients who were retested was two to three times normal. The half-life of fluoride in serum has been estimated to be 2.4 to 4.3 hours,[21] and after the ingestion of a low dose, the serum fluoride concentration usually returns to normal within 24 hours[22]. The prolonged elevation of serum and urinary fluoride concentrations may have been due to the continued ingestion of water with a high fluoride concentration. This explanation is unlikely, since water system 1 was shut off immediately after the outbreak was recognized, most residents discarded all water obtained from the system, and fluoridation of water system 2 was discontinued. Renal disease and exercise are associated with decreased fluoride excretion, thus lengthening the time that serum fluoride concentrations remain elevated[15]. However, only one person reported having renal disease, none used nephrotoxic drugs, and there is no reason to suspect that the case patients differed substantially from the control subjects with respect to other factors.

The lowest estimated dose of fluoride that caused symptoms was 0.3 mg per kilogram; 16 percent of the case patients received an estimated dose of less than 1.0 mg per kilogram. The lowest level at which an effect was observed – a level of less than 1 mg of fluoride per kilogram – is similar to that reported in some studies,[19,23] but lower than that identified in one report[24]. Disordered mineral homeostasis and cellular damage, including abnormalities in serum magnesium, phosphorus, and lactate dehydrogenase concentrations, persisted for at least 19 days. These effects suggest that both follow-up of individual patients and studies of the long-term effects of acute fluoride poisoning may be indicated.

The correlations of the estimated dose of fluoride with the duration of symptoms and with urinary and serum fluoride concentrations imply that our dose estimates are valid. We made several assumptions, however, and the findings must therefore be cautiously interpreted. We relied on interviews conducted with residents four to five days after the outbreak and did not include water consumed in food in our estimate of the fluoride dose. Although the fluoride concentration in the water system was probably not constant, we assumed that the outbreak was caused by water with a fluoride concentration of 150 mg per liter. Finally, most case patients vomited within minutes after ingesting water with a high fluoride concentration, and the dose estimates did not account for the fluoride lost in this way.

We identified two possible causes of the outbreak. The fluoride pump could have been activated without activation of the water pump, or the fluoride concentrate could have been siphoned into the well. In addition, a series of human errors contributed to this incident. The water-system operator had no formal training and lacked a basic understanding of the operation of the fluoridation unit. Fluoride-test results had not been submitted to or monitored by state regulators. When elevated fluoride concentrations were discovered before the outbreak, the recommendation to disconnect the fluoride pump was not implemented.

The findings of our investigation should be of concern both to health care providers of patients with acute fluoride poisoning and to public health and other officials responsible for water fluoridation. The efficacy of fluoridation in preventing dental caries has been well documented, and the safety of this practice is supported by the extreme rarity of incidents of overfluoridation. We believe that the practice of fluoridation of public water systems should continue. However, public health officials must make certain that standard safety equipment is installed, that water-system operators are properly trained, and that routine, systematic monitoring and follow-up of fluoride concentrations in water systems and inspection of fluoridation units are undertaken.

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SOURCE INFORMATION

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Neurotoxicity of Sodium Fluoride in Rats

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MULLENIX, P. J., P. K. DENBESTEN, A. SCHUNIOR AND W. J. KERNAN. *Neurotoxicity of sodium fluoride in rats.* NEUROTOXICOL TERATOL 17(2) 169–177, 1995.—Fluoride (F) is known to affect mineralizing tissues, but effects upon the developing brain have not been previously considered. This study in Sprague–Dawley rats compares behavior, body weight, plasma and brain F levels after sodium fluoride (NaF) exposures during late gestation, at weaning or in adults. For prenatal exposures, dams received injections (SC) of 0.13 mg/kg NaF or saline on gestational days 14–18 or 17–19. Weanlings received drinking water containing 0, 75, 100, or 125 ppm F for 6 or 20 weeks, and 3 month-old adults received water containing 100 ppm F for 6 weeks. Behavior was tested in a computer pattern recognition system that classified acts in a novel environment and quantified act initiations, total times and time structures. Fluoride exposures caused sex- and dose-specific behavioral deficits with a common pattern. Males were most sensitive to prenatal day 17–19 exposure, whereas females were more sensitive to weanling and adult exposures. After fluoride ingestion, the severity of the effect on behavior increased directly with plasma F levels and F concentrations in specific brain regions. Such association is important considering that plasma levels in this rat model (0.059 to 0.640 ppm F) are similar to those reported in humans exposed to high levels of fluoride.

Fluoride Neurotoxicity Central nervous system

DENTAL fluorosis has been on the rise since the 1950s, indicating that our total fluoride exposure is increasing (9). Fluoride, including sodium fluoride (NaF), has been added to public water supplies for over 40 years in the United States as a preventative measure against dental caries. Other sources of fluoride exposure include processed beverages, toothpastes, mouth rinses, dietary supplements, and food. Although dental fluorosis causes discoloration of teeth, it is not considered a public health concern because it does not hinder tooth function or oral health. In addition, no clear link has been established between fluoride and cancer risk, bone fractures, birth defects, or problems of the gastrointestinal, genito-urinary, or respiratory systems (1). Therefore, the impetus to limit total fluoride exposure in the United States is currently based on cosmetic concerns and a general desire not to expose the public to any more fluoride than the amount necessary to prevent dental caries.

One concern that has not been fully investigated is the link between fluoride and effects on the central nervous system (CNS). In vitro studies have shown that intracellular fluoride can alter the kinetic properties of calcium currents in hippocampal neurons (22). Fluoride is a normal component of cerebrospinal fluid (21), but it has not been found to accumulate there during endemic fluorosis or nervous system disease (21,41). Yet, there have been reports from Chinese investigators that high levels of fluoride in drinking water (i.e., 3–11 ppm) affect the nervous system directly without first causing physical deformations from skeletal fluorosis (13,20,40). One study of adult humans found attention affected by sublingual drops containing 100 ppm of sodium fluoride (39), an exposure level potentially relevant to humans because toothpastes contain 1000 to 1500 ppm fluoride (8,48) and mouthrinses contain 230–900 ppm fluoride (48).

Many years of ubiquitous fluoride exposure have not resulted in obvious CNS problems such as seizures, lethargy, salivation, tremors, paralysis, or sensory deficits. Still unexplored, however, is the possibility that fluoride exposure is linked with subtle brain dysfunction. The present study evaluates the neurotoxic potential of sodium fluoride in an animal model. It uses behavioral methodology that focuses on behavioral repertoire, responses to novelty and the temporal or sequential organization of spontaneous behavior, all important

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TABLE 5

CONSISTENT BEHAVIORAL EFFECTS OF FLUORIDE EXPOSURE STARTED AT WEANING

Behavior	Females Control	Females 100 ppm F for 6 Weeks	Females Control	Females 125 ppm F for 16 Weeks	Males Control	Males 125 ppm F for 16 Weeks
Sit						
BI (±SE)	20.7 ± 3.0	16.0 ± 1.8	22.4 ± 2.2	15.2 ± 1.8*	57.7 ± 3.3	42.8 ± 3.5†
BTT (±SE)	76.6 ± 19.3	37.9 ± 5.1	66.8 ± 10.9	37.7 ± 5.5*	245.6 ± 21.8	174.4 ± 23.6*
Groom						
BI	13.8 ± 2.6	6.5 ± 1.1*	8.1 ± 2.0	5.2 ± 1.2	30.0 ± 5.5	14.3 ± 2.2*
BTT	29.8 ± 6.3	9.4 ± 1.8†	20.1 ± 6.2	11.4 ± 3.4	70.3 ± 16.1	35.8 ± 8.9
Turn						
BI	123.5 ± 5.5	123.1 ± 5.1	110.7 ± 3.8	105.9 ± 5.5	97.2 ± 5.0	81.7 ± 5.4*
Head turn						
BI	61.9 ± 3.5	57.4 ± 2.9	67.3 ± 2.2	58.6 ± 1.5†	68.1 ± 4.0	58.5 ± 5.0
BTT	75.8 ± 5.3	66.8 ± 3.7	78.8 ± 2.9	69.4 ± 1.9†	84.9 ± 5.5	72.7 ± 7.0
Groom/explore (cluster)						
BI	12.6 ± 3.1	8.5 ± 0.9	15.4 ± 1.9	8.6 ± 1.0†	37.5 ± 3.0	23.7 ± 2.9†
BTT	17.3 ± 4.8	10.7 ± 1.2	19.5 ± 2.4	11.5 ± 1.4†	49.5 ± 4.3	32.5 ± 4.6†
Groom/attention (cluster)						
BI	26.5 ± 4.4	16.1 ± 2.4*	20.4 ± 2.9	12.6 ± 1.8*	72.1 ± 5.2	46.1 ± 4.1‡
BTT	60.7 ± 11.8	43.2 ± 9.0	40.3 ± 8.6	21.5 ± 3.6*	184.9 ± 19.8	131.4 ± 18.7
Groom (cluster)						
BI	10.4 ± 2.5	4.6 ± 0.9*	6.9 ± 1.6	4.3 ± 1.1	22.6 ± 3.8	11.7 ± 2.0*
BTT	22.7 ± 6.2	7.0 ± 1.6*	13.9 ± 3.7	8.2 ± 2.4	42.4 ± 7.8	23.6 ± 4.5*
Stand						
BTT	576.0 ± 22.1	607.9 ± 12.0	608.1 ± 14.9	629.2 ± 17.7	532.5 ± 20.2	599.0 ± 22.0*
Attention (cluster)						
BTT	494.9 ± 19.9	529.5 ± 13.4	505.3 ± 14.8	528.7 ± 20.0	418.4 ± 21.4	499.3 ± 20.9*

*$p < 0.05$, t test; †$p < 0.01$, t test; ‡$p < 0.001$, t test.

distribution and time sequence of behavioral acts were calculated using equations for $K(t)$ as previously reported (27,28,33). The K function was calculated for specific behavioral acts (e.g., sit, rear) or sequences of specific behavioral acts (e.g., sit . . . rear) (33) and for combined acts (e.g., attention or attention/groom) or sequences of combined acts (e.g., attention . . . explore or attention/explore . . . groom/attention) (28). For each of these, a $\Delta K(t)$ [the difference between $K(t)$ for the fluoride animals and matched controls] was calculated for eight time points (2,5,10,20,30,45,100, and 200 s). At any one time point, when K values increase (compared to controls) for a behavior, it means that that particular behavior (or sequence) is "clustering" in time (as seen in hypoactivity), while a decrease means it is "dispersing" in time (it had increased regularity of timing between initiations as seen in hyperactivity). Whenever a behavioral act was initiated less than 10 times on average per animal, control or experimental, $K(t)$ values were not determined for that behavior and related sequences. The bootstrap technique was used for estimating SD at each time point of the K-function for a behavior, and the ad hoc criteria for significance of a difference between control and exposed groups have been described (23,25,27,28,33,34).

An RS statistic was determined for each fluoride treatment. The ad hoc RS statistic distinguishes low level behavioral ef-

TABLE 6

EFFECTS OF 100 ppm FLUORIDE FOR 6 WEEKS STARTING IN 3 MONTH-OLD-RATS

	Body Weight (g ± SD) Control	Body Weight (g ± SD) Exposed	Plasma F (ppm ± SD) Control	Plasma F (ppm ± SD) Exposed	Behavior (RS Statistic)
Females	331.8 ± 41.6	319.8 ± 36.1	0.010 ± 0.002	0.077 ± 0.040*	0.200‡
	$n = 21$	$n = 22$	$n = 5$	$n = 5$	$n = 20$ pairs
Males	620.3 ± 45.3	609.0 ± 72.1	0.012 ± 0.005	0.059 ± 0.027†	0.053
	$n = 24$	$n = 22$	$n = 6$	$n = 5$	$n = 18$ pairs

*$p < 0.05$, t test; †$p < 0.01$, t test; ‡$p < 0.001$.

fects from noise (24). This statistic encompasses all data produced in an experiment into one simple statistic. This is an advantage considering that the computer system generates over 100 behavioral measures of three distinctly different types (initiations, total times, and time structures) per experiment. The RS statistic indicates whether behavior is changed overall and the confidence level associated with that change. Statistical significance was set at the $p < 0.01$ level.

RESULTS

Prenatal Exposures

No maternal or offspring toxicity was indicated by reduced body weight in dams during treatment or in their pups soon after birth. Yet, prenatal exposure to sodium fluoride altered behavioral outcome in male offspring when exposure occurred on GDs 17–19 (Table 1). This effect consisted entirely of time structure changes in 11 behaviors and behavioral sequences, 10 of which were significantly dispersed compared to matching controls as illustrated in Fig. 1. These behavioral effects did not coincide with reduced body weight nor elevated plasma fluoride levels at 9 weeks of age (Table 1). At 3 weeks of age, plasma fluoride levels also were not elevated despite prenatal exposure on GD 17–19; plasma fluoride levels were no different in prenatal fluoride females (0.007 ppm ± 0.003 SD; $n = 7$) compared to matched controls (0.006 ppm ± 0.002 SD; $n = 7$) or in prenatal fluoride males (0.004 ppm ± 0.002 SD; $n = 8$) compared to controls (0.004 ppm ± 0.003 SD; $n = 8$).

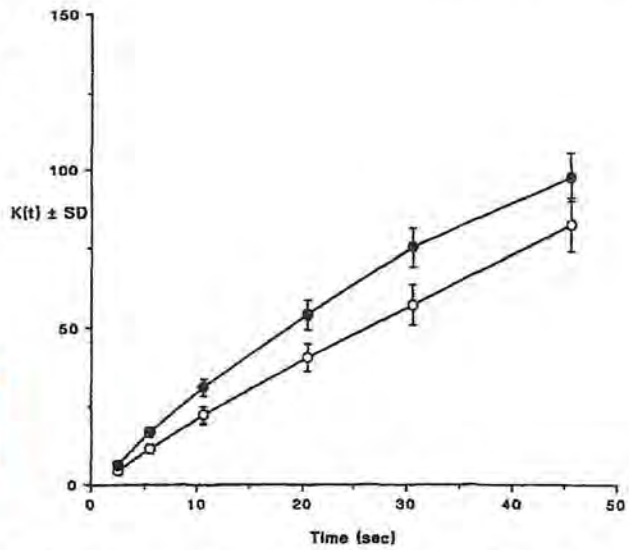

FIG. 4. Exposure to fluoride at the adult stage significantly altered (RS = 0.200; $p < 0.001$) behavior of female rats (●) compared to respective controls (○). This example K function illustrates time-structure changes typical of the adult F effect. Significant clustering (increased K values) is shown for the behavior groom/attention, which prenatal F, in contrast, significantly dispersed (Fig. 1A). Error bars indicate ± SD.

Weanling Exposures

When fluoride exposures began at 21 days of age, effects on body weight depended on the fluoride concentration in the drinking water (Table 2). Concentrations below 125 ppm did not affect body weight gain at any time during a 5- to 6-week exposure. In contrast, at 125 ppm body weight was reduced throughout 20 weeks of exposure in both sexes. The 11 survivors of a 10-day exposure to 175 ppm F also had stunted growth compared to matched controls at 9 weeks of age. However, by 18 weeks of age, stunting among the 175 ppm female survivors was ameliorated (Table 2).

Plasma fluoride levels were significantly increased in all exposed animals, but again the increase depended upon the fluoride concentration given in the drinking water (Table 3). At 75 and 100 ppm fluoride in drinking water of females for 6 weeks, plasma fluoride levels increased respective of dose. When concentration in the drinking water was 125 ppm for 6 weeks, plasma fluoride levels increased compared to controls but not to levels expected considering results observed at lower drinking water concentrations (Table 3).

Fluoride in drinking water of weanlings altered behavior in both sexes (Table 4). The duration and concentration of exposure determined whether significant effects occurred. In females, a 6-week exposure to 100 or 125 ppm was sufficient to alter behavior, whereas in males an 11-week exposure to 125 ppm in drinking water significantly affected behavior. Too few 175 ppm fluoride females (11 in total) survived after a 10-day exposure to determine an RS statistic for that group. A relationship between behavioral effects and plasma fluoride levels was observed in females exposed for 6 weeks to 75, 100, or 125 ppm fluoride. Figure 2 illustrates that as plasma fluoride levels increased, the RS statistic increased, with significant behavioral impact estimated to occur at a plasma fluoride level of approximately 0.107 ppm. Significant behavioral impact in males, however, did not occur until plasma levels exceeded 0.126 and 0.170 ppm (Table 3 and Table 4).

Regardless of sex, duration of exposure, or the fluoride concentration in the drinking water of weanlings, a common pattern among behavioral disturbances developed. Table 5 includes all behaviors that were significantly affected in BI and/or BTT by at least one fluoride exposure. Age and sex influenced the BI and BTT of these behaviors in controls, but still a general effect of fluoride emerged. Whether exposure lasted 6 or 16 weeks, at the 100 or 125 ppm level, in males or females, the same direction of change with respect to controls occurred for a certain array of behaviors and related behavioral clusters. Whereas the act of standing and the related attention cluster tended to increase in total time, the other acts consistently decreased in initiations and total times.

Adult Exposures

Male and female adult rats given 100 ppm fluoride for 6 weeks had significantly increased plasma fluoride levels with no effect on body weight, whereas behavior was affected only in females (Table 6). Compared to females exposed at weaning, females exposed as adults had a lower plasma fluoride level (0.077 ppm) associated with significant behavioral impact. However, the same pattern of BI and BTT changes seen with weanling exposures (Table 5) also developed in females exposed as adults. For example, initiations of sitting, the groom/attention cluster, and the groom/explore cluster in adult female controls (42.9 ± 3.0; 50.4 ± 5.4; 23.9 ± 2.4 SE, respectively) were more frequent than in adult exposed females (30.2 ± 3.0; 34.7 ± 3.7; 15.3 ± 1.8 SE, respectively; $p < 0.01$). Another similarity appeared among BTS effects when adult and weanling exposed rats approached 5 months of age (Fig. 3). Other BTS effects appeared to differ

development. Whether the hippocamus is indeed the brain region most susceptible to fluoride is a possibility deserving consideration in future studies.

Interruption of normal brain development often results in responses that are sex-dependent. The brain responds differently to drugs depending on which hormones are present at the time and whether the brain is male or female (30). In male primates the orbital cortex matures earlier than in females, and such developmental differences are thought responsible for the consequences of perinatal injuries appearing more frequently in males (18). This type of developmental difference might explain why transient peaks of fluoride on prenatal days 17–19 affected males and not females. The effects of chronic fluoride exposures at weanling and adult stages may have involved still other sexual dimorphisms. There are developmentally regulated sexual dimorphisms in hypothalamic somatostatin and growth-hormone-releasing factor signaling, growth hormone secretion and even hepatic metabolism (5,29,38). The sexually dimorphic control of growth would be especially important to fluoride distribution. The rate of fluoride uptake by bone depends on age or the stage of skeletal development; fluoride is deposited in mineralizing new bone more readily than in existing bone (49). As males experience greater and more prolonged growth spurts than females, their plasma fluoride might be directed more to bone than to brain, perhaps explaining why longer exposures and higher plasma fluoride levels were needed in males to affect behavior. Fluoride's tendency to seek developing bone may also explain why adult female rats had behavioral effects at a lower plasma fluoride concentration than did weanling female rats. Levels of fluoride in plasma and bone must be correlated with those in specific brain regions of both sexes to fully understand behavioral consequences.

Rats ingested 75–125 ppm fluoride for weeks to attain plasma fluoride levels of 0.059-0.640 ppm. Six weeks of consuming 75 and 100 ppm fluoride produced higher plasma fluoride levels than did 125 ppm. Perhaps a taste aversion limited water consumption at the 125 ppm level, prolonging the period needed to attain plasma levels that were achieved in 6 weeks by the two lower exposure levels. Regardless, it was fluoride levels in plasma, not fluoride levels of exposure, which best predicted effects on behavior. Similar plasma fluoride levels of 0.076–0.25 ppm have been found in humans ingesting 5–10 ppm fluoride in drinking water (19,37,42), and plasma levels as high as 0.28 to 0.43 ppm have been measured in children drinking water containing 16 ppm fluoride (44). This plasma fluoride range also occurs in certain therapies. Fasting serum fluoride levels of 0.2 to 0.3 ppm are used in the treatment of osteoporosis (31), and plasma fluoride levels as high as 1.44 ppm are found in children 1 h after receiving topical applications of an acidulated phosphate fluoride (1.23%) gel (14,15).

Because humans occasionally are exposed to high amounts of fluoride and plasma levels as high as those found in this rat study, neurotoxic risks deserve further evaluation. This is the first laboratory study to demonstrate that CNS functional output is vulnerable to fluoride, that the effects on behavior depend on the age at exposure and that fluoride accumulates in brain tissues. Experience with other developmental neurotoxicants prompts expectations that changes in behavioral function will be comparable across species, especially humans and rats (16,43). Of course behaviors per se do not extrapolate, but 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. Substances that accumulate in brain tissue potentiate concerns about neurotoxic risks, but the conditions leading to fluoride deposits in any species are still not clear such that quantitative extrapolations are not possible at this time. Thus, conclusions concerning the neurotoxic potential of fluoride require further rat and human studies, both focused on the relationship of plasma fluoride levels with the brain, behavior, and skeletal growth.

ACKNOWLEDGEMENTS

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Bottled Water, Fluoride Intake, and Risk of Decay in Young Children

October 23, 2007

Americans love their bottled water. In 2004, Americans consumed an estimated 26 billion liters of store-bought water, equaling one eight-ounce glass per American each day. Because bottled water tends to be low in fluoride and more Americans now drink less from fluoridated public sources, dentists have wondered whether some kids today might be at greater risk of tooth decay. In the Summer issue of the *Journal of Public Health Dentistry*, NIDCR grantees take a look at this issue using secondary data from the Iowa Fluoride Study, which evaluated fluoride intake dental fluorosis, and bone development in young children. The researchers determined that children who frequently drank bottled water did have significantly lower fluoride intakes than those who did not. However, they found that less than 10 percent of their cohort of 413 children frequently drank bottled water, and "no conclusive evidence of an association with increased caries" was found by age nine. The researchers encouraged further research, particularly because their study was not designed to look specifically at this issue. To read more about this article, please visit PubMed (The authors are Barbara Broffitt, MS; Steven M. Levy, DDS, MPH; John J. Warren, DDS, MS; Joseph E. Cavanaugh, PhD. The title of the article is, "An Investigation of Bottled Water Use and Caries in the Mixed Dentition.")

* Children who drank bottled water instead of fluoridated tap water had significantly lower fluoride intakes but no associated increase in dental caries (cavities).

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An investigation of bottled water use and caries in the mixed dentition.

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2007 University of Iowa College of Dentistry Research Study

Abstract

OBJECTIVES: Bottled water consumption in the United States has greatly increased in the past decade. Because the majority of commercial **bottled water** is low in fluoride, there is the potential for an increase in **dental caries**. In these secondary data analyses, associations between **bottled water** use and **dental caries** were explored.

METHODS: Subjects (n = 413) are in the Iowa Fluoride Study, which included **dental** examinations of the primary (approximately aged 5) and early erupting permanent (approximately aged 9) dentitions by trained dentist examiners. Permanent tooth **caries** and primary second molar increments were related to **bottled water** use using logistic and negative binomial regression models. All models were adjusted for age and the frequency of toothbrushing.

RESULTS: Bottled water use in this cohort was fairly limited (approximately 10 percent). While **bottled water** users had significantly lower fluoride intakes, especially fluoride from **water**, there were no significant differences found in either permanent tooth **caries** (P = 0.20 and 0.91 for prevalence and D(2+)FS, respectively) or primary second molar **caries** (P = 0.94 and 0.74 for incidence and d(2+)fs increment, respectively). Results for smooth surfaces differed somewhat from those for pit and fissure surfaces, but neither showed significant differences related to **bottled water** use. *

CONCLUSION: While **bottled water** users had significantly lower fluoride intakes, this study found no conclusive evidence of an association with increased **caries**. Further study is warranted, preferably using studies designed specifically to address this research question. *

PMID: 17899900 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances, Grant Support

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON. D.C. 20460

OFFICE OF WATER

MEMORANDUM

DATE: May 1, 1990
SUBJECT: Fluoride Conference to Review the NTP Draft Fluoride Report
FROM: Wm L. Marcus, Ph.D., Senior Science Advisor, Criteria & Standards Division, ODW (WH-550D)
TO: Alan B. Hais, Acting Director, Criteria & Standards Division, ODW (WH-550D)

The conference was held in RTP at the NIEHS headquarters on April 26, 1990. The subject of the conference was a peer review of the NTP draft report on the toxicology and carcinogenesis studies of Sodium Fluoride in F344/N Rats and B6C3F Mice (Drinking Water Studies) NTP Report Number 393. Dr. Robert Scala was to chair this meeting but was unable to attend because of ill health. Dr. Michael Gallo was appointed acting Chairperson. One of the attenders seated with the panel members was David Rall, Ph.D., M.D., Director of NIEHS. Dr. Rall took an extremely active interest in the proceedings and remained seated for the entire proceedings with only two minor interruptions.

The most disturbing part of the report was the continual reference to the historical controls as having the same or higher cancers as the test groups. On pages 89 - 90 of the report starting with the last paragraph the authors state the following:

An important consideration which limits the usefulness of the historical control data base in the current studies is that the diet used in all other NTP studies had not been closely monitored for fluoride content. Fluoride concentrations in typical batches of NHI-07 diet range between 28 and 47 ppm (.7 and 1.2 mg/kg/day)(Rao and Knapka (1), 1987). Assuming a minimum bioavailability of 60% (Tests show 66% absorption page I-18), the historical database animals actually constitute a group receiving sufficient fluoride to place them between the low- and mid-concentration group in the current (the studies reviewed at RTP at the conference). The fact that this fluoride is available for absorption from the standard diet is supported by the levels of fluoride found in the bones of animals maintained on this diet in the six months studies (Appendix I). (The levels in the bones of the rats on the standard NHI chow was ten [10] times the levels of those fed the semisynthetic diet and deionized water, 0.922 vs 0.0901). If the fluoride [is] in fact influencing the "spontaneous " or background incidence of osteosarcoma in male rats, comparisons with those in the historical database maybe misleading. This forces an even greater reliance on the within-study comparisons, ie., the incidences of the dosed groups compared with the concurrent control, in the interpretation of the results of the sodium fluoride studies.

When I plotted a bar graph of osteosarcoma in male rats and placed the historical controls on the graph 0.6% is just where expected. This helps demonstrate a relationship between osteosarcoma and fluoride. The purpose of such graphs is to predict occurrence. Since the historical controls comprise some 6,000 animals, this data point is extremely significant compared to the other three. Osteosarcoma is an extremely rare animal tumor and may be the result of the variable high fluoride content in the feed. In order to demonstrate this, all that need be done is require that the fluoride content of animal chow be lowered dramatically and that fluoride be removed from the water given to the animals under study.

The dose of fluoride to which the concurrent controls were exposed is 0.2 mg/kg/day. A 70 kg man who drinks 2 liters daily is exposed to 0.03 mg/kg/day. The "control" animals were exposed to an amount of fluoride six to seven (6-7 X) greater. Lois Gold, Ph.D. of the review panel concluded that, "this group of animals therefore, can hardly be termed a control group. It can best be described as a lowest dosed group." This is an important consideration because as the document reports on page 9, the levels of fluoride in bone are linearly dependent upon dose and length of exposure ("depends upon total intake") in people. The level of fluoride in

performed to determine the carcinogenicity of fluoride this should not have been addressed. There appear to be at least four different publications from the U.S., Canada, and New Zealand that have reported similar or lower tooth decay rates in nonfluoridated areas as compared to fluoridated areas (4,5,6,7). Therefore, the entire question of the efficacy of fluoridation based on extensive and multiple studies has been called into question. Our job is to set safe levels for fluoride in drinking water based on the scientific evidence.

The problem with this meeting was the inability of independent reviewers to get to see the slides prior to the meeting. We must perform our own scientific review of the slides and write our conclusions for use in the development of the revised fluoride regulation.

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NOTE: Due to his criticisms of the tumor downgradings, Dr. Marcus was **fired** by the EPA. The US Secretary of Labor, Robert Reich, later ruled that EPA fired Marcus out of "retaliation" for Marcus' stance on fluoride, and ordered EPA to reinstate Marcus with full back pay and compensation. To learn more about EPA's firing of Marcus, see:

- Reich Orders EPA to Reinstate Scientist - *National Whistleblower Center February 10, 1994*
- Scientist Who Spoke Out on Fluoride Ordered Reinstated to Job - *The Associated Press February 11, 1994*
- EPA Ordered to Reinstate Whistleblower - *The Associated Press December 18, 1992*

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LOW-LEVEL FLUORIDATION AND LOW-LEVEL RADIATION
TWO CASE HISTORIES OF MISCONDUCT IN SCIENCE

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Abstract

Poor, malnourished children, especially infants, are the most sensitive barometer of fluoride toxicity. Low- level fluoridation (fluoridation of drinking water) and low-level radiation are similar in many respects. Paradoxical effects of fluoride must be considered in determining harmful effects of both low-level fluoridation and low-level radiation. It is not surprising that low-level fluoridation is associated with paradoxical effects. It would be surprising if it were not. The occurrence of paradoxical effects with low- level fluoridation and low-level radiation shows that there is no threshold level below which fluoride and radiation are harmless. My article in Appendix C shows that fluoridation does not prevent dental caries. Iodination of drinking water was discontinued in the 1920s becaue it was harmful and did not prevent goiter. Fluoridation of drinking water should be discontinued now because it is harmful and does not prevent dental caries.

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Dedication

This report is dedicated to Salvador Allende, M.D., for the same reasons1 that my first report, *Increasing Death Rates in Chile Associated with Artificial Fluoridation of Drinking Water, with Implications for Other Countries*, was dedicated to him. Dr. Allende was elected President of Chile on September 4, 1970, and was assassinated by a military junta on September 11, 1973. As a result of health measures he instituted, the birthweight of babies increased for the first time in 50 years. Dr. Allende, as a doctor and as President, was concerned about the poor people of Chile. These are the people in all countries who, because they are malnourished, are most susceptible to the harmful effects of fluoridation.

My research on the harmful effects of fluoridation in Chile was the first study specifically concerned with poor, malnourished people. I chose Chile for my research because (a) the majority of the population of Chile is poor and malnourished, and (b) pro-fluoridationists have never adequately studied the effect of fluoridation on poor, malnourished people as a specific group of the total population.

In the United States and other developed countries, poor and malnourished people are a minority that is statistically drowned out in the total population which is researched for harmful effects of fluoridation. The increased death rates associated with fluoridation in Chile tell us that fluoridation is also killing poor, malnourished people in all countries that have fluoridation.

Prologue

Opponents of fluoridation have for decades pointed out numerous errors, omissions, and inaccuracies in what proponents of

fluoridation have published. This present report continues that criticism. However, it is qualitatively different because (a) it reports the widespread occurrence of paradoxical effects and emphasizes the importance of paradoxical effects in evaluating the safety of fluoridation, (b) it points out similarities between fluoridation, which I call low-level fluoridation, and low-level radiation, and (c) it highlights the well-earned position of fluoridation as a well-documented case history in the well-recognized category of scientific misconduct.

Fluoride is now recognized as a legally sanctioned environmental pollutant2 that is part of an increasing number of chemicals which are threatening our survival as a species. Fortunately, however, "more and more scientists insist that they are in a better position to understand the significance and implications" of science "for society than are the official decision-makers who may be paying their salaries or subsidizing their work. The point is that the real division is no longer between science and the humanities - the two cultures described by scientist-philosopher C. P. Snow - but between those who attach primary importance to human life and those who view their own discipline as sovereign."3

We ... see ... the difficulty that may arise in the attempt to persuade others to accept a new ... way of reasoning. We cannot convince others of it by formal argument for, so long as we argue within their framework, we can never induce them to abandon it. Demonstration must be supplemented, therefore, by forms of persuasion which can induce a conversion. The refusal to enter the opponent's way of arguing must be justified by making it appear altogether unreasonable.— Michael Polanyi, physical chemist

Mitchell, Thompson and Borman's research shows that fluoridation is harmful

Mitchell *et al*'s report *No Association between Fluoridation of Water Supplies and Sudden Infant Death Syndrome*,4 unjustifiably exonerated fluoride as a cause of sudden infant death syndrome (SIDS). The authors interpreted their data correctly, but then, by a verbal legerdemain shell game, drew the erroneous conclusion which their title reflects. The very fact that the straight line in their Figure 1 is not horizontal suggests an association between fluoride and SIDS.

What Mitchell et al's data clearly indicate is an inverse relationship between fluoride concentration in the drinking water and SIDS. Their interpretation of their results also clearly recognize this inverse relationship. "If anything" they wrote, "the higher the SIDS mortality rate the lower the fluoride concentration." However, in their very next sentence, they contradicted that interpretation by concluding that their "study clearly shows ... no indication of a relationship between fluoridation ... and SIDS".

According to Mitchell *et al*, "Analysis was carried out to find the correlation between variables and then simple linear regression was used".4 Their arbitrary selection of linear regression provided a straight line which is very different from the curve of a paradoxical effect (which I shall define and discuss). The typical paradoxical effect curve that I have inserted in their Figure 1, reproduced below, shows the increase in deaths as the fluoride concentration decreases in the very low concentration range. Dr. Albert W. Burgstahler, in the University of Kansas Department of Chemistry, kindly provided the paradoxical effect curve. This was derived by a computer-generated least squares best line fit.

Mitchell *et al* apparently did not know that the inverse relationship, which they acknowledged, suggests a paradoxical effect.5,6 This phenomenon is paradoxical because there is a critical dose below which one observes an increased adverse effect. This paradoxical effect is precisely what Mitchell *et al 's* data clearly reveal. Within that low concentration range, the infant death rate increased as the concentration of fluoride decreased. Consequently, there is a relationship between fluoride concentration and infant deaths, but it is an inverse relationship.

At concentrations above the low concentration range, dose-responses show the direct, linear relationship with which we are familiar. Increasing doses are increasingly toxic until a particular dose kills most or all the test subjects. This is what one expects and observes. Consequently, there are two different dose- responses to fluoride — a paradoxical effect at very low levels and a linear relationship at higher levels. These two dose-responses are not mutually exclusive; one does not preclude the other.

The paradoxical effect curve explains what the data of Mitchell *et al* clearly reveal and what they clearly acknowledge; namely that there are more deaths at the low doses of fluoride than at the higher doses. The straight line which they derived from their linear regression analysis does not explain the increased deaths at the lower doses. Mitchell *et al* and all other researchers who are interested in knowing whether fluoridation produces harmful effects should familiarize themselves with paradoxical effects5,6 and understand that they "cannot exclude" an "explanation" they "have not considered".7

Paradoxical effects show that fluoridation is not safe at any level

There many reasons why fluoridation has been highly controversial since its conception half a century ago. We can now add another reason — ignorance of paradoxical effects. If Mitchell *et al* had been familiar with paradoxical effects, Occam's razor would have directed them to a paradoxical effect. The cluster of infant deaths at very low fluoride levels suggests that the relationship between fluoride concentration and SIDS is paradoxical, not linear.

Most research which purports to demonstrate the safety of fluoridation has not been concerned with very low concentrations of fluoride, at which paradoxical effects occur, for three reasons. (1) Individuals vary significantly in fluoride uptake. (2) There is considerable individual variation. (3) It has been unjustifiably assumed that there is a threshold level; namely, the sacrosanct one

part per million in drinking water, below which fluoridation is safe. The occurrence of paradoxical effects at very low levels of fluoride means that there is no threshold level below which low-level fluoridation is safe. There is also no threshold level below which low-level radiation is safe. We call fluoridation low-level fluoridation because that term associates it with the well-known low-level radiation. Both are harmful and similar in other ways.

The paradoxical effect in the report by Mitchell *et al* is similar to what has been observed in a variety of fluoride systems where paradoxical effects occur.5 Paradoxical effects may be involved in SIDS in some fluoridated cities in Australia."8 The data in the Australian report, which claimed that there was no linear relationship between fluoridation and SIDS, should be reexamined to see if there are inverse (paradoxical) relationships.

Paradoxical effects occur in complex systems where they are influenced by conditions that vary from time to time within the same system.6 For these reasons, paradoxical effects may not always appear in a very low concentration range. But a linear dose-response always appears at higher concentrations which, in the case of fluoride, begin at the arbitrarily defined safe level of one part per million. Therefore, the relationship between fluoride concentration and SIDS may be linear and/or paradoxical, depending on the concentration range of fluoride and other variables. This variability and, at times, even irreproducibility of results are characteristic of paradoxical effects.6

Statistics can conceal paradoxical effects

Because Mitchell *et al* used linear regression, the only conclusion they could draw from their straight line is that there is no linear relationship between fluoride concentration and SIDS. But they unjustifiably concluded that there is no relationship with fluoride at all. The fact that their statistics reveal no significant linear correlation does not mean that there is no other significant correlation. Their linear regression analysis may be mathematically correct, but it is inappropriate to ascertain whether there is another kind of relationship; namely, a paradoxical effect. Like the Sufi Mulla Nasrudin, they looked for the key in the wrong place.

There is "a famous Sufi story" about "Mulla Nasrudin, an enlightened fabled teacher. While on his hands and knees, peering on the street for a lost key, he was approached by a friend. 'You lost your key here, Mulla?' his friend inquired. 'No,' said Nasrudin, 'I lost it in my house.' 'Then why are you looking here?' asked his friend. 'Because,' said Nasrudin, 'the light is better here.'" — Larry Dossey

It is paradoxical that statistics, employed to assure the validity of conclusions drawn from data, can be responsible for concealing paradoxical effects." 6 "The fact that statistical analysis of experimental data does not reveal paradoxical effects does not mean that such phenomena do not exist. On the contrary, statistical methods of analysis can effectively prevent recognition of paradoxical effects if the methods do not consider these phenomena. With scattered points, statistical methods are too frequently used to determine where a straight line should be drawn. To often, the statistical approach assumes that straight lines are the correct lines. Deviations or irregularities caused by paradoxical effects have too often been attributed to experimental variation or errors.6 More information about paradoxical effects and risk assessment is in Appendix B.

The pig mentality

"If artificial fluoridation causes deaths among individuals who are for one reason or another more sensitive to fluoride toxicity than in the total population taken as a whole, then the controversy over whether fluoridation does or does not reduce caries becomes purely academic because it is criminal to implement a so-called public health measure which kills certain people even if it does reduce tooth decay in some of the survivors."1

We have been told that fluoridation is economical because it lowers the cost of dental care. But, even if that were true, "let us get our priorities right. If it is economic to poison people, then there must be something wrong with economics." 9

With respect to economics, let us look at fluoride and what I call the *pig mentality*. In 1952, seven years after fluoridation was started, some U.S. government agencies were concerned about possible harmful effects of fluoride. But they were more concerned with safeguarding pregnant pigs than pregnant women and their unborn children. Their reason for giving priority to the welfare of pregnant pigs was that pregnant pigs were economically more important than pregnant women.

The following testimony, which reports this shocking revelation, is taken from a U.S. Congressional investigation held in 1952.10

Dr. Miller: The United States Department of Agriculture made some examination as to what happened in brood sows. They recommended to the farmers that fluoride not be added to the water or feed of brood sows because it did something to pigs that were unborn.

Dr. Porterfield: Yes.

Dr. Miller: Do you think it might be wise for the Public Health Service or some group of people to inquire what might happen to pregnant women and the unborn child when they are given fluoride? Do you think it is necessary to complete the examinations that have already been started on that subject?

Dr. Porterfield: I do not think there is enough money, sir, from the Federal Government or any other source, to pursue all of the possible hypotheses that may be proposed for most of our programs. We have to screen them from the point of view of greatest probability, and since we can find no cause from the physicians or the dentists or the investigating scientist pointing to this, it would seem to us not of a high priority to devote money for something that has shown no suggestive indications.

Dr. Miller: Would you say that the agricultural Department went off on a tangent then when they investigated what might happen to pigs or brood sows?

Dr. Porterfield: No, sir, I think there is a difference.

Dr. Miller: It is alright to do it with pigs, but you do not want to do it with women. Is that the attitude you take?

Dr. Porterfield: They have different objectives in mind, sir. There is more money available for matters that have economic value than there is for health.

Have the fluoridationists, like Dr. Faustus, no understanding of "the morality of knowledge" (Erich Heller) and no "insight into ultimate meanings"? (Victor Lange) Did they, like Faustus, "outwit the Devil by creating a Hell of" their "own"? (Victor Lange11) No wonder fluoridation calls to mind Albert Einstein's lament: "Strange that science, which in the old days seemed harmless, should have evolved into a nightmare that causes everyone to tremble." And Linus Pauling's comment: "Most problems in the modern world are the result of the contributions of science."

More criticism of Mitchell, Thompson and Borman's research

There are additional reasons why the research of Mitchell *et al* has "been weighed and found wanting". The variables they considered were SIDS, mean daily temperature and median fluoridation. The validity of their research is questionable because they did not consider other important variables. Walker pointed out that Mitchell *et al* did not consider a significant intake of fluoride from sources other than fluoridated water.8 The National Health Council and the Medical Research Council of Australia reported that babies were being overdosed with fluoride from many sources, especially formula foods prepared with fluoridated water.8 It would be surprising if that overdosing did not also occur in New Zealand where Mitchell *et al* did their research. Mitchell *et al* provided no information at all about "background fluoride"; that is, fluoride from other sources; e.g., air, food, tea (dry tea leaves are high in fluoride) and baby formulas prepared with fluoridated water. The terms background fluoridation and background radiation apply to fluoride and radiation from sources that are not always taken into consideration.

Mitchell *et al* (like Nelson and Taylor whom they cite) found a correlation between mean daily temperature and SIDS. People generally drink more liquids in warmer weather. One would therefore like to know, for example, whether the dead infants had been nursed and how much water and tea their mothers consumed. Tea is notoriously high in fluoride. But Mitchell *et al* did not estimate each infant's total daily fluoride intake. The correlation of infant deaths with mean daily temperature suggests that more infants may die in hotter weather when mothers and infants consume more tea and other fluids and therefore more fluoride. Finally, Mitchell *et al* and all proponents of fluoridation apparently also do not understand why it is inappropriate to apply the results of random testing to an individual.12

Another variable overlooked by Mitchell *et al* is nutrition, especially calcium intake. The consumption of milk, which is the major source of calcium for infants, is especially important. Our research on fluoridation in Chile (like many other studies) points out that malnourished infants comprise the human population that is most susceptible to fluoride toxicity. It is also well known that calcium protects against fluoride. When Salvador Allende, M.D. became president of Chile in 1970, he initiated a government program under which "pints of ... free ... milk were delivered ... daily ... to pregnant mothers, nursing mothers and every child under the age of 15." 1 At that time, "half the children in Chile under 15 years were undernourished, and 600,000 were mentally retarded thorough lack of protein, especially during the first months of life." 1 This was the health status of half the children who were being fluoridated in Chile.

I am not implying that malnutrition and/or calcium deficiency were significant factors in SIDS researched by Mitchell *et al*. No one knows because Mitchell *et al* did not provide that and other information. To properly evaluate the role of fluoride in SIDS, it is necessary to consider nutrition, especially calcium intake, and total fluoride intake.

Promoters of fluoridation are in Plato's cave

"Plato's famous parable of the cave describes a group of people who are chained inside a cave in such a way that they can see only the shadows on the wall of the cave. These shadows are the only world that these people know. One day one of them escapes into the world outside the cave. At first he is blinded by the sunlight, but when he recovers, he realizes that this is the real world, and what he previously considered to be the real world was, in fact, only the projection of the real world onto the wall of the cave. Unfortunately, when he returned to the people who were still chained inside the cave, they thought he was mad." — G. Zukav

Those who are for and against fluoridation have little in common other than the issues they disagree on. They cannot dialogue objectively because they have different realities. They see things differently, and have different criteria for determining validity. Our lives are enriched by artists for whom "beauty is in the eyes of the beholder." But our lives are often endangered when scientific

truth is in the eyes of the beholder.

"There's something rotten in Denmark"

Mitchell, Thompson and Borman's publication4 is a classic, textbook case history of the pathology of (i.e., what is wrong with) epidemiological surveys which have concluded that fluoridation is safe. Such studies, are invalid for the following reasons.

1. Researchers assumed that there is only one dose-response to fluoride and that dose-response is linear. They do not know that there are two distinctly different dose-responses which occur within two different concentration ranges of fluoride. The dose-response which they completely overlooked is the paradoxical, non-linear dose-response. This occurs only with low-level fluoridation, just as it also occurs only with low- level radiation,13,14 where it is described as supra-linear, quadratic and non-linear. (I shall shortly discuss low-level radiation and what it has in common with low-level fluoridation.) The reasons why paradoxical effects occur at low levels of fluoride and other chemicals,5 and why supra-linear dose-responses occur at low levels of radiation are beyond the scope of this report, but have been explained elsewhere.5,6,13,14,15

2. Researchers did not selectively study minority populations, such as infants, that are most susceptible to fluoride toxicity. But it is not enough to study infants. One must select infants who are malnourished and whose mothers received little or no prenatal care. Otherwise, as I discussed in detail in my report on deaths association with fluoridation in Chile, "the relatively well-nourished majority overwhelms ... the undernourished minority which is most susceptible to fluoride toxicity." 1

The importance of selecting a minority population of infants that are malnourished and disadvantaged in other ways is clearly revealed by the shockingly high variation of infant deaths in different sections of Philadelphia. This variation is directly related to poor nutrition, inadequate prenatal care and other factors.16 No one knows how many poor, malnourished children in Philadelphia, which is fluoridated, are being killed or otherwise harmed by fluoridation?

Spittle recognized the importance of working with a malnourished minority,17 which I had pointed out in my Chile report. Both Brown18 and the same Mitchell,19 who criticized my Chile report, did not recognize (1) the above-mentioned inadequacies in the report of Mitchell *et al*, and (2) the importance of focusing research a malnourished minority.

The 1994 report by the New Zealand Public Health Commission,20 which endorsed fluoridation, accepted without question the erroneous conclusion of the report by Mitchell *et al*,4 and Brown18 and Mitchell's19 unjustified criticism of my report on fluoridation in Chile. The New Zealand report referred to my article in its text, but did not cite it in its bibliography. The results of Mitchell *et al* which, despite their inadequacies, show that fluoridation is harmful as very low levels, are all the more significant because the infants they researched were not specifically selected as a malnourished population. Despite that limitation, their results support my report of increased deaths associated with fluoridation in Chile.

This New Zealand Public Health Commission report has as little scientific validity as a British report on the effectiveness of fluoridation drafted by a special Committee on Research into Fluoridation. This is Report No. 122 published by the British Department of Public Health and Social Security in London. I challenge Brown18 and Mitchell,19 who criticized my report on fluoridation in Chile, to publish a criticism of my analysis21 (See Appendix C) of that British report. This British report has to be seen to be believed. This and many other reports that support fluoridation reveal incompetence, bias, and arrogance, and are examples of pseudoscience. One does not know whether to accuse the authors of misconduct in science or conclude that they just don't know any better.

Those who do research in Plato's cave do not realize that: (1) All they see are only shadows on the wall. (2) They "can fool some of the people all of the time, and all of the people some of the time, but" they "cannot fool all of the people all of the time." (3) "No man was ever so much deceived by another as by himself. (Greville) and (4) "The learned fool writes his nonsense in better language than the unlearned, but still 'tis nonsense." (Benjamin Franklin)

Low-level fluoridation and low-level radiation are both harmful

"New scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a generation grows up that is familiar with it." Max Planck, the father of quantum physics

The history of progress is the history of controversy. The antifluoridation movement has made both history and progress. The report you are now reading contributes to both. Its objective is to provide new information about the nature of the sand upon which the house of fluoridation has been built. It points out the importance of paradoxical effects which have not received adequate attention with respect to fluoridation. These effects occur at low levels of fluoride and radiation. We call fluoridation low-level fluoridation because that term associates it with the well-known low-level radiation. Both are harmful and similar in other ways.

For low-level radiation, we now know that "linearity underestimates the true cancer risk per rad when one derives values from studies based on higher doses of radiation than the" low "doses at which we wish to apply those values." 13 We now know that linearity also underestimates the risk of low-level fluoridation. This is why we criticize those who have disregarded paradoxical effects associated with low-level fluoridation.

Low-level fluoridation, like low-level radiation, may produce adverse effects that appear after prolonged periods of time. For this reason, a cause and effect relationship is not always clear. The adverse effects of large doses of fluoride and radiation, with which this report is not concerned, occur sooner after exposure and are therefore clearly associated with the cause.

Low-level fluoridation and low-level radiation have both been controversial for decades. Both have used human beings as guinea pigs. They have killed and continue to kill untold numbers of people. There is no threshold level below which fluoride and radiation are harmless. Background radiation, such as radon gas, is harmful; and background fluoride (from sources other than drinking water; i.e., air, food and tea) is harmful. Topical application of fluoride and topical application of radiation (e.g., for skin cancer) are harmful. The dose-response to both low-level fluoridation and low-level radiation is not linear but paradoxical.

Low-level fluoridation, like low-level radiation, is a major pollutant which environmentalists should recognize as such. Like other pollutants, the harmful effects of both low-level fluoridation and low-level radiation have a history of denial which is associated with scientific, professional and academic misconduct. Tolerance levels for low-level fluoridation and low-level radiation are not based on scientific findings. Instead they are determined by special interest groups which have enough money to buy enough political clout to influence government and other high-level agencies.2 "The wages of sin are death." But those who die from low-level fluoridation and low-level radiation are not the sinners, but their victims.

Supra-linear (paradoxical) effects of low-level radiation

Paradoxical effects may not make sense to those who are unfamiliar with these peculiar dose-responses. Nevertheless, these phenomena, disquieting as they may be, are irrefutable. A wide variety of paradoxical effects has been reported with fluoride5 and many other chemical substances.6 In radiation, the paradoxical effect is known as a non-linear, quadratic and supra-linear dose-response.13,14 It is also called the Petkau effect.15 All these peculiar phenomena, associated with both chemicals and radiation, are characterized by a low concentration range within which the adverse effect increases as the dose decreases.

Gould and Goldman, in their book *Deadly Deceit. Low-Level Radiation, High-Level Cover-Up*,15 report the results of Charles Walden *et al* who observed a supra-linear effect of ionizing radiation on human chromosomes. "Their findings contradict the conventional scientific dogma that the dose- response is linear, and that a straight line can be used to estimate low-dose effects from studies of high doses." Gould and Goldman also discuss the "Petkau effect." In 1971, Abram Petkau, a physician and biochemist, observed an unusual and entirely unexpected effect of radiation. He found that low levels of radiation produced more damage to fresh beef brain cellular membranes than higher doses did.

Gofman pointed out, in his book *Radiation and Human Health*,13 that "Enthusiasts of nuclear power and of medical irradiation are forever hoping, quite understandably, that there will be found some threshold — a dose of radiation below which no harm would occur." But "It turns out that nuclear-power and medical-irradiation enthusiasts have all been going in exactly the wrong direction, They have consistently suggested that linearity may overestimate the true cancer risk per rad. The real problem is that linearity underestimates the true cancer risk per rad when one derives values from studies based on higher doses of radiation than the doses at which we wish to apply those values."

According to Gofman and O'Connor (in their book *X-Rays: Health Effects of Common Exams*), "It is natural for everyone, ourselves included, to wish that radiation would be less harmful per rad at low dose-ranges than at high dose-ranges... Those who cling to this wish, in spite of all the evidence, claim that the linear 'hypothesis' exaggerates the risk of getting cancer from irradiation at low doses. But wishful thinking is gradually yielding to evidence." 14

The books by Gofman13 and Gofman and O'Connor14 are replete with reports which prove that low doses of radiation are in many cases more harmful than higher doses. These data fit what is called a supra-linear dose response curve, which is significantly different from a linear curve. Gofman and O'Connor14 conclude that the "linear model may actually underestimate the risk of getting cancer and leukemia. There is, unfortunately, evidence which is accumulating and growing ever stronger that the cancer risk per rad of dose is worse in the low-dose range than in the high dose... Moreover, during the nearly four years of extraordinary scrutiny and widespread peer review of the book13 in professional journals, scientific symposia and in trials concerning radiation injury, no one has made a single scientifically valid refutation of any of its data, methods, or conclusions. Probably no work in this field has received more review by peers." 14

Who is John W. Gofman?

Because it is so difficult for some to accept the unusual supra-linear effects, let us familiarize ourselves with the credentials of the individual who has done decades of research on these phenomena. John W. Gofman is a physician with a doctorate in nuclear/physical chemistry, who is recognized as one of the world's leading medical experts on low-level radiation. He has been Professor of Medical Physics at the University of California in Berkeley, and a member of the Clinical Faculty at the University of California School of Medicine in San Francisco.

As a graduate student at Berkeley, he was one of those who discovered uranium-233, and demonstrated that it was fissionable. In 1941-1943, he developed a method for isolating plutonium and provided the plutonium first used at the Manhattan Project. From 1962-1969, he was Associate Director of the Lawrence Livermore Laboratory, and set up the Laboratory's Biomedical Division. From 1963-1972, he directed research in that Division. This research, requested by the Atomic Energy Commission, evaluated

ionizing radiation and chromosome injury as causes of human cancer. Gofman has received many awards and honors, including a citation from the American College of Cardiology. He has written six books.

Fluoridation is iatrogenic and pathological science

Fluoridation is iatrogenic science because it creates more serious problems than the problem it was originally designed to resolve, but did not. Fluoridation also conforms to what Irving Langmuir, the 1932 Nobel laureate in chemistry, called the dynamics of "pathological science — the science of things that aren't so. The basic progression is that sloppy work by sloppy scientists gets picked up by even worse scientists, who do worse and worse work... But the kicker is that this kind of bad science may not completely die for a very long time, but just take on more and more peculiar forms." 22

One of these forms was pointed out by Sutton in his cogent article *Are Most Fluoridation Promoters Neurotics?*23 Sutton quoted Kurt Thoma, Professor of Oral Pathology at Harvard University: "The neurotic depends on opinions other than his own and is swayed by remarks of others without analyzing the facts. He feels that his opinions must be enforced, and even if proven in error he will not 'give in' because this hurts his ego ideal."

This is why the pathology of fluoridation is so easily diagnosed. Its distinctive syndrome consists of hype, brouhaha, hullabaloo, echolalia, pleonasm, tautology, propaganda, weasel words, propaganda, recycled nonsense, double speak,24 the invention of reality, 25 denial, the graying of reality and the manufacture of consent,26 Fluoridation is part of "the new age mythology"27 in which, as Werner Erhard proclaimed, "Reality is make-believe." Wishful thinking is presented as scientifically established fact to achieve self-serving ends. An egregious example of the pathology of fluoridation is Report No 122, compiled by a special Committee on Research into Fluoridation and published by the British Department of Public Health and Social Security in London. See Appendix C for my analysis21 of this British report, which erroneiously concludes that fluoridation is effective in preventing tooth decay.

The denial syndrome

Unfortunately, those who question fluoridation are ignored as if they did not exist, or are attacked and derogated by foxes who are guarding the fluoridation chicken coop. A recent example of this is the hit- and-run attempt to discredit John Yiamouyiannis. This is discussed in the section "Truth will come to light. Murder cannot be hid."

A clinical psychologist whom I consulted about fluoridation referred me to the psychiatric definition of *denial* which includes "refusal to admit ... reality... Known also as negation, denial is a primitive defense ... consisting of an attempt to disavow the existence of unpleasant reality.28

Denial is not isolated and sporadic, but may be pandemic in science, medicine, academia, and elsewhere. It occurs in the controversial fluoridation of drinking water which, contrary to what authorities claim, does not prevent dental caries and is not safe.1,23 In quantum physics, physicists have for decades refused to acknowledge an inconsistency in Einstein's special theory of relativity.29 They also have been slow to recognize Bohm's alternative.30 Quantum theory is itself paradoxical because it "demands conflicting or mutually incompatible descriptions — an example of this is the description of an electron as both a wave and a particle." A well-known scientist wrote an unfavorable review of one of Velikovsky's books without (she admitted) having read it. Other well-known scientists who edited prestigious scientific journals rejected papers, which Velikovsky submitted for publication, without (they admitted) having read them.31

Hendershot, editor of the *Journal of the American Dental Association,* provided another example of denial. I wrote Hendershot to ask if he would be interested in seeing my report on harmful effects of fluoridation in Chile.1 When he did not reply, I sent him copies of my report on three separate occasions, one month after another. He rejected my report three times without ever having even seen it. To publicize his censorship, my report, which then appeared in the *Journal of Arts, Science and Humanities*, included a photograph of three envelopes, each of which contained a copy of my manuscript and was addressed to Hendershot. These letters were certified so that the recipient had to sign a receipt of delivery. All three envelopes were stamped **REFUSED - RETURN TO SENDER.**

Misconduct in science

Misconduct and denial are two sides of the same coin because denial is a form of misconduct and misconduct often involves denial. Fluoridation is an example par excellence of denial and misconduct in science but it is in good company, whatever that means. The 1992 report on *Responsible Science. Ensuring the Integrity of the Research Project*, Volume I (by the National Academy of Sciences, the National Academy of Engineering and the Institute of Medicine)32 received a "cool response" and "can be credited with adding silt to muddy waters".33

Some areas of higher education are also hotbeds of misconduct by academic robber barons in administration, research, and teaching.34,35,36 The May/June, 1994, Special Issue of *The Journal of Higher Education* was devoted to "Perspectives on Research Misconduct".35 In some colleges and universities, plagiarism, falsification of data, and other kinds of individual and institutional misconduct appear to be pandemic.30 Much of this pollution of the ethical environment of research and graduate education is covered up by structured silence.36 Structured silence denies misconduct by ignoring it. Unanswered questions are ignored, as if they did not exist. Denial preserves the illusion that all is well, and perpetuates false public images of academia and science. Brown18 and Mitchell19 used structured silence when they selectively criticized my data but not Briner and Carmona's data,

included in my report.1

The most recent and most comprehensive report36 of misconduct in colleges, universities and science was rejected for publication by Koshland, the editor of *Science*. This is a prestigious journal published by the American Association for the Advancement of Science. Koshland had previously claimed that 99.9999% of scientific reports are accurate and truthful, without having any justification for using that figure! He then did not publish a report36 which proved him wrong.

Thirty years earlier, Abelson, editor of the same journal, *Science*, did not publish one of Velikovsky's papers, without having read it.31 In 1992, the same Abelson was a member of the panel which produced the *National Academy of Sciences report on Responsible Science, Ensuring the Integrity of the Research Process*.32

Several years before Abelson rejected Velikovsky's paper, without having read it, there was a high-level effort to censor scientific publications which presented new ideas that were at variance with what so-called authorities defined as truth. The American Association for the Advancement of Science seriously considered, but fortunately did not approve, a resolution "that henceforth any publication that presents new scientific hypotheses should not be allowed to be printed without the imprimatur of a proper professional body." 31 If this resolution had been accepted and implemented, it would avoid the problem of having to deny something because that something would never have appeared in print. There would thus be nothing to deny and therefore no controversy.

Those who are opposed to fluoridation usually find it impossible to publish in so-called reputable dental and medical journals. So they publish in whatever ways they can. Pro-fluoridationists then criticize them and derogate their research because they did not publish in reputable journals. That is precisely what Brown18 and Mitchell19 did to me and my report on fluoridation in Chile. They not only criticized my research, but also derogated the journal in which it appeared and the university which published that journal.

"Those who ignore history are destined to repeat it"

People have been and are still being harmed by fluoride because those who are responsible for fluoridation have, among other things, ignored history. They have ignored what happened when the drinking water of several cities was iodinated in the 1920s. Iodination of Rochester, NY, water began on April 24, 1925.37 It was discontinued officially because it "did not seem practical owing to the great waste." 38 However, complaints of adverse results engendered widespread opposition. "Iodination was practiced for a short time in Sault Ste. Marie, MI, and Virginia, MN, but was speedily abandoned because of numerous objections from residents." In Duluth, MN, "objections ... prevented the inauguration of" iodination of the drinking water.37 "Iodination of the Anaconda, Montana, water supply began in April, 1925, and was continued in October, 1925, April, 1926, and October, 1926. Children in the Anaconda schools [were] also receiving 10 milligrams of chocolate-iodine tablets once a week for 30 weeks during the school year."37

"Some physicians [were] apprehensive lest the 'promiscuous distribution of iodine,' as they put it, to those not in need of the element, cause a marked increase in hyperthyroidism."37 This was actually observed in Derbyshire, England, where it was reported that "An increase in the prevalence of goiter among children following the use of iodine [including 'iodized water'] is most unusual."37 This increase in the prevalence of goiter in Derbyshire may well be due to a paradoxical effect of iodine. Iodine is a close relative of fluorine and both are in the same chemical family know as halogens. Data suggestive of a paradoxical effect of fluorides and iodides on the clotting of milk by pepsin were published in 1928.39 "Thyroid disorders associated with iodine deficiency and excess" also suggests that iodine produces paradoxical results.40

The results of iodination of drinking water in the above-mentioned cities led Robert Olesen, Surgeon in the United States Public Health Service, to conclude in 1927 that "So far, there is considerable doubt as to the ability of iodinized water to reduce the incidence of endemic goiter." And, "The iodination of public water supplies, in its present state of development, can not be recommended for widespread use."37 Olesen's report was published in *Public Health Reports* issued weekly by the United States Public Health Service.37 One year before Olesen's report appeared, Hartsock pointed out, in the *Journal of the American Medical Association*, that "The continuous use of iodine over a long period of time should never be prescribed for adults, and when its periodic use is prescribed, frequent observations of the pulse and weight should be made."38 In 1931, Weston concluded, in the *American Journal of Public Health and the Nation's Health*, that "The addition of iodine in drinking water [to prevet goiter] has also proved disappointing."41

I should not have implied, without qualification, that proponents of fluoridation have ignored history. What they have learned from history is that they should not permit opponents of fluoridation to publish in professional medical and dental journals. As I already pointed out, that is precisely what Hendershot, editor of the *Journal of the American Dental Association*, did to me.

The fluoridators have also ignored the history of what Schubert and Lapp called "radioactive poisons" that were used therapeutically for over half a century with disastrous results." 42 Following the therapeutic use of radon drinking water in 1903 and 1904, first radium salts and then Thorotrast (a commercial product which contained a radioactive isotope and became popular in 1929) continued to be used well into the 1960s. In 1913, the *Journal of the American Medical Association* reported that "the value of [radon] is unquestionably established." Over 80% of 1038 patients with a variety of ailments, recalcitrant to other treatments, "were considered ... by 20 foreign doctors ... to have been improved by the use of radium emanation." Radium was also injected into

mental patients to treat psychoses and other mental problems.

In 1916, an article in the journal *Radium* declared that "Radium had absolutely no toxic effects, it being accepted as harmoniously by the human system as is sunlight by the plant." Radium therapy was listed in the New and Non-official Remedies of the American Medical Association until 1932.42 In 1936, Percy Brown, M.D., who died from overexposure to X-rays, published his book *American Martyrs to Science through the Roentgen Rays*.43 This book presented the biographies of professionals who died from the effects of X-rays.

In the 1950s, articles in medical journals recommended Thorotrast treatment for children. In 1953, a Denver company was marketing a contraceptive jelly containing radium.42 In the 1940s, 1950s and 1960s, hundreds if not thousands of military personnel and civilians were given radium treatments to prevent and cure colds, hearing loss and other ear ailments, and adenoid problems. The victims attributed head and neck cancers, miscarriages, and thyroid and other problems to the radium treatment.44

Fluoridation déja vu

For half a century, promoters of low-level fluoridation and low-level radiation have denied repeated and continuous warnings about the dangers they both pose.

In 1957, Schubert and Lapp pointed out that "One of the strangest aspects of the attitude toward radiation poisoning is that as late as 1924 — nearly twenty-five years after the discovery of radium — no one seemed to understand that when radioactive substances were taken into the body they emitted radiations just as damaging as those produced by an X-ray machine. This seems incomprehensible in view of the fact that it was well known by then that all kinds of radiation — whether X-rays, alpha rays, beta rays, or gamma rays — damage tissues." 42

Actually, many people not only understood but warned about the dangers of radiation. Schubert and Lapp themselves comment on numerous reports of injury and death, caused by radiation, which continuously appeared in newspapers and in medical and scientific journals. But the so-called experts ignored these reports while people died, in some cases agonizing deaths.

In the case of fluoridation, the so-called experts also have also ignored repeated warnings about the toxicity of fluoridation while people have been harmed and in some cases killed. For information about the political, economic and social syndrome of low-level fluoridation pathology, read Joel Griffiths' *Fluoride: Commie Plot or Capitalist Ploy*.2

Sartor Resartus

I shall now respond to criticism of my report on fluoridation in Chile1 by Brown18 and Mitchell.19

I did not select the three communities in Chile which I researched. They were the ones selected by the National Health Service of Chile. The demographic data I used are taken from official government reports. In my report, I also analyzed Briner and Carmona's data and took issue with their conclusions. Briner and Carmona were high-ranking officials in the National Health Service of Chile. Brown and Mitchell criticized my conclusion that fluoridation is harmful because the three communities are not comparable in certain respects. But they did not criticize Briner and Carmona's conclusion (based on data from the same communities) that fluoridation is safe. Brown and Mitchell's selective criticism is a form of structured silence, as I have already pointed out.

Brown and Mitchell also ignored Briner and Carmona's erroneous claim that fluoridation had no effect on the death rates of individuals with congenital malformations. In fact, Briner and Carmona's data revealed that fluoridated Curico had 244% more such deaths than non-fluoridated San Fernando, and 288% more such deaths than the entire country of Chile taken as a whole.

Finally, neither Brown nor Mitchell commented on any of the other serious errors and inadequacies in Briner and Carmona's publication, about which my report presented detailed information. Their silence about the deficiencies in Briner and Carmona's work raises questions about their objectivity.

Briner and Carmona were the two highest ranking officials in the National Health Service of Chile, Section of Odontology, when they presented their report in 1965 at the Fifth International Odontological Congress of Chile. The Commission of Dental Health of that Congress endorsed the safety of fluoridation in Chile on the basis of their report.

The *Journal of Arts, Science and Humanities* and Anthony University exist

Brown18 and Mitchell19 attempted to cast doubt about the validity of my Chile report by pointing out that it was published in an obscure journal. They thus obscured the real issue which is why responsible scientists and other professional researchers have been blackballed and denied the opportunity to publish their criticism of fluoridation in professional dental and medical journals in the United States.

Despite the fact that my report on fluoridation in Chile was published in an obscure journal, that report was directly responsible for terminating fluoridation in Chile. As soon as it was printed, I sent copies to every dental and medical officer in the Pan-American Health Organization and the National Health Service of Chile. I also sent copies to professors in the faculties of medicine, dentistry and pharmacy in the University of Chile. Shortly thereafter, fluoridation was discontinued in Chile. However, the fight may not be

over. Present-day bureaucrats may not know that some 20 years ago fluoridation was discontinued in Chile because it was killing people in the experimental city of Curaco..

The existence of the *Journal of Arts, Science, and Humanities* and Anthony University which published that journal has also been questionsed (The name Anthony University has since then been changed to Susan B. Anthony University.) The university was establihsed as a not-for-profit corporation in the State of Missouri on June 13, 1973. This can be verified by directing an inquiry to the Secretary of State, Department of State, Jefferson City, Missouri.

Doubts about the existence of the *Journal of Arts, Science and Humanities*, which contains my report, can also be easily laid to rest. This journal was copyrighted in 1976, which is its legally documented year of birth. The copyright and date of publication can be verified by directing an inquiry to the Library of Congress, Copyright Office, Washington, D.C. Copies of this publication can be ordered from the Copyright Office, Library of Congress.

Additional evidence that the *Journal* exists is the fact that copies of that journal, containing my report on fluoridation in Chile, have been distributed by the National Institute of Dental Research. This is part of the National Institutes of Health in the U.S. Public Health Service (Bethesda, Maryland). On October 28, 1986, John S. Small, Information Specialist at the National Institute of Dental Research, wrote me as follows on official, government letterhead

Dear Dr. Schatz:

We would appreciate having a few more reprints (3-5) or your permission to reproduce several copies of your January 1976 article on fluoridation in Chile (Anthony University *Journal of Arts, Science, and Humanities*. v. 2, no. 1)

The needed copies would be for distribution to interested health professionals or writers specializing in health sciences as requests arise.

A postage-free envelope is enclosed for your use in sending copies or your note or permission to make copies. Thank you.

"Truth will come to light. Murder cannot be hid"

The *hit-and-run tactic* is an appropriate way to describe how proponents of fluoridation attempt to discredit those who oppose them. They publish a critique of one sort or another in a professional journal, but the individual they attack cannot publish his rebuttle in the same journal. An example of this *hit- and-run* is the recent attempt to discredit John Yiamouyiannis by John Hunt, chief executive of the British Dental Society, and four of his colleagues with supposedly impressive credentials.45 Unfortunately, few if any readers of the British Dental Society, in which Hunt *et al* published their critique, will see Yiamouyiannis' reply 46 They will therefore not be able to decide for themselves "where ... misleading statements are coming from, who is using 'deception by omission,' and whose references do not support their claims."46

In his reply, Yiamouyiannis poses an important question, "If one doesn't 'have a complete knowledge of the detailed and voluminous scientific literature on the relationship of water fluoridation to dental caries,' or close to [that], how [is he] going to respond to someone with an opposing viewpoint who does? [Will it be] by name-calling, by character assassination, by distortions, by misrepresentations, by undocumented fabrication?"46

But there are other important questions that should be asked about low-level fluoridation because of what we know about low-level radiation. Does low-level fluoridation, like low-level radiation, involve something far more serious than the usual misconduct of science? John Gofman's realization of the profound responsibility that scientists have to warn people about the danger of low-level radiation are best described in his own words.

"I was stupid in those days. In 1955, '56, people like Linus Pauling were saying that the bomb fallout would cause all this trouble. I thought, 'We're not sure. If you're not sure, don't stand in the way of progress.' I could not have thought anything more stupid in my life.

"The big moment in my life happened while I was giving a health lecture to nuclear engineers. In the middle of my talk it hit me! What the hell am I saying? If you don't know whether low doses are safe or not, going ahead is exactly wrong. At that moment, I changed my position entirely."47

In 1979, Gofman expressed his feelings as follows. "There is no way I can justify my failure to help sound an alarm over these activities many years sooner than I did. I feel that at least several hundred scientists trained in the biomedical aspect of atomic energy - myself definitely included - are candidates for Nuremburg-type trials for crimes against humanity for our gross negligence and irresponsibility. Now that we know the hazard of low-dose radiation, the crime is not experimentation - it's murder." 48

Now, back to questions about fluoridation which is still highly controversial after half a century. Are the harmful effects of low-level fluoridation due to "gross negligence and irresponsibility"? If so, is low-level fluoridation a "crime against humanity? If it is,

should those responsible for the harmful effects of low- level fluoridation be considered "candidates for Nuremburg-type trials for crimes against humanity."?

Acknowledgement

I salute John Yiamouyiannis and others for what they has been doing to inform people about the dangers of low-level fluoridation, just as I salute John Gofman and others who have been informing people about the dangers of low-level radiation. Many of these people, however, pay a high price for what they do because they have publicly questioned the integrity of the scientific establishment.

Gofman has recounted some of that happened to him.47Robert O, Becker, who refused to keep silent about electropollution - the dangers of manipulating our electomagnetic environment - has told the sad story of what happened to him. His account is in the last chapter in his book *The Body Electric*, that he co-authored with Gart Selden.49 Becker explained as follows why he revealed the retribution he experienced.

"I've taken the trouble to recount my experience in detail for two reasons. Obviously, I want to tell people about it because it makes me furious. More important, I want the general public to know that science isn't run the way they read about it in the newspapers and magazines. I want lay people to understand that they cannot automatically accept scientists' pronouncements at face value, for too often they're self-serving and misleading. I want our citizens, nonscientists as well as investigators, to work to change the way research is administered. The way it's currently funded and evaluated, we're learning more and more about less and less, and science is becoming our enemy instead of our friend."49

Both sides of the coin are important

"The importance of scientists' writing their own personal accounts of their dicoveries is now recognized. "For the historian of science, few documents are as valuable as the description of a discovery by the scientists involved in the action. Unfortunately few scientists take the time to record for posterity the course of events which led to the discoveries which were the fruit of their labor." (Lechevalier)50

"I have often thought how much more interesting science would be if those who created it told how it really happened, rather than reported it logically and impersonally, as they often do in scientific papers." (Beadle)50

"Over the years, the story of streptomycin's discovery has been terribly garbled. I think … it would be a great service if … Dr. Schatz told his own accurate and interesting account of his finding. Streptomycin turned out to be a milestone in the history of drugs to treat tuberculosis and other infections. Dr. Schatz's role has been largely ignored. The record about this discovery should be set straight." (Doris Jones Ralson, a fellow graduate student of Schatz when he did the streptomycin research)50

Our survival as a species is now threatened

I agree that personal accounts of discoveries by the scientists who made those discoveries are important. That is why I wrote *The True Story of the Discovery of Streptomycin.*, which my friend and colleague Doris Jones Ralston suggested I do.50 However, it may be even more important for whistleblowers to publish detailed accounts of how the scientific establishment has attempted to silence and punish them.

We are now at a critical time in history because our survival as a species is threatened as a result of our global devastation of nature. Science is the main force that has been used for the manipulation, exploitation, and devastation of nature. It is therefore important for the history of science, for the welfare of life on this planet, and for our survival as a species that those who have been pilloried for questioning the integrity of science and exposing misconduct by scientists tell, in their own words, the stories of what happened to them.

Fluoridation, is a major environmental pollutant,2 which along with many other chemicals is now a major part of the threat to our survival. Those scientists and other professionals who have opposed fluoridation have a unique oportunity to make a major contribution to history, to science, and to the survival of our species by telling the stories of how they were persecuted for their continued determination to inform their fellow men and women about the dangers of fluoridation.

Epilogue

"Until about a hundred years ago, rational men lived like spies in an enemy country. They never walked abroad unless disguised in irony or allegory. To have revealed their true selves would have been fatal.

"Today their status is more that of guerillas. They snipe from cover, ambush stragglers, harass retreating rear guards, cut communications, and now and then execute swift forays against detached units of the enemy. But they dare not yet risk an open engagement with the main force; they would be massacred. Their life is dangerous but exciting and is warmed by a sense of camaraderie not often known among the dull conscripts of orthodoxy.

"This" report "is intended as a sort of handbook for ... recruits in the ... cause of common sense. It indicates where the main armies of ignorance are now encamped and tells in a secret code what garrisons are undermanned or mutinous. It tries to show the use of

cover and camouflage and the techniques of infiltration and retreat. It maps road blocks and mine fields and shows how to rig a booby trap. It warns of counterespionage and gives — again in code — the ... infallible signs to know a fool.

*"When the recruit has finished with it, he can toss it over the walls into the enemy's barracks. It may encourage desertion."*51

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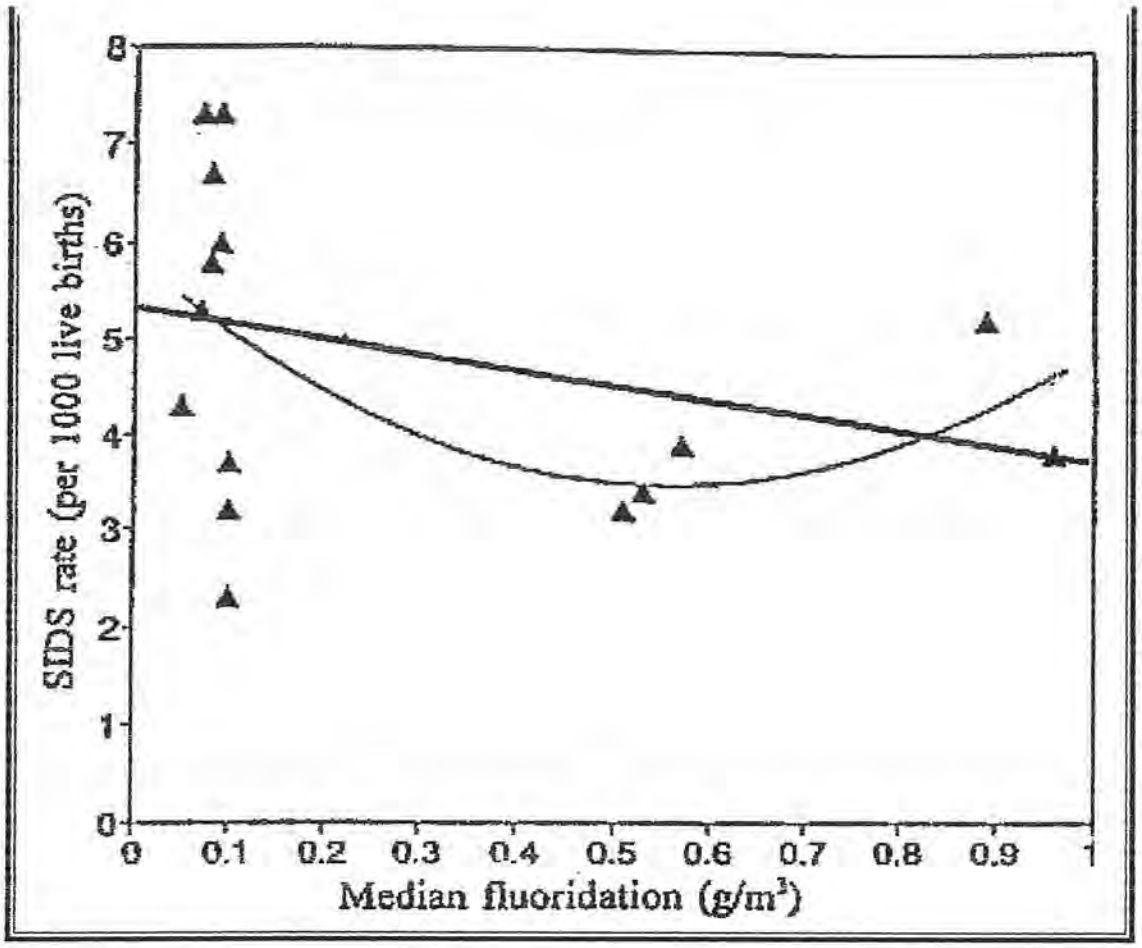
Appendix A:

Who is Albert Schatz, the author of this report?

FIGURE 1,
Figure 1. Mean SIDS mortality rates (1980-1984) and median fluoridation in reticulated water supplies for New Zealand health districts.



Appendix B: Risk assessment and paradoxical effects

This is not the place to review the literature on the limitations of risk assessment. Suffice it to say that we need adequate and reliable risk assessments for many pharmacological products, food additives, chemical environmental pollutants such as pesticides, radioactive contamination, hazardous wastes, and other harmful and potentially harmful substances that pollute our air, water, food, homes, work places, schools, recreational areas, etc. Unfortunately, risk assessment is too often little more than guesswork or a trade-off. Also unfortunately, political considerations not infrequently influence decisions as to how much exposure is permitted. What is even more deplorable is that there is no risk assessment at all for many toxic and potentially toxic substances to which we are frequently exposed.

It is not surprising that the risk assessments of low-level fluoridation and low-level radiation are highly controversial issues because there is disagreement on methods of determining risks and interpretation of research results. At the same time, it is inconceivable that meaningful risk assessment can be done without ascertaining whether paradoxical effects are involved. If they are, then risk assessment becomes considerably more complex, time-consuming, and costly. Nonetheless, the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and other state and federal agencies should seriously consider paradoxical effects.

In 1964, Schatz , Schalscha, and Schatz published the first review of paradoxical effects6 in which they pointed out that "Paradoxical effects occur more frequently and are more widely distributed than one would ordinarily assume from scattered reports.... Paradoxical effects have been produced by radiation, temperature, mutagenic and carcinogenic chemicals, steroid hormones, dextran, detergents, trace metals, herbicides, fungicides, insecticides, germicides, antibiotics, drugs, and a host of other agents...

"Since numerous chemical and physical agents cause paradoxical effects by different mechanisms in many biological systems, these reactions will no doubt become increasingly important in pharmacology, toxicology, chemotherapy drug idiosyncrasies, air pollution, chemical carcinogenesis, fluoridation, fallout, radiation effects, nutrition. biogeochemistry, the weathering of rocks and minerals, soil formation and soil fertility, and many other areas"6 including behavioral toxicology.

Also in 1964, Schatz and Martin published the first review on *The Importance of Paradoxical Effects of Fluoride with Respect to Fluoridation and the Toxicology of Fluoridation.*5

Thirty years later, in 1994, Milton Wainwright (in the Department of Molecular Biology and Biotechnology, at the University of Sheffield, England) published a review of our two reports which he called *Strange bumps in the data - mycological implications of the paradoxical concentration effect.*52 In his review, Wainwright commented as follows, "Schatz himself experienced difficulty in publishing his work on paradoxical effects in 'front-ranking' journals. His work on the subject, including two reviews, which are well written and thought-provoking by any standards, were eventually accepted for publication in *Compost Science* 6 and the *Pakistan Dental Review*5 and so have probably been read by only a few microbiologists.

"I hope this article has highlighted the fact that unusual bumps in data are not always the result of an experimenter having a bad day. Perhaps under the umbrella of Schatz's 'paradoxical effect', this potentially important phenomenon will gain respectability and receive the attention it deserves."52

It is interesting that Wainwright was the first to publish information on (a) the importance of my work on paradoxical effectsx and (b) my role in the discovery of streptomycin. 53

Unfortunately, the FDA, the EPA, other agencies, and individuals concerned with toxicology and other areas in which paradoxical effects undoubtedly occur, have yet to pay attention to this important phenomena which may literally influence not only health but also determine whether people live or die.

Aside from paradoxical effects, there is another reason to doubt the claim that low-level fluoridation is safe. When radiation and medication are administered, the dose is quantitatively adjusted daily for each individual. But fluoridation disregards "the uniqueness of each individual and the degree of variability of response among individuals.12 Individuals differ in how much water they consume daily. Furthermore, the fluoride content of drinking water varies from day to day. It is not invariably one part per million, which it is supposed to be. Therefore, the risk assessment of fluoridation is based on an average daily intake of fluoride from a source whose fluoride content varies daily. Consequently, no one knows how much fluoride each individual ingests daily from drinking water, and from other background sources. This is "playing with fire" because fluoride is a highly toxic substance. For these reasons, independently of paradoxical effects, it is not surprising that low-level fluoridation is harmful to some people. It would be surprising if there were no harmful effects.

"The fluoridation bottom line floats to the top when realizing governments and responsible scientific documentation on fluorides and fluoridation confirm that after 50 years of forced fluoridation, no government has felt it necessary or morally obligated to study the effect of fluoridation on human fertility and fluoride damage to the foetus, and the subsequent birth of babies.

"No drug except fluoride is allowed such evil medical exception from government, pharmaceutical and poison laws, and that evil is compounded when the same responsible people force fluoridation against the wish of the people.

"As it cannot be judged democratic, one may consider it the enemy of freedom, honesty, science, and morality, all based on their [the promoters' of fluoridation] fear of the dreadful truth about fluoridation and fluoride chemicals…

"Hidden on page 91 of the U.S. Department of Health and Human Services [in the section *Review of Fluoride, Benefits and Risks,* 1991] the authors make this recommendation: 'Conduct studies on the reproductive toxicity of fluoride using various dose levels including minimally toxic maternal dose.'

"Question - Why not?"54

Appendix C: The failure of fluoridation in England[21]

The title of this Appendix is the title of an article which I published in 1972.[21] It is reproduced on pages 17,18,19, and 20 of this report because (a) it is not otherwise readily available and (b) as I have already said, "It has to be seen to be believed." My 1972 publication shows that fluoridation does not prevent dental caries.

The information in the following two paragraphs was inadvertently left out of the original manuscript of the 1972 article when it was submitted for publication.

"There is a flaw in this British study which the authors were unaware of. The flaw invalidates epidemiological surveys that show less decay in fluoridated children than in non-fluoridated children of the same age. The flaw involves the difference in the age of the children versus the post-eruption age of their teeth; that is, the age of the teeth after they appear above the gum line. Although the two groups of children are the same age, the teeth of the children in the two groups are not the same age because fluoride delays tooth eruption.

"The teeth of fluoridated children, which erupt later, are younger than the teeth of non-fluoridated children, which erupt earlier.

Because the teeth of the fluoridated children are younger, they have been exposed to cariogenic conditions in the mouth for less time than the teeth of non-fluoridated children. Because of this shorter exposure to cariogenic conditions, the teeth of fluoridated children understandably have less decay. Therefore, the less tooth decay that occurs in fluoridated children cannot be attributed to any cariostatic action of fluoride. This conclusion is supported by the fact that the rate at which tooth decay occurs is the same in both groups, as shown in Figure 1."

©Albert Schatz

FIGURE 1, Curves showing that dental caries develops at the same rate in the permanent teeth of fluoridated and non-fluoridated children

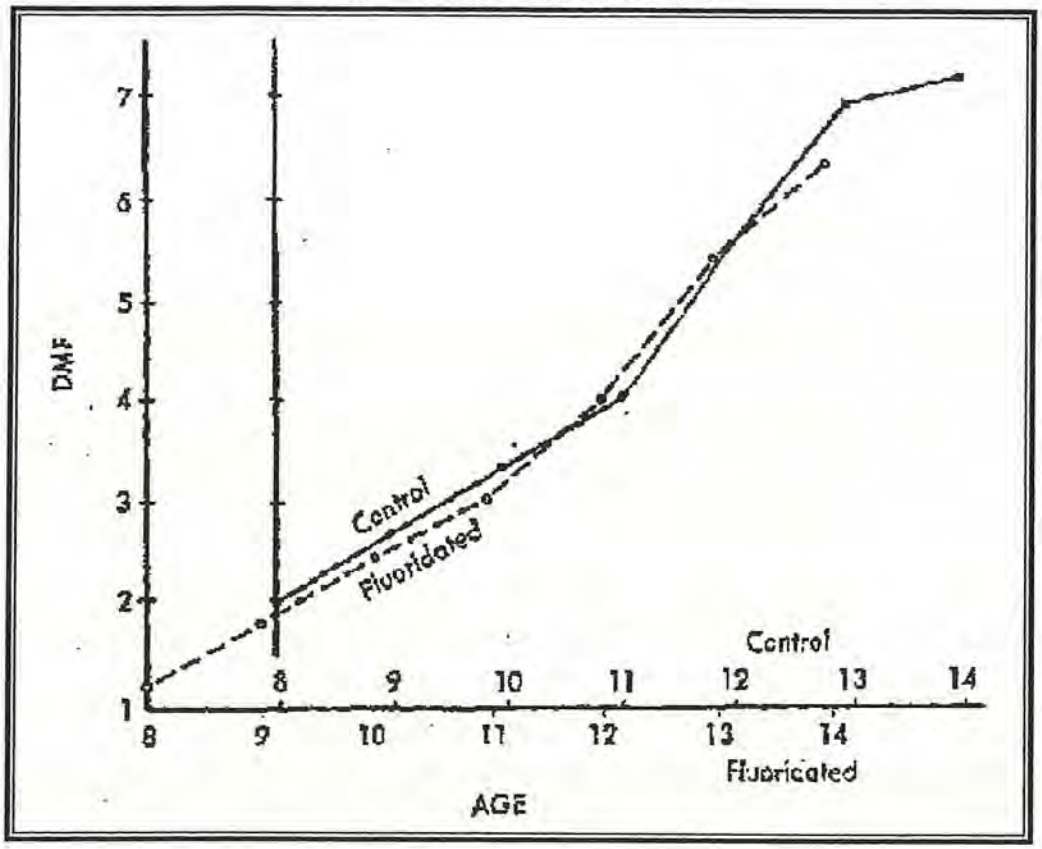


TABLE I

DMF for permanent teeth of fluoridated and non-fluoridated children.

Average DMF per child

Age	Fluoridated Areas	Control Areas	% Difference in DMF
8	1.2	2.0	67*
9	1.8	2.7	50
10	2.4	3.3	37
11	3.0	4.0	33
12	4.0	5.6	40
13	5.4	6.9	28
14	6.3	7.2	14

*67% = (2.0 - 1.2)/1.2 x 100.

Newsweek, Feb. 5, 1990

SCIENCE

Don't Drink the Water?

Brush your teeth, but the fluoride from your tap may not do much good—and may cause cancer

Remember the great fluoride debate? Back in the 1950s, every voice of authority, from the U.S. Public Health Service to the PTA, supported adding fluoride to the water supply as an effective and totally safe way to promote healthy teeth. The only opponents seemed to be John Birchers and other extremists who regarded the scheme as a diabolical communist plot. In the years since, most of the nation's major cities fluoridated their water, and the issue appeared closed. No less an objective voice than Consumer Reports declared in 1978, "The survival of this fake controversy . . . represents one of the major triumphs of quackery over science in our generation."

In fact, the debate never ended. Now it may explode as never before, posing new challenges to medical dogma and giving parents one more thing to worry about. Government researchers have new evidence that casts doubt on the benefits of fluoridation and suggests that it is not without risk. The most incendiary results come from the National Toxicology Program (NTP), which in 1977 was ordered by Congress to determine whether fluoride causes cancer. This week NTP plans to release data showing that lab rats given fluoridated water had a higher rate of a rare bone cancer called osteosarcoma. According to a memo by the Environmental Protection Agency, "very preliminary data from recent health studies . . . indicate that fluoride may be a carcinogen."

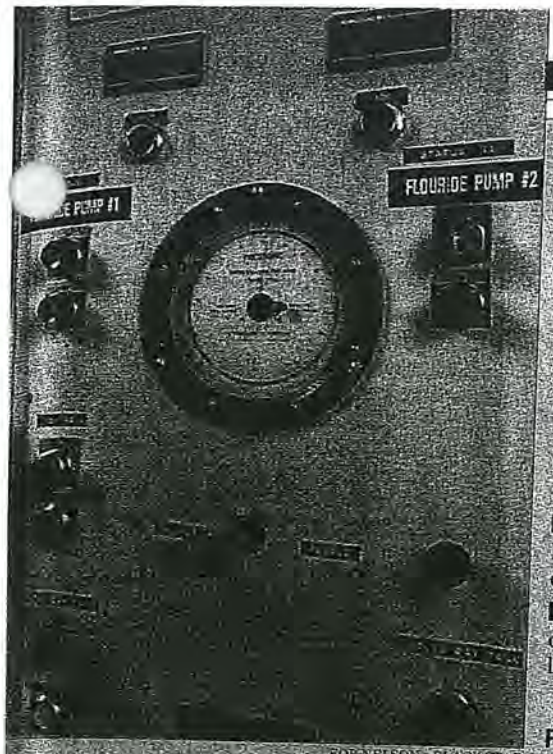
Fluoridation proponents are already criticizing the NTP study, but it will be harder to discredit or ignore than the hundreds of earlier experiments, of varying quality and from around the world, that have linked fluoride to mottled teeth, skeletal damage, genetic defects and other ills. During the two-year experiment, rats and mice drank water with different levels of sodium fluoride. None of the animals drinking fluoride-free water developed cancer, nor did any of those drinking water with the lowest fluoride concentration, 11 parts per million (ppm). But of the 50 male rats consuming 45-ppm water, one developed osteosarcoma. Four of 80 male rats drinking 79-ppm fluoride developed osteosarcoma. No mice or female rats showed signs of bone cancer. Although the anima drank higher concentrations of fluori than people do (the legal standard is fo ppm), such megadosing is standard toxic logical practice. It's the only way to dete an effect without using an impossib arg number of test animals to stand th humans exposed to the substance.

Although the final NTP report will n be released for months, several indepen ent toxicologists find the results signif cant. Most important, the rats who did n drink fluoride did not get cancer, indica ing that the malignancies are "not a fluke, says EPA scientist William Marcus. Ther is also a convincing relationship betwee dose and response: the more fluoride, th more cancers. Pathologist David Kaufma of the University of North Carolina warn that the rat data must be examined to see i the cancers appeared in the long bones o the arms and legs, as osteosarcomas do i humans, or in other places, which migh make the results less relevant to people Still, Kaufman says the NTP data "make fluoride look like a weak carcinogen. It's obviously something to worry about"—bu not panic over. There are about 750 cases o osteosarcoma in the United States annual ly; even if fluoride caused all of them—an impossibility—the lifetime risk to any individual from drinking fluoridated tap water would still be only about one in 5,000.

Too crude: If fluoride causes bone cancer in lab rats, then why, after 45 years of fluoridation, haven't researchers seen a rash of osteosarcomas in fluoridated cities? Because epidemiology is too crude to de even if the cancers are there. In the 19 os, the National Cancer Institute found no sign of higher cancer rates in fluoridated

From the beginning, controversy: *In 1965, the protests reached the reservoir's edge*

UPI-BETTMANN NEWSPHOTOS



ROB NELSON—BLACK STAR

Fluoride Facts

- Fluoride—in water or toothpaste—helps teeth resist decay. It seems to work by redepositing calcium and other ions in tooth enamel, repairing and strengthening it.
- 53% of the U.S. population drinks water containing fluoride. 121 million people have artificially fluoridated water, 9 million drink from naturally fluoridated supplies.
- 41 of the 50 largest U.S. cities have fluoride in the water; those that don't include L.A. and San Diego.
- The legal standard for fluoride in drinking water is four parts per million; for toothpastes, 1,100 ppm.

Fluoridation: *Atlanta's waterworks*

cities. But that reassuring finding may be misleading. According to Donald Taves, a fluoride expert, if the difference were anything less than 7 percent it would not be detectable. Another obstacle to definitive epidemiology is mobility: just because someone got osteosarcoma in a fluoridated city does not mean he had been living there all his life.

The NTP results assume an added importance when combined with recent data on the shrinking benefits of fluoridation. According to the American Dental Association (ADA), tooth decay is anywhere from 50 to 70 percent less in fluoridated areas. But figures from the National Institute of Dental Research (NIDR), part of the National Institutes of Health, suggest otherwise. A 1987 survey of almost 40,000 schoolchildren found that tooth decay had declined sharply everywhere. Children who had always lived in fluoridated areas had 18 percent less decay, compared with their peers who had lived in nonfluoridated areas. This 18 percent translates into a difference of fewer than one cavity per child. Similarly, in a 1986 paper in the British journal Nature, Australian researcher Mark Diesendorf assessed 24 studies from eight countries and found that cavity rates had declined equally in fluoridated and nonfluoridated areas, suggesting fluoridated water isn't that important.

How can that be? "A good case can be made that it has to do with fluoride in toothpaste and rinses," says dental-health expert Brian Burt of the University of Michigan. And even if drinking fluoridated water is slightly risky, there is no hint that fluoridated toothpaste—as long as you don't swallow any—is dangerous. Tooth decay may also be declining because of better diet and hygiene. Also, foods and beverages processed with fluoridated water are ubiquitous. (Many bottled waters, though, do not have fluoride.) As a result, argues Alan Gray, a leading pro-fluoridation dentist in Canada, "it is becoming difficult to provide accurate, ethical advice" about fluoridation.

Among environmental controversies, fluoridation is unique in that one side has consistently denied that questions of risk or benefit even exist. The ADA states, "Anti-fluoridation groups attempt to create the illusion of a scientific controversy [which is] merely a ploy to create doubt about a well-researched, well-demonstrated preventive measure." But even well-researched articles raise hackles. When, in 1988, Chemical & Engineering News presented a balanced report on fluoridation, it attracted the wrath of the medical establishment. Says Taves, "Too many scientists lost their objectivity. This has become a religion on both sides."

Safe water: And that undercut the scientific process. The NIDR kept files on people perceived as threats to fluoridation. Political decisions were at odds with expert advice: a panel convened by the surgeon general in 1983 expressed concern, in closed sessions, about skeletal and dental damage from fluoride. At one point, a member said, "You would have to have rocks in your head, in my opinion, to allow your child much more than two parts per million [fluoride]." Said another, "I think we all agree on that." Even so, in 1986 EPA *raised* the fluoride standard from about two ppm to four.

This month EPA opened a review of the standard. Once EPA receives the official NTP report, it will establish a target "safe" fluoride level. The Safe Drinking Water Act requires that the level be zero for carcinogens, but the standard may be based on what is technically feasible. Fluoridation can be stopped immediately, but many communities with naturally fluoridated water—up to 12 ppm—would have to remove it. As EPA wrestles with the standard, fears John Sullivan of the American Water Works Association, "confusion will reign": local laws will still require fluoridation, a practice that may cause cancer.

As they await EPA's decision, pro-fluoridationists are invoking arguments of social justice. Dental researcher Ernest Newbrun of the University of California, San Francisco, contends that fluoridation promotes the health of children of "all races and all socioeconomic classes," not only those with enough money or discipline or access to the health system to take a fluoride supplement every day. He and others say it is morally wrong not to provide the benefits of fluoride. Although the NIDR's and other surveys suggest that fluoride in toothpastes and dental rinses also ensures healthy teeth for those who use the products, those who do not might suffer.

No one can foresee how the fluoride debate will play out this time. But since the 1950s, the country's environmental consciousness has been heightened. In the end, deciding whether or not to fluoridate turns less on science than on values. The sheer weight of good research may finally, after four decades, begin to inform those judgments and even overwhelm the unscientific rhetoric that has characterized both sides of the debate for far too long.

SHARON BEGLEY

PHOTOS BY JACQUES CHENET—NEWSWEEK

After every meal: *Toothpastes to fight cavities*

NoFluoride.com

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Don't Drink the Water?

Brush your teeth, but the fluoride from your tap may not do much good - and may cause cancer.

Excerpts from the Feb 5, 1990 Newsweek article:

Remember the great fluoride debate? Back in the 1950s, every voice of authority, from the U.S. Public Health Service to the PTA, supported adding fluoride to the water supply as an effective and totally safe way to promote healthy teeth... The most incendiary results come from the National Toxicology Program (NTP), which in 1977 was ordered by Congress to determine whether fluoride causes cancer. This week NTP plans to release data showing that lab rats given fluoridated water had a higher rate of a rare bone cancer called osteosarcoma. **According to a memo by the Environmental Protection Agency, "very preliminary data from recent health studies ... indicate that fluoride may be a carcinogen."**

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Political decisions were at odds with expert advice

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the more fluoride, the more cancers

There is also a convincing relationship between dose and response: the more fluoride, the more cancers. Pathologist David Kaufman of the University of North Carolina warns that the rat data must be examined to see if the cancers appeared in the long bones of the arms and legs, as osteosarcomas do in humans, or in other places, which might make the results less relevant to people. Still, Kaufman says the NTP data "make fluoride look like a weak carcinogen...

If fluoride causes bone cancer in lab rats, then why, after 45 years of fluoridation, haven't researchers seen a rash of osteosarcomas in fluoridated cities? Because epidemiology is too crude to detect it even if the cancers are there. In the 1970s, the National Cancer Institute found no sign of higher cancer rates in fluoridated cities. But that reassuring finding may be misleading. According to Donald Taves, a fluoride expert, if the difference were anything less than 7 percent it would not be detectable. Another obstacle to definitive epidemiology is mobility: just because someone got osteosarcoma in a fluoridated city does not mean he had been living there all his life.

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Sharon Begley

http://www.pr.com/press-release/9026

Anti-Fluoridation Portland Dentist Hails New Harvard Study

Dr. Kyung L. Boen is among a sprinkling of dentists in the Portland Metropolitan area that are against adding fluoride to the water supply known as fluoridation. Dr. Boen believes that anti-fluoridation advocates in the United States have been partially vindicated by a new Harvard study and a recent National Academy of Sciences report. Dr. Boen is confident that a complete vindication of her anti-fluoridation stance and an ADA fluoridation support reversal will come within the next decade.

Portland, OR, April 09, 2006 --(PR.com)-- Dr. Kyung L. Boen is among a sprinkling of dentists in the Portland Metropolitan area that are against adding fluoride to the water supply known as fluoridation. While she advocates limited fluoride dental applications that are applied directly to the teeth, she generally promotes using a fluoride substitute such as Xylitol, which is safe for young children and even infants. Dr. Boen believes that anti-fluoridation advocates in the have been partially vindicated by a new Harvard study and a recent National Academy of Sciences report. Dr. Boen is confident that a complete vindication of her anti-fluoridation stance and an American Dental Association (ADA) fluoridation support reversal will come within the next decade.

It was reported this week that young boys who drink fluoridated water, considered safe by federal guidelines, are at an increased risk of developing bone cancer than boys who drink unfluoridated water, according to a new study published in the May issue of the Harvard journal, Cancer Causes and Control. A team of Harvard University scientists, led by Dr. Elise Bassin, found a 5-fold increased risk of developing Osteosarcoma in teenage boys who drank fluoridated water at ages 6, 7, and 8. The research, funded by the National Institute of Environmental Health Sciences, reinforces previous findings in both humans and animals.

This is only two weeks after the prestigious National Academy of Sciences' National Research Council recommended the immediate reduction of fluoride in drinking water. The committee reported that children exposed to the current maximum allowable concentration of fluoride in drinking water risk developing severe tooth enamal fluorosis, which is a condition characterized by teeth discoloration, enamel loss, and pitting of the teeth. The majority of the committee stated that the damage to teeth caused by severe enamel fluorosis is a toxic effect that is consistent with prevailing risk assessment definitions of adverse health effects. Additionally, the majority concluded that people who consume water containing that much fluoride, over a lifetime, are likely at increased risk for bone fractures.

Most interestingly for many to learn may be that relative to their body weight, infants and young children are exposed to 3 to 4 times as much fluoride as adults. Moreover, on average, approximately 10 percent of children in communities with water fluoride concentrations near or at 4 mg/L develop severe tooth enamel fluorosis. That means thousands and thousands of American children are being slowly poisoned and doomed to suffer enamel loss and pitted teeth due to this high-concentration of fluoride in their drinking water.

Some of the countries that do not fluoridate their water supply include Austria, Belgium, Bulgaria, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Japan, Luxembourg, Netherlands, Norway, Philippines, Romania, and Sweden. Yet despite the fact that these countries have decided strongly against water-supply fluoridation, they have experienced the same significant declines in dental cavities as the United States. Approximately 68 percent of Americans currently have access to optimally fluoridated water.

The reported hazards to human health from ingesting fluoride include acute toxic hazard, such as to people with impaired kidney function, as well as chronic toxic hazards of gene mutations, cancer, reproductive effects, neurotoxicity, bone pathology and dental fluorosis. Most of the beverages we drink, such as beer, soda and juice, are made with fluoridated water. Fish and other foods contain fluoride. The fruits and vegetables we eat often are grown with fertilizers

that contain fluoride, thus they can have high concentrations of fluoride such as grapes and watermelon. Most Americans cook their foods in fluoridated water.

Dr. Boen graduated from the renowned Oregon Health & Sciences University School of Dentistry in 1994. Five years later, she received her Fellowship from the Academy of General Dentistry. Dr. Boen is a solo-practitioner in her high-tech dental clinique and perhaps only one of a handful of dentists on the West Coast that personally offers invisalign, full orthodontics, i.v. sedation, CEREC 3D porcelain restorations, and Waterlase MD laser dentistry. The doctor holds dental licenses in Oregon, Washington and California.

For information: http://www.mkdentalclinique.com or
Contact: Mark B. Boen, J.D., Business Manager

Dental fluorosis is the 1st visible sign of fluoride poisoning. ~~of the~~ a discoloring ~~of the~~ teeth).

COMMUNITY AND HEALTH & HUMAN SERVICES STUDIES

Town of Wilmington

Board of Health

121 Glen Road
Wilmington, Massachusetts 01887

Fluoridation

A Discussion on Whether the Board of Health
Should order the Fluoridation of the Municipal Water Supply

By Gregory Erickson, Director of Public Health

February 15, 2000

Near the beginning of 1999, the Wilmington Board of Health began to investigate the proposition that the town's water supply should once again be fluoridated. In an effort to learn the latest information about fluoride, I began my own research on the subject. In doing so, I have looked at the background, history, science and research presented to date, and, have encountered many areas which have raised a good deal of concern. In pursuing suitable explanations to these concerns, I have only encountered even more concerns.

As is the case with many public programs, it is common to find disagreement, even after serious investigation and debate on the issues, and even among friends and long standing associates. Such is the case with the issue of fluoridating the water supply for the Town of Wilmington. As Director of Public Health, I have made my own observations and study and I have done so independently with the intent of making a responsible recommendation to the Board of Health and to the public.

Board of Health has divided the fluoridation issue into three main categories:
(1) Is it safe?
(2) Is it effective?
(3) Is it right for the Town of Wilmington?

I have divided my observations into the same categories for the sake of consistency. My concerns are based on government documents, research papers, personal communications, personal interviews, a related seminar, and two Board of Health hearings. I have formulated a recommendation which I feel focuses on the major concerns that should be considered by the Board of Health and the public at large.

The First Issue: Is Fluoridation safe?

I have discussed this one issue with both of the authors of the paper **Applying the NAEP Code of Ethics to the Environmental Protection Agency and the Fluoride in Drinking Water Standard,** by Robert J Carton, Ph.D. and J. William Hirzy, Ph.D. Both are presently scientists, employed by the Environmental Protection Agency (EPA) and they have confirmed to me the authorship and authenticity of their paper which describes in detail the procedure that the EPA used to raise the Maximum Contaminant Level (MCL) of fluoride in drinking water from 1.0 ml/L to 4.0 mg/L and how it was done inappropriately, with a succession of irregularities, and in violation of the EPA's own Code of Ethics. As a result of this, in 1997, the National Federation of Federal Employees Union (local 2050)

which is comprised of the scientists, researchers, and attorneys who work for the EPA has taken the unanimous position to oppose the fluoridation of public water supplies.

This point, taken by itself, causes a great deal of concern to me. I question how the EPA as a governmental agency charged with the responsibility of insuring safe drinking water standards for the nation can recommend the fluoridation of water supplies when its own scientists working there are unanimously opposed to it. These EPA employees have taken other actions to openly oppose the fluoridation of water supplies, such as the writing of several papers on the issue, making videos, and actively lobbying the Governor of California, for example, to not fluoridate the water supplies of that state.

Considering that these are the professionals who comprise the scientific community that sets the standards for toxicity and enforcement of the drinking water standards for the nation, this point alone, without adequate explanation, is sufficient for anyone to reject the notion that fluoridation is safe. On this point, I remain open to any explanation that can be offered up to adequately counter the logical conclusion.

Another concern is that the EPA has reclassified fluorosis from that of a "health effect" to a "cosmetic effect", and has done so without the benefit of hearings or scientific input. This includes all levels of fluorosis, including severe fluorosis. It is the position of the EPA that there is no "health effect" until there is a "loss of tooth function". This means, in layman's terms, that one must loose a tooth or teeth, or loose the function of a tooth or teeth in order for a "health effect" to exist. Up to that point, one can have permanently stained, cracked, pitted and mottled tooth enamel, and a "health effect" is not considered to be present, according to the EPA. This is a completely absurd and unacceptable position. I don't think that any parent would accept this standard for their own child. As a public health administrator, I cannot accept it for the Town of Wilmington.

Point in fact: Fluoride causes fluorosis of the teeth. This is not a debatable issue. In fact, the discovery that fluoride causes less cavities to occur was a result of the correlation found between the occurrence of fluorosis and the occurrence of less cavities, where in Texas, naturally occurring fluoride existed at higher levels. It has been presumed that by adding fluoride to the water supply, it would result in better dental health. However, history has shown that by adjusting the fluoride at a lower level (1.0 mg/L) which causes less fluorosis negates the effect of the fluoride with regard to dental health. Those who support fluoride have said that this is mild fluorosis fox the most part. And this is true, for the most part. What of the lesser part?

The **Executive Summary, Review of Fluoride Benefits and Risks** by the U: S. Public Health Service, Department of Health and Human Services, February 1991, states that:,

"Moderate and severe forms of dental fluorosis, considered by some investigators as presenting a cosmetic problem, do not appear to produce adverse dental health effects, such as the loss of tooth function, and represents less than six percent of the cases of fluorosis nationally."

So according to the Public Health Service, it's acceptable that 6% of the 300 children born to residents of the Town of Wilmington in 1999 (actual statistic) should be expected to have moderate to severe [not mild] dental fluorosis. That's 18 children in a "one year" age group. If the Town of Wilmington continues to have 300 children added to the rolls in each coming year, the school system should be expected to have [18 x 12] = 216 children in the school system with moderate to severe fluorosis. Of those, how many will have severe fluorosis? One? Two? This is a totally unacceptable tradeoff. This is

taken from a governmental document which purports to support fluoridation. [Note: total fluorosis (mild, moderate and severe) is expected to be 22% of our 300, or 66 of our children per year]

Point in fact: Fluoride also causes crippling skeletal fluorosis. This is not debatable. Just as the EPA ignores fluorosis as a "health effect", the EPA ignores all of the precursor signs of crippling skeletal fluorosis as a "health effect" (such as arthritic pain, rigidity of the spine, and the mal shaping of bones) and recognizes skeletal fluorosis as a "health effect" only at the onset of actual crippling. This means that a person can be experiencing the preliminary signs of crippling skeletal fluorosis, including real arthritic pain and malformation of the skeleton, but the EPA says it's not a "health effect" because you're not crippled yet? How ever absurd this seems to the reader, this is the rational that the EPA has used to raise the MCL from 1.0 mg/L to 4.0 mg/L, allowing the so called "optimum" level of 1.0 mg/L to neatly fit into it's standards.

Why? It would seem that there must be some reason that would cause the U.S. EPA to go against its own scientists and encourage states and municipalities to fluoridate their water supplies in the face of the information given above.

For your consideration, a letter from the EPA, signed by Rebecca Hanmer, Deputy Assistant Administrator for Water, which states:

"Water treatment chemicals, including fluosilicic acid have been evaluated for their potential for contributing to the contamination of drinking water. The Water Treatment Chemicals Codex, published by the National Academy of Sciences, prescribes the purity requirements for fluosilicic acid and other fluoridation chemicals.

In regard to the use of fluosilicic acid as a source of fluoride for fluoridation, this Agency regards such use as an ideal environmental solution to along-standing problem. By recovering by-product fluosilicic acid from fertilizer manufacturing, water and air pollution are minimized, and water utilities have a low-cost source of fluoride available to them."

As the letter states, one motivation for the EPA allowing the disposal of "fluosilicic acid and other fluoridation chemicals" into our water supplies is because it is "an ideal environmental solution to a long-standing problem". Note that "other fluoridation chemicals" would include sodium fluoride which is recommended by the Massachusetts Department of Public Health for the Town of Wilmington. Sodium fluoride is a hazardous waste. produced by the aluminum industry, and hydrofluorosilic acid is a hazardous waste produced by the fertilizer industry.

Sodium fluoride is a very toxic and very reactive chemical. It's toxicity is very well documented. As a by product of industry, it is a hazardous waste, which if properly disposed of would need to be taken to a class 1 landfill at the cost of approximately $7000 per truckload. How convenient for industry, that the EPA was so willing to make these adjustments to the MCL to facilitate the disposal of their hazardous wastes into the drinking water supplies.

It is true that nearly all of the water in any municipal water system never gets consumed. Most goes down the drains of America, washes the cars, waters the lawns, laundry, and so on. What little percentage is consumed, goes through the body and only 50% of the fluoride is absorbed. So what's the problem. The fluoride that is absorbed goes to the teeth and bones. It can cause fluorosis of the teeth and crippling skeletal fluorosis as described above. There are many other mechanisms that have only recently come to light which also go to the issue of whether fluoride is safe.

The very well known research by Dr. Phyllis Mullinex has shown that fluoride causes Central Nervous System disorder in rats. The levels at which the rats were exposed were appropriate for the comparative study of fluoride's effect in humans. Dr. Mullinex was dismissed from her position as chairman of the toxicology department at Forsythe immediately after publishing her work. A subsequent law suit ended in a settlement with sealed results. Forsythe was endowed with a grant from Colgate.

Fluoride has been shown to be an equivocal cause of cancer in rats. There are several other associated disorders that have been positively linked to fluoridated water supplies. Among them are increased occurrence of hip fracture, Down's Syndrome, earlier onset of menses, delayed eruption of teeth, a reduction in IQ of approximately 10 points, and the occasional person who simply happens to be hypersensitive to fluoride because of some other medical reason resulting in an allergic type reaction, and the occasional death or multiple deaths caused by accidental over fluoridation.

And finally on the question of "safety", many have claimed that the AMA endorses or supports fluoridation. I wish to include a quote from a letter from Dr. Flanagan, Assistant Director of the American Medical Association which states in part: .

"this Association endorses the principle of fluoridation of public water supplies to reduce the incidence of dental caries; it does not become involved in endorsement of the fluoridation of water supplies of specific cities.

The American Medical Association is not prepared to state that "no harm will be done to any person by water fluoridation."

The American Medical Association has not carried out any research work, either long-term or short-term, regarding the possibility of any side effects."

The fact is, I have found no study ever being done, not by any governmental agency, or any professional organization, such as the AMA, the ADA, the FDA, or the EPA, not the USPHS or the CDC. No agency has determined that fluoride is safe.

The Second Issue: Is it Effective?

Higher levels of fluoride have been correlated to fewer caries but when fluoride is reduced to a level at which there is a lower risk of fluorosis, the correlation no longer exists. No credible study has produced factual proof that fluoridation of a water supply at the so called "optimum" level is beneficial to dental health.

Virtually all studies comparing fluoridated and non fluoridated communities, or other fluoridated and non-fluoridated populations in subsets not necessarily limited to communities, have shown that there is no difference between the resultant dental condition. In fact, some studies have shown that the non-fluoridated populations have slightly better dental condition than do the fluoridated communities.

Some early studies which are used to support the claim that fluoridated communities have better results are not dependable. Many of the early studies were manipulated to give the false appearance of effectiveness because industry and a willing government was determined to find a solution to their "long-standing problem". This has been documented by sworn court testimony in subsequent civil proceedings. Additionally, many credible studies have been done which show clearly that at the so called "optimum" level, there is no difference in dental condition.

Finally, there was a very recent paper published in Community Dentistry and Oral Epidemiology by Kumar and Swango, 1999, which demonstrates that the many current sources of fluoride in food products, fruit juices, and other sources today results in excessive fluorosis and concludes with the recommendation of lowering the intake of fluoride, not increasing it.

The Third Issue: Is it Right for the Town of Wilmington?

After reading hundreds of documents, I have found that much of the most condemning information has come from the EPA itself. These are by far the most troubling. No other drug, or medicine has such a wide spread application, and yet has had so little scrutiny as to its safety. To purchase sodium fluoride tables, one is required to first obtain a prescription. Yet to fluoridate an entire community no prescription is necessary.

Sodium fluoride tablets can be purchased by prescription at a local drug store at a cost of $6.99 per hundred (1 tablet per day for 100 days which equals $26/year) and a dentist can prescribe tablets at a regular visit at no additional cost to the parents. If individual parents wish to supply fluoridated water to their children, let them have that freedom of choice. The common complaint is that they forget to give the tablets to their children.

Recommendation:

Fluoride is not a nutrient as many have claimed, only being adjusted to it's "optimum" level. Fluoride is a toxin, like arsenic and lead, occurring naturally in the environment. We have come to discover that many of the elements that we commonly used were dangerous to health. We have removed lead from paint, once a primary ingredient, and from pipes and solder, as we have learned that it caused lead poisoning. We have removed asbestos from our schools and public buildings because of the remote possibility that the smallest exposure could cause asbestosis. We have done this by passing laws prohibiting the use of these elements. We should look at the many countries that have prohibited the use of fluoride in water supplies. We should look at the long list of cities in the U.S. that have changed their position and reversed their previous action to fluoridate, and have rejected its use.

As a society, we have done many things in the name of science and good health, like sulfur drugs and thalidomide, Laetrile and Fen-phen, only to find out that they were wrong and we rejected their use. There is no compelling reason to fluoridate an entire community, adults and children, with a toxic chemical at any dose, in the face of such compelling evidence against it, especially when there are alternatives available.

Therefore my recommendation to the Board of Health and the Town of Wilmington is to not go forward with the fluoridation of the municipal water supply.

Respectfully submitted,

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Comments on
Proposed HHS Recommendation for
Fluoride Concentration in Drinking Water
for Prevention of Dental Caries

Prepared for the
Department of Health and Human Services

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Submitted at the request of the
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These comments on the proposed HHS recommendation for fluoride concentration in drinking water are submitted to the Department of Health and Human Services (HHS) in response to their January 13, 2011, request for public comments (Federal Register 2011). These comments are not to be considered a comprehensive review of fluoride exposure or toxicity.

The author of these comments is a professional in the field of risk analysis, including exposure assessment, toxicity evaluation, and risk assessment. She has recently served on two subcommittees of the National Research Council's Committee on Toxicology that dealt with fluoride exposure and toxicity, including the NRC's Committee on Fluoride in Drinking Water. She has also authored an Environmental Protection Agency report on fluoride toxicity.

These comments are submitted at the request of the International Academy of Oral Medicine and Toxicology (IAOMT), and their preparation was supported in part by the IAOMT. Opinions and conclusions expressed herein are those of the author.

Summary. The Department of Health and Human Services (HHS) has proposed a new recommendation regarding fluoride concentrations in drinking water (Federal Register 2011), the primary change being from a recommended range of 0.7-1.2 mg/L fluoride in drinking water (0.7-1.2 ppm) based on ambient local temperatures, to a single value of 0.7 mg/L (0.7 ppm), regardless of temperature. The main concern is the prevention of dental fluorosis, a condition ranging from mild spotting of the teeth to severe pitting and staining. Dental fluorosis is caused by excessive fluoride ingestion during the early years of childhood, before the permanent teeth erupt. The HHS recommendation is intended to limit the risk of dental fluorosis while maintaining caries protection (Federal Register 2011), something that was suggested earlier by Heller et al. (1997), based on an analysis of a national survey of children conducted in 1986-1987.

The HHS is to be commended for recommending a reduced concentration of fluoride in drinking water. However, several important concerns remain:

(1) The proposed reduction in fluoride concentration in drinking water is insufficient to achieve the HHS goal of a significant reduction in the nationwide prevalence of dental fluorosis.

(2) The HHS recommendation does not address a number of other health concerns for the American population with respect to fluoride exposures.

(3) Available data do not support a role of community water fluoridation in improving dental health.

(4) HHS remains in the precarious position of recommending indiscriminate administration of a drug to the American population, without individual evaluation of need, appropriate dose, efficacy, or side effects.

These concerns are discussed in more detail below. If HHS is serious about limiting the risk of dental fluorosis and protecting the health of the American population, HHS should revise its proposed recommendation to call for an immediate end to community water fluoridation.

(1) The proposed reduction in fluoride concentration in drinking water is insufficient to achieve the HHS goal of a significant reduction in the nationwide prevalence of dental fluorosis.

The previous range of recommended fluoride concentrations was based on ambient temperature and the assumption that people's water consumption varies with outdoor temperature. Thus the recommended fluoride levels vary from 0.7 mg/L in Florida and parts of Arizona and Texas to 1.2 mg/L in Alaska, Maine, Michigan, Minnesota, and North Dakota. The new HHS recommendation will therefore have a larger effect on the northern states than on the southern states, with some areas seeing no change in the recommended fluoride concentration. The proposed change will also put the U.S. in agreement with Canada, which in 2009 recommended a fluoride concentration of 0.7 mg/L for all parts of the country (Health Canada 2009). However, the HHS has offered no data by state or region to show that the northern states have the highest prevalence of dental fluorosis or that reducing the fluoride concentration in northern states will bring the national prevalence of dental fluorosis down to an "acceptable" level. In addition, the Centers for Disease Control and Prevention (CDC) has reported that the black population in the U.S. has higher rates of dental fluorosis, including higher rates of moderate and severe dental fluorosis (CDC 2005). Since the black population is greatest in the southern states, reducing the fluoride concentration in the northern states but not the southern states cannot be expected to produce a significant reduction in dental fluorosis in the black population as a whole.

The 1986-1987 survey data mentioned by HHS (Federal Register 2011) show a clear dose response for fluorosis prevalence and severity with fluoride concentration (Heller et al. 1997; Table 1; Fig. 1). Unfortunately, the more recent 1999-2004 survey did not include water fluoride concentrations. The increase in total fluorosis prevalence (40.7% in 1999-2004 vs. 22.6% in 1986-1987 for children ages 12-15; Beltrán-Aguilar et al. 2010) probably represents both a higher fraction of the population receiving fluoridated water and higher total fluoride exposures for a given water fluoride concentration. Although increased fluoride intake from other sources such as toothpaste could be contributing to higher total fluoride exposures, a simple decrease in milk consumption with higher consequent intake of water and water-based beverages would also contribute to higher fluoride intake for a given water fluoride concentration.

Reducing fluoride concentrations in fluoridated community water will, at best, bring down fluorosis prevalence for that group only to the level experienced by the part of the group with water fluoride already at 0.7 mg/L. For example, based on the 1986-1987 data as reported by Heller et al. (1997), reducing fluoride concentrations in fluoridated community water would bring the fluorosis prevalence for that group down from about 30% (for the 0.7-1.2 mg/L group; Fig. 1) to about 27% (for 0.7 mg/L; see Fig. 2 of the Heller et al. paper), a relatively small decrease. However, elimination of fluoridation entirely, for the whole population, would be expected to bring the fluorosis prevalence down to that of the low-fluoride population (e.g., for the 1986-1987 cohort, from 30% to around 13%; Fig. 1), a much more substantial decrease.

HHS bases its recommendation partly on observations that water consumption among children does not depend greatly on ambient temperature (Federal Register 2011). The National Research Council (NRC 2006) also indicated that for much of the U.S. population, water consumption does not depend on outdoor temperature. However, the NRC also identified a number of population subgroups that have high water consumption, including people with high activity levels (more of a concern for older children and adults) and people with medical conditions such

as diabetes insipidus and diabetes mellitus (applicable to all ages). People in hot areas who are unable to afford air conditioning would be another subgroup of concern (applicable to all ages). Perhaps the most important population subgroup is composed of infants fed formula prepared with tap water. A substantial number of infants have water consumption rates in excess of 0.1 L/kg/day (100 mL per kg body weight per day; NRC 2006; EPA 2004a). At the proposed fluoride concentration of 0.7 mg/L in drinking water, these infants would still have fluoride intakes at and above 0.07 mg/kg/day, and some will exceed 0.15 mg/kg/day (NRC 2006). The only U.S. study to have looked at dental fluorosis and individual fluoride intake at various ages (the Iowa study) reported that for children with fluoride intakes above 0.06 mg/kg/day during the first 3 years of life, fluorosis rates were as high as 50% (Hong et al. 2006b). Eight individuals in the cohort were considered to have severe fluorosis (Hong et al. 2006b); their individual intakes were not reported, so one must assume that they did not necessarily have the highest intakes of the cohort. Thus a large fraction of infants and young children fed formula made with fluoridated tap water can be expected to develop dental fluorosis even at a water fluoride concentration of 0.7 mg/L.

The National Research Council considers severe dental fluorosis to be an adverse health effect and reports the general consensus in the literature that both severe and moderate dental fluorosis should be prevented (NRC 2006). Health Canada (2009) considers moderate dental fluorosis to be an adverse effect. The Iowa study indicates that high fluoride intake during the first 2 years of life is most important with respect to development of dental fluorosis of the permanent maxillary central incisors (the "top front teeth")—the teeth that most affect a person's appearance—although fluoride intake up to at least 4 years old was also important (Hong et al. 2006a). The American Dental Association has issued a brief statement to the effect that parents should not prepare infant formula with fluoridated water if they are concerned about the possibility of their child developing dental fluorosis (ADA 2007). This is an admission that dental fluorosis is undesirable, and that fluoridated tap water is not "safe" for all individuals. The CDC (2005) reports a higher likelihood of moderate and severe fluorosis for minority and low-income children. HHS should remember that while encouraging breastfeeding of infants is certainly appropriate, in many family situations breastfeeding is not possible (e.g., in cases of adoption or of ill-health or death of the mother). Especially since most assistance programs for low-income families do not cover the cost of bottled water or ready-to-feed formula, it is essential that tap water be safe for use in infant formula, without putting infants at increased risk of dental fluorosis.

In summary, the change in recommended water fluoride concentration proposed by HHS, while definitely a step in the right direction, is unlikely to bring about a substantial change in the prevalence of dental fluorosis in the U.S. In particular, infants and young children fed formula made with fluoridated tap water can still be expected to have high rates of dental fluorosis in their permanent teeth. Children with diabetes insipidus or diabetes mellitus and children in hot areas whose homes are not air conditioned can also be expected to have a substantial risk of developing dental fluorosis. To bring about a significant decrease in the prevalence and severity of dental fluorosis, HHS should recommend elimination of community water fluoridation throughout the entire U.S.

(2) The HHS recommendation does not address a number of other health concerns for the American population with respect to fluoride exposures.

The HHS recommendation addresses only dental fluorosis, while ignoring a long list of other health concerns for the U.S. population. Dental fluorosis itself has been associated with increased risks of various adverse health effects, including thyroid disease, lowered IQ, and bone fracture (Alarcón-Herrera et al. 2001; Zhao et al. 1996; Li et al. 1995; Lin et al. 1991; Desai et al. 1993; Yang et al. 1994; Jooste et al. 1999; Susheela et al. 2005). To the best of my knowledge, no studies in the U.S. or Canada have looked for associations between dental fluorosis and risk of other adverse effects. However, the failure to look for adverse health effects does not demonstrate the absence of adverse health effects.

The National Research Council (2006) indicated that the Environmental Protection Agency's (EPA's) present drinking water standards for fluoride (maximum contaminant level goal [MCLG] and maximum contaminant level [MCL], both at 4 mg/L) are not protective of human health, based on preventing severe dental fluorosis, stage II skeletal fluorosis, and increased risk of bone fractures. Given the wide range of water intake within the American population and the presence of other sources of fluoride intake, one can reasonably expect that a "safe" level of fluoride in drinking water would be at least a factor of 10 below the "unsafe" level of 4 mg/L. EPA's MCLG is defined as a "non-enforceable health goal which is set at a level at which no known or anticipated adverse effect on the health of persons occurs and which allows an adequate margin of safety" (EPA 2006). Dental fluorosis, skeletal fluorosis, and increased risk of bone fracture are all reasonably well known and acknowledged adverse health effects from fluoride exposure. However, EPA is also required to consider the "anticipated" adverse effects (which may occur at lower levels of fluoride exposure than the "known" effects) and allow for an adequate margin of safety. HHS should insist that EPA properly consider all of the anticipated adverse health effects, with an adequate margin of safety. The proposed HHS recommendation for water fluoridation at 0.7 mg/L is not adequate to protect against known or anticipated adverse effects and does not allow an adequate margin of safety to protect young children, people with high water consumption, people with kidney disease (resulting in reduced excretion of fluoride), and other potentially sensitive population subgroups.

In addition to the "known" adverse health effects of dental fluorosis, skeletal fluorosis, and increased risk of bone fracture, "anticipated" adverse health effects from fluoride exposure or community water fluoridation include (but are not limited to) carcinogenicity, genotoxicity, endocrine effects, increased blood lead levels, and hypersensitivity (reduced tolerance) to fluoride. These effects (described in more detail below) are not as well studied as the dental and skeletal effects, which should indicate that a greater margin of safety is necessary to ensure protection of the population—"in the face of uncertain evidence it is important to act in a manner that protects public health" (Tickner and Coffin 2006). In addition, it should be noted that some of these effects may occur at lower fluoride exposures than those typically associated with dental or skeletal effects, such that protection against the dental or skeletal effects does not necessarily ensure protection against other anticipated adverse health effects. Again, elimination of community water fluoridation is the best way to reduce fluoride exposures to a level at which adverse health effects are unlikely.

A few comments regarding the interpretation of the available fluoride studies may be helpful. As Cheng et al. (2007) have described, a "negative" study may simply mean that the study was not

sufficiently sensitive to demonstrate a moderate (as opposed to large) effect. This is often due to use of too small a sample size. In addition, study populations are often grouped by community, water source, or fluoride concentration in the water, rather than by individual intake. Due to the wide variation in drinking water intake, this approach results in study groups with overlapping intakes and makes it difficult to detect dose response relationships that do in fact exist.

The few studies that have looked at age-dependent exposure to fluoride have found increased risks of adverse effects (e.g., Bassin et al. 2006 for osteosarcoma; Danielson et al. 1992 for hip fracture risk); studies that have not looked at age-dependent exposure cannot be assumed to provide evidence of no effect. Similarly, studies that have used a measure of current exposure where a cumulative measure would be more appropriate, or vice versa, cannot be assumed to demonstrate lack of an effect.

Studies of fluoride toxicity in laboratory animals are sometimes dismissed as irrelevant because the exposures or fluoride concentrations used were higher than those expected for humans drinking fluoridated tap water. It is important to know that animals require much higher exposures (5-20 times higher, or more; see NRC 2006; 2009) than humans to achieve the same effects or similar fluoride concentrations in bone or serum. In other words, humans are considerably more sensitive to fluoride than are most animal species that have been studied.

A number of adverse health effects can be expected to occur in at least some individuals when estimated average intakes of fluoride are around 0.05 mg/kg/day or higher (NRC 2006; 2009). For persons with iodine deficiency, average intakes as low as 0.01-0.03 mg/kg/day could produce effects (NRC 2006). The next few sections briefly summarize some (not all) of the adverse health effects, known and anticipated, that should be considered in any reevaluation of the drinking water standards for fluoride. Most of these effects have been reviewed in detail by the NRC (2006), although the NRC did not specifically evaluate health risks over the whole range of fluoride intakes or attempt to identify a "safe" level of fluoride exposure.

Skeletal fluorosis

Bone fluoride concentrations in the ranges reported for stage II and III skeletal fluorosis will be reached by long-term fluoride exposures of 0.05 mg/kg/day or higher (estimated from NRC 2006). Bone fluoride concentrations, radiologic changes, and symptoms are not clearly correlated (Franke et al. 1975), and most U.S. studies do not categorize cases by stage. Recent case reports include fluorosis attributed to excessive ingestion of tea or toothpaste (Whyte et al. 2005; Hallanger Johnson et al. 2007; Kurland et al. 2007). Most of the literature addresses high fluoride exposures over a few years; there has been essentially no investigation of effects of low exposures over many years and no effort to identify fluorosis of any stage in the U.S. "Arthritis" (defined as painful inflammation and stiffness of the joints) is the leading cause of disability in the U.S., currently affects at least 46 million adults in the U.S. (including 50% of the population > 65 years old), and is expected to affect 67 million adults in the U.S. by 2030 (CDC 2006). The possibility that a sizeable fraction of "bone and joint pain" or "arthritis" in U.S. adults is attributable to fluoride exposure has not been addressed, although it is plausible, given what is known about fluoride intakes.

Increased risk of bone fractures

The NRC (2006) concluded that lifetime exposure to fluoride at an estimated average daily intake of 0.08 mg/kg/day (average adult fluoride intake with water at 4 mg/L) is likely to result in higher bone fracture rates, and the available information suggests an increased likelihood of bone fracture for daily fluoride intakes of 0.05 mg/kg/day (average adult fluoride intake at 2 mg/L). The Agency for Toxic Substances and Disease Registry (ATSDR) has identified a chronic-duration Minimal Risk Level (MRL) for oral exposure to fluoride of 0.05 mg/kg/day, based on an increased risk of bone fracture (ATSDR 2003). The NRC's findings (NRC 2006) indicate that the ATSDR's MRL is not protective enough. The available studies consider fluoride intake only in terms of the concentration in the local drinking water, and most use fluoridated water (1 mg/L, corresponding to an average daily intake of 0.03 mg/kg/day for adults) as a control. Thus there is probably considerable overlap in exposures between groups, making effects more difficult to distinguish, and the entire dose response range of interest has not been well studied. The findings in humans are consistent with animal studies that have found increased brittleness of bones with increased fluoride exposure (Clark and Mann 1938; Turner et al. 1997; 2001).

Danielson et al. (1992) reported an increased relative risk for hip fracture in a fluoridated area of 1.27 (95% CI 1.08-1.46) for women and 1.41 (95% CI 1.00-1.81) for men. These authors reported a difference between women exposed to fluoride prior to menopause and those exposed afterwards. For women exposed prior to menopause, the fracture risk was considerably higher than for those not exposed to fluoride. Many studies of fracture risk have not looked at age-specific exposure, or have involved women exposed only after menopause, when fluoride uptake into bone is probably substantially lower.

The Iowa study reported effects on bone mineral concentration and bone mineral density with average childhood fluoride intakes of 0.02-0.05 mg/kg/day (Levy et al. 2009). Linear correlation between dental fluorosis and risk of bone fracture has been reported for children and adults (Alarcón-Herrera et al. 2001). Bone fracture rates in children in the U.S. may be increasing (e.g., Khosla et al. 2003), but fluoride exposure has not been examined as a possible cause or contributor.

Carcinogenicity

Three U.S. courts have found water fluoridation to be injurious to human health, specifically that it may cause or contribute to the cause of cancer and genetic damage (described in detail by Graham and Morin 1999). The NRC's committee on fluoride toxicology unanimously concluded that "Fluoride appears to have the potential to initiate or promote cancers," even though the overall evidence is "mixed" (NRC 2006). Referring to the animal studies, the committee also said that "the nature of uncertainties in the existing data could also be viewed as supporting a greater precaution regarding the potential risk to humans." The committee discussed the limitations of epidemiologic studies, especially ecologic studies (those in which group, rather than individual, measures of exposure and outcome are used), in detecting small increases in risk—in other words, the studies are not sensitive enough to identify small increases in cancer risk; therefore a "negative" study does not necessarily mean that there is no risk (see also Cheng et al. 2007).

While the NRC did not assign fluoride to a specific category of carcinogenicity (i.e., known, probable, or possible), the committee did not consider either "insufficient information" or "clearly not carcinogenic" to be applicable. The committee report (NRC 2006) includes a discussion of how EPA establishes drinking water standards for known, probable, or possible carcinogens; such a discussion would not have been relevant had the committee not considered fluoride to be carcinogenic. The question becomes one of how strongly carcinogenic fluoride is, and under what circumstances.

The case-control study by Bassin et al. (2006) is the only published study thus far to have looked at age-dependent exposure to fluoride. This study reported a significantly elevated risk of osteosarcoma in boys as a function of estimated age-specific fluoride intake. Osteosarcoma is a bone cancer that commonly results in amputation of an affected limb and may result in death. At the very least, this study indicates that similar studies of pediatric osteosarcoma that have not looked at age-dependent intake cannot be considered to show "no effect."

While a few other studies (e.g., Gelberg et al. 1995) have looked at individual fluoride exposure (as opposed to group or ecologic measures of exposure), these have looked at total fluoride exposure until time of diagnosis or treatment. Given that there is a "lag time" of a few years between onset of a cancer and its diagnosis, use of cumulative fluoride exposure until time of diagnosis is potentially misleading, as fluoride exposure during the last several years (during the "lag time") cannot have contributed to the initiation of a cancer but could have a significant effect on the estimate of cumulative fluoride exposure.

The 1990 National Toxicology Program (NTP) study on sodium fluoride officially concluded that "there was *equivocal evidence of carcinogenic activity* of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas in dosed animals" (NTP 1990; italics in the original). According to the published report, a "small number of osteosarcomas occurred in mid- and high-dose male rats. These neoplasms occurred with a significant dose response trend, but at a rate within the upper range of incidences previously seen in control male rats in NTP studies" (NTP 1990). It is important to realize that the historic controls from previous studies had not had the special low-fluoride diet used for this study, and therefore more properly constitute a low- to mid-range exposed group rather than a control group. This and other concerns were described in a memo within the Environmental Protection Agency (Marcus 1990) and reported in the press (Hileman 1990). These concerns and the testimony before the U.S. Senate of the union representing EPA scientists (Hirzy 2000) should be taken seriously by the HHS.

In humans, osteosarcomas tend to occur most commonly in young people (pediatric cases) or the very old (adult or geriatric cases), with a higher incidence in males than in females (Bassin et al. 2006). Sergi and Zwerschke (2008) indicate that 60-75% of cases are in patients between 15 and 25 years old. In the NTP 2-year study, fluoride exposure was begun when the animals were 6 weeks old, as is typical for NTP and similar studies (Hattis et al. 2004). Puberty in the rat typically occurs at about 32 days of age in females and 42 days in males (e.g., Gray et al., 2004; Evans 1986). Thus, the age of 6 weeks in the NTP study probably corresponds to pubertal or post-pubertal animals. The cases of osteosarcoma in the rats were reported in the late stages of the test, and probably corresponded to geriatric osteosarcomas in humans. In Bassin's study, the age range for which the fluoride-osteosarcoma association was most apparent was for exposures at ages 4-12 years, with a peak for exposures at age 6-8 years (Bassin et al. 2006). Very likely,

the fluoride exposures in most of the animal studies have started after the age corresponding to the apparent most susceptible age in humans, and thus these animal studies may have completely missed the most important exposure period with respect to initiation of the majority of human osteosarcomas. Therefore, this animal study cannot be interpreted as showing no evidence of causation for pediatric osteosarcoma, although, properly interpreted, it does show evidence for causation of geriatric osteosarcoma.

Genotoxicity

Genotoxicity, or the ability to damage the genetic material (genes and chromosomes) of cells, is considered indicative of potential carcinogenicity. A number of mammalian *in vitro* systems have shown dose-dependent cytogenetic or cell transformational effects from fluoride exposure (reviewed by NRC 2009). Several reports suggest an indirect or promotional mechanism, e.g., inhibition of DNA synthesis or repair enzymes, rather than a direct mutagenic effect (Lasne et al. 1988; Aardema et al. 1989; Aardema and Tsutsui 1995; Meng and Zhang 1997). Human cells seem to be much more susceptible to chromosome damage from fluoride than are rodent cells (Kishi and Ishida 1993).

A recent paper by Zhang et al. (2009) describes a new testing system for potential carcinogens, based on induction of a DNA-damage response gene in a human cell line. Sodium fluoride tests positive in this system, as do a number of other known carcinogens, representing a variety of genotoxic and nongenotoxic carcinogenic mechanisms. Known noncarcinogens—chemicals not associated with carcinogenicity—did not test positive. The system described by Zhang et al. (2009) is considerably more sensitive than the older systems for most chemicals examined; a positive effect was seen at a fluoride concentration of about 0.5 mg/L, or a factor of 10 lower than in other systems.

A fluoride concentration of 0.5 mg/L in urine will routinely be exceeded by many people consuming fluoridated water (NRC 2006); for people with substantial fluoride intake, serum fluoride concentrations may also reach or exceed 0.5 mg/L. Acute fluoride exposures (e.g., accidental poisoning, fluoride overfeeds in drinking water systems) have resulted in fluoride concentrations in urine well in excess of 5 mg/L in a number of cases (e.g., Penman et al. 1997; Björnhagen et al. 2003; Vohra et al. 2008). Urine fluoride concentrations can also exceed 5 mg/L if chronic fluoride intake is above about 5-6 mg/day (0.07-0.09 mg/kg/day for an adult; based on NRC 2006). Thus, kidney and bladder cells are probably exposed to fluoride concentrations in the ranges at which genotoxic effects have been reported *in vitro*, especially when the more sensitive system of Zhang et al. (2009) is considered. Based on the results of Zhang et al. (2009), most tissues of the body are potentially at risk if serum fluoride concentrations reach or exceed 0.5 mg/L. In addition, cells in the vicinity of resorption sites in fluoride-containing bone are potentially exposed to very high fluoride concentrations in extracellular fluid (NRC 2006) and thus are also at risk for genotoxic effects.

Endocrine effects

The NRC (2006) concluded that fluoride is an endocrine disruptor. Endocrine effects include altered thyroid function or increased goiter prevalence (at fluoride intakes of 0.05-0.1 mg/kg/day,

or 0.01-0.03 mg/kg/day with iodine deficiency), impaired glucose tolerance (at fluoride intakes above 0.07 mg/kg/day), a decrease in age at menarche in girls in fluoridated towns, and disruptions in calcium metabolism (calcitonin and parathyroid function, at fluoride intakes of 0.06-0.15 mg/kg/day or higher). ATSDR's toxicological profile for fluoride (ATSDR 2003) refers to an animal study of thyroid function that would give a lower MRL (value not given) than the MRL derived for bone fracture risk (0.05 mg/kg/day).

Thyroid dysfunction and Type II diabetes presently pose substantial health concerns in the U.S. (NRC 2006). Of particular concern is an inverse correlation between subclinical maternal hypothyroidism and the IQ of the offspring. In addition, maternal subclinical hypothyroidism has been proposed as a cause of or contributor to development of autism in the child (Román 2007; Sullivan 2009). Steingraber (2007) has described the decrease in age at puberty of U.S. girls and the associated increased risk of breast cancer. Calcium deficiency induced or exacerbated by fluoride exposure may contribute to other health effects (NRC 2006).

Increased blood lead levels

An increased likelihood of elevated blood lead levels is associated with use of silicofluorides (usually H_2SiF_6 or Na_2SiF_6) as the fluoridating agent (NRC 2006; Coplan et al. 2007). Approximately 90% of people on fluoridated water are on systems using silicofluorides (NRC 2006). The chemistry and toxicology of these agents, especially at low pH (e.g., use of fluoridated water in beverages such as tea, soft drinks, or reconstituted fruit juices), have not been adequately studied (NRC 2006). Associations between silicofluoride use and biological effects in humans have been reported, in particular, elevated levels of blood lead in children and inhibition of acetylcholinesterase activity (reviewed by Coplan et al. 2007). A recent study in rats found significantly higher concentrations of lead in both blood and calcified tissues of animals exposed to both silicofluorides and lead (Sawan et al. 2010).

In addition to biological effects of silicofluorides, the interaction of silicofluorides (as the fluoridating agent) and disinfection agents (specifically, chloramines) also increases the leaching of lead from plumbing fixtures into drinking water (Maas et al. 2005; 2007). A recent Congressional investigation discussed the failure of the CDC to publicize information about high lead levels in drinking water and children's blood in Washington, D.C. (Leonnig 2010). The interaction of silicofluorides and chloramines is the probable explanation for the high lead levels (Maas et al. 2005; 2007). EPA considers lead to be a probable human carcinogen and to have no practical threshold with respect to neurotoxicity (EPA 2004b)—in other words, there is considered to be no safe level of lead exposure, and the MCLG for lead is zero (EPA 2006a).

Additional adverse health effects

Fluoride intake is likely to affect the male reproductive-hormone environment, beginning at intakes of around 0.05 mg/kg/day (reviewed by NRC 2009). A "safe" intake with respect to male reproductive effects is probably somewhere below 0.03 mg/kg/day.

The NRC has reviewed the possible association between exposure to fluoridated water (approximately 0.02 mg/kg/day for adults) and increased risk of Down syndrome (trisomy 21) in children of young mothers, discussed a possible mechanism, and recommended further study

(NRC 2006). Fetuses with Down syndrome are less likely to survive to birth, due both to higher natural fetal loss and to a high rate of pregnancy termination (Buckley and Buckley 2008; Forrester and Merz 1999; Siffel et al. 2004; Biggio et al. 2004).

Hypersensitivity or reduced tolerance to fluoride has been reported for exposure to fluoridated water (approximately 0.02 mg/kg/day for adults) or use of fluoride tablets (approximately 1 mg/day). Symptoms include skin irritation, gastrointestinal pain and symptoms (nausea, vomiting, diarrhea, constipation), urticaria, pruritus, stomatitis, chronic fatigue, joint pains, polydipsia, headaches, and other complaints (Waldbott 1956; 1958; Feltman and Kosel 1961; Grimbergen 1974; Petraborg 1977; Spittle 2008; reviewed by NRC 2006). Patients were often unaware that their drinking water contained fluoride. Symptoms improved with avoidance of fluoridated water and recurred with consumption of fluoridated water or with experimental challenge with sodium fluoride. Double-blind tests of patients have confirmed hypersensitivity to fluoride (Grimbergen 1974; Waldbott 1956; 1958). Many of the observed symptoms represent true allergic phenomena, while others (e.g., gastrointestinal symptoms) could be due to a lower level of tolerance for fluoride (intoxication at lower exposure; Waldbott 1956; 1958).

(3) Available data do not support a role of community water fluoridation in improving dental health.

HHS continues to consider community water fluoridation to be important in the prevention of dental caries (Federal Register 2011). However, the question of whether water fluoridation actually produces a benefit requires further attention.

The University of York has carried out perhaps the most thorough review to date of human studies on effects of fluoridation. Their work (McDonagh et al. 2000) is cited by HHS and others as showing the safety and efficacy of water fluoridation, but it actually does neither (Wilson and Sheldon 2006; Cheng et al. 2007). The report mentions a surprising lack of high quality studies demonstrating benefits, and also finds little evidence that water fluoridation reduces socioeconomic disparities:

> Given the level of interest surrounding the issue of public water fluoridation, it is surprising to find that little high quality research has been undertaken. (McDonagh et al. 2000)
>
> Water fluoridation aims to reduce social inequalities in dental health, but few relevant studies exist. The quality of research was even lower than that assessing overall effects of fluoridation. (Cheng et al. 2007)
>
> Evidence relating to reducing inequalities in dental health was both scanty and unreliable. (Wilson and Sheldon 2006)

The apparent benefit is modest, about a 15% difference in the proportion of caries-free children (McDonagh et al. 2000). The American Dental Association (2005) states that "water fluoridation continues to be effective in reducing dental decay by 20-40%," which would translate to less than 1 decayed, missing, or filled permanent tooth (DMFT) in older children and adolescents (based on U.S. data from CDC 2005).

Neither McDonagh et al. (2000) nor the ADA (2005) mentions that fluoride exposure appears to delay the eruption of permanent teeth, although this has been known since the 1940s (Short 1944; NRC 2006). A delay in tooth eruption alters the curve of caries rates with respect to age and complicates the analysis of age-specific caries rates (Psoter et al. 2005; Alvarez 1995; Alvarez and Navia 1989). Komárek et al. (2005) have calculated that the delay in tooth eruption due to fluoride intake may explain the apparent reduction in caries rates observed when comparisons are made at a given age, as is usually done.

Most studies of benefits of fluoride intake or fluoridation have failed to account for a number of important variables, including individual fluoride intakes (as opposed to fluoride concentrations in the local water supplies), sugar intake, socioeconomic variables, and the general decline in caries rates over the last several decades, independent of water fluoridation status. When World Health Organization data on oral health of children in various countries are compared, similar declines in caries over time are seen in all developed countries, regardless of fluoridation status (Cheng et al. 2007; Neurath 2005).

The only peer-reviewed paper to be published from California's major oral health survey in the 1990s reported no association between fluoridation status and risk of early childhood caries (Shiboski et al. 2003). The paper did not address other types of caries.

A number of sources (reviewed by NRC 2006), including the CDC (2001), indicate that any beneficial effect of fluoride on teeth is topical (e.g., from toothpaste), not from ingestion. Featherstone (2000) describes mechanisms by which topical fluoride has an anti-caries effect and states that "[f]luoride incorporated during tooth development [i.e., from ingested fluoride] is insufficient to play a significant role in caries protection." Also:

> The fluoride incorporated developmentally—that is, systemically into the normal tooth mineral—is insufficient to have a measureable effect on acid solubility. (Featherstone 2000)
>
> The prevalence of dental caries in a population is not inversely related to the concentration of fluoride in enamel, and a higher concentration of enamel fluoride is not necessarily more efficacious in preventing dental caries. (CDC 2001)

Fluoride concentrations in drinking water or saliva are too low to be contributing significantly to a topical anti-caries effect, especially since most drinking water is not "swished" around the teeth before being swallowed. CDC (2001) states that "The concentration of fluoride in ductal saliva, as it is secreted from salivary glands, is low—approximately 0.016 parts per million (ppm) in areas where drinking water is fluoridated and 0.006 ppm in nonfluoridated areas. This concentration of fluoride is not likely to affect cariogenic activity."

The single study that has examined caries experience in relation to individual fluoride intakes at various ages during childhood (the Iowa study) has found no association between fluoride intake and caries experience; caries rates (% of children with or without caries) at ages 5 and 9 were similar for all levels of fluoride intake (Warren et al. 2009). The authors state that "the benefits of fluoride are mostly topical" and that their "findings suggest that achieving a caries-free status may have relatively little to do with fluoride *intake*" (emphasis in the original). Most of the children with caries had "relatively few decayed or filled surfaces" (Warren et al. 2009). The authors' main conclusion:

> Given the overlap among caries/fluorosis groups in mean fluoride intake and extreme variability in individual fluoride intakes, firmly recommending an "optimal" fluoride intake is problematic. (Warren et al. 2009).

The national data set collected in the U.S. in 1986-1987 (more than 16,000 children, ages 7-17, with a history of a single continuous residence) shows essentially no difference in caries rates in the permanent teeth of children with different water fluoride levels (Table 1; Fig. 2; data obtained from Heller et al. 1997; similar data can be obtained from Iida and Kumar 2009). Analysis in terms of mean DMFS (decayed, missing, or filled tooth surfaces) for the group (Fig. 3), as opposed to caries prevalence, shows an apparent 18% decrease between the low-fluoride (< 0.3 mg/L) and fluoridated (0.7-1.2 mg/L) groups. In absolute terms, this is a decrease of about 1/2 (0.55) of one tooth surface per child. One possible explanation is delayed tooth eruption, which was not considered in the study. Note that the mean DMFS for the highest fluoride group is higher than for either of the two intermediate groups, also indicating that DMFS scores are not solely a function of water fluoride concentration. When the data are examined by the distribution of DMFS scores (Fig. 4), no real difference in caries experience with respect to water fluoride concentration is observed.

The available data, responsibly interpreted, indicate little or no beneficial effect of water fluoridation on oral health. The HHS should not assume or suppose beneficial effects of community water fluoridation and should not continue to support or encourage water fluoridation, even at the proposed level of 0.7 mg/L.

(4) HHS remains in the precarious position of recommending indiscriminate administration of a drug to the American population, without individual evaluation of need, appropriate dose, efficacy, or side effects.

The U.S. Food and Drug Administration (FDA) considers fluoride in toothpaste to be a non-prescription drug (e.g., FDA undated-a; undated-b) and fluoride "supplements" (usually tablets or lozenges) to be prescription drugs (e.g., Medline Plus 2008). The goal of community water fluoridation is to provide a dental health benefit to individuals and to the population generally (Federal Register 2010), and EPA's recent reference (Federal Register 2010) to a "treated population" acknowledges this use of drinking water systems to deliver a drug to entire populations. This in effect puts local governments and water treatment personnel in charge of administering a chemical (i.e., a drug) to the population in an effort to improve individual and population health (Cross and Carton 2003; Cheng et al. 2007). In this context, HHS should be aware that many people consume more fluoride from tap water than from either non-prescription (toothpaste) or prescription (tablets or lozenges) fluoride sources, without any monitoring for either efficacy or side effects, without the "drug information" or warning labels generally provided for drugs, and without any semblance of informed consent.

In addition, most fluoridation operations use fluorosilicates (usually H_2SiF_6 or Na_2SiF_6) rather than sodium fluoride (NaF). As described above, the chemistry and toxicology of these compounds have not been adequately studied, although important differences in biological effects between silicofluorides and simple fluorides (e.g., NaF) have been reported (Coplan et al. 2007; NRC 2006; Masters et al. 2000; Masters and Coplan 1999). HHS no doubt is aware of the variety of effects (both targeted effects and side effects) associated with fluoride-containing,

FDA-approved, pharmaceutical agents (e.g., Prozac, Sevoflurane, Fenfluramine). The NRC (2006) discussed the increased toxicity of aluminofluorides and beryllofluorides vs. fluoride alone, as well as the different mechanisms of action of the different chemical combinations. Thus it is irresponsible for HHS to recommend addition of fluoride, or a particular concentration of fluoride to be added, without a comprehensive review of the substances (H_2SiF_6 or Na_2SiF_6,) that are actually added. HHS should also be aware that fluoridation chemicals often contain impurities such as lead and arsenic, for which EPA has set MCLGs of zero (EPA 2006), such that a water supplier is actually adding contaminants for which the ideal maximum amount in drinking water is zero.

HHS refers to a plan to "enhance surveillance of dental caries, dental fluorosis, and fluoride intake" (Federal Register 2011). CDC conducts periodic biomonitoring studies (e.g., CDC 2009), in which a number of chemicals in blood or urine of members of the U.S. population are measured. The HHS has made no mention of whether fluoride will be added to the list of chemicals, although this was recommended by the National Research Council (NRC) in 2006 and would be an obvious action to take if CDC or HHS is truly interested in knowing how much fluoride exposure is received by the American public.

In summary, HHS should not continue to promote or encourage uncontrolled exposure of the U.S. population to a drug that, at best, is not appropriate for many individuals (e.g., those who do not want it, those whose water consumption is high, formula-fed infants) and for which the risks are inadequately characterized and inadequately disclosed to the public. HHS should act in the interest of public health by eliminating community water fluoridation in the U.S. at the earliest possible date.

Table 1. Caries prevalence and fluorosis prevalence with water fluoride concentration.[a]

Water fluoride concentration mg/L	Children with no caries %	Mean DMFS score[b]	Children with fluorosis[c] %	Mean severity of fluorosis[d]
< 0.3	53.2	3.08	13.5	0.30
0.3 - < 0.7	57.1	2.71	21.7	0.43
0.7 - 1.2	55.2	2.53	29.9	0.58
> 1.2	52.5	2.80	41.4	0.80

[a] Data for permanent teeth of children ages 5-17 (caries experience and DMFS score) or 7-17 (dental fluorosis), with a history of a single residence, from Tables 2 and 5 of Heller et al. (1997).
[b] Decayed, missing, or filled tooth surfaces (permanent teeth).
[c] Includes very mild, mild, moderate, and severe fluorosis, but not "questionable."
[d] Dean's Community Fluorosis Index.

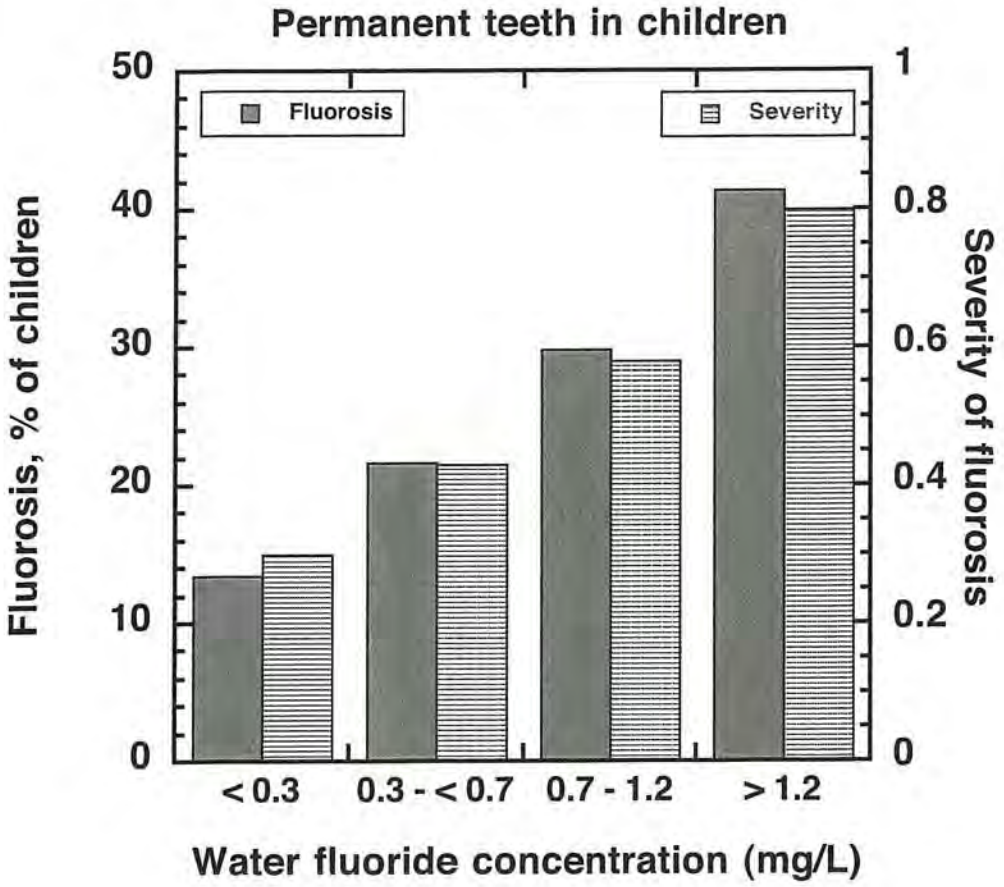

Fig. 1. Fluorosis prevalence and severity with water fluoride concentration for children ages 7-17 with a history of a single continuous residence. Data are shown as (left) % of total children having fluorosis (very mild, mild, moderate, or severe, but not questionable) or (right) severity of fluorosis by Dean's Community Fluorosis Index. Numerical values are provided in Table 1 of these comments and were obtained from Table 5 of Heller et al. (1997).

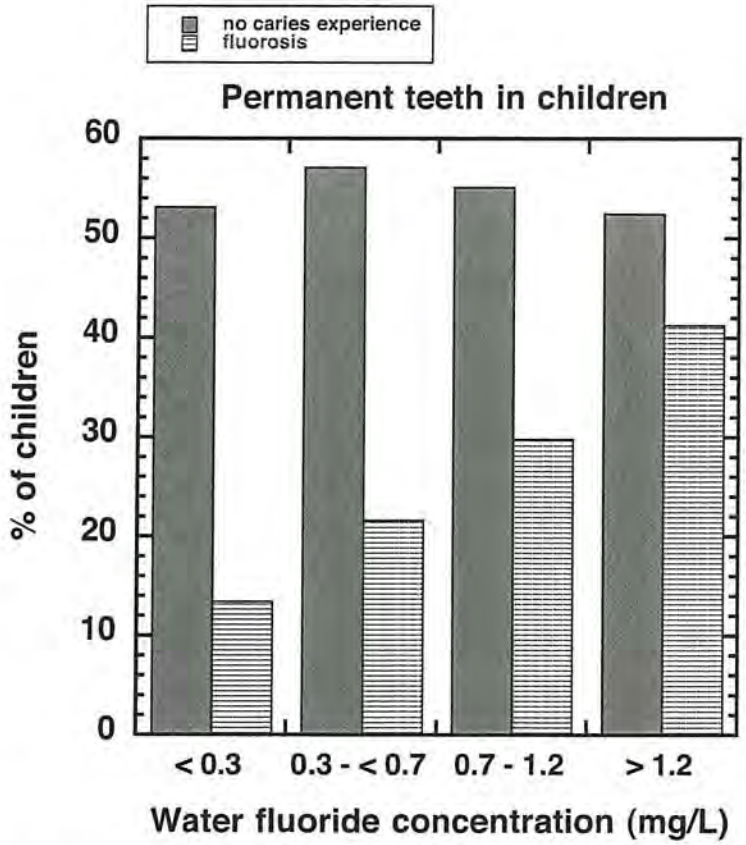

Fig. 2. Percent of children with no caries experience in the permanent teeth (DMFS = 0) and with fluorosis, with respect to water fluoride concentration. Data are shown as % of total children having no caries experience (blue) or having fluorosis (very mild, mild, moderate, or severe, but not questionable; red). Numerical values are provided in Table 1 of these comments and were obtained from Tables 2 and 5 of Heller et al. (1997).

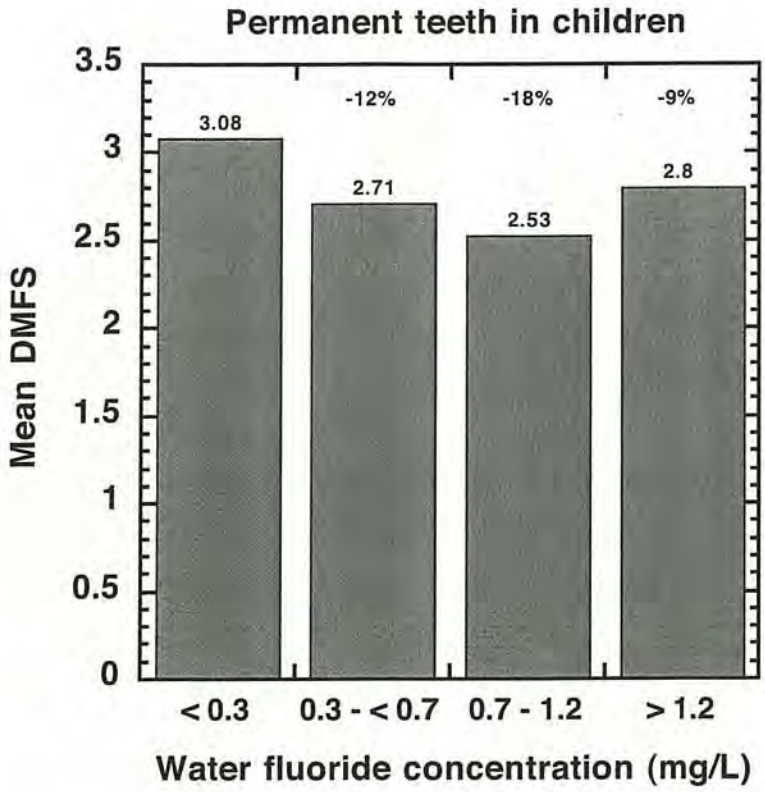

Fig. 3. Mean DMFS score (decayed, missing, or filled permanent tooth surfaces in permanent teeth), with respect to water fluoride concentration. Numerical values are provided in Table 1 of these comments and were obtained from Table 2 of Heller et al. (1997). The percent difference with respect to the lowest fluoride group is also provided.

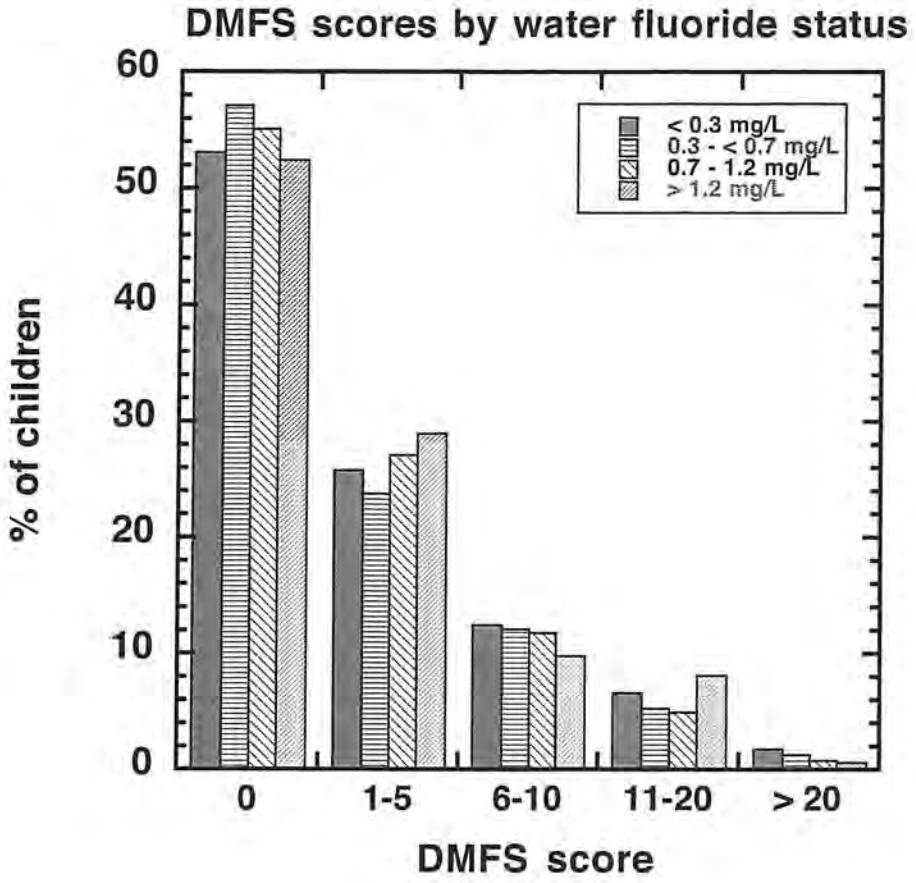

Fig. 4. Percent of children by DMFS score, with respect to water fluoride concentration. Data are shown as % of total children in a given group according to the number of decayed, missing, or filled tooth surfaces in the permanent teeth (DMFS). Data were obtained from Table 2 of Heller et al. (1997).

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