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December 16, 2005

Public Information and Records Integrity Branch (PIRIB) (7502C)
Attention: **Docket ID Number OPP-2005-0174**
Office of Pesticide Programs (OPP)
Environmental Protection Agency, 1200 Pennsylvania Ave., NW.
Washington, DC 20460-0001

James J. Jones
Director, Office of Pesticide Programs
U.S. EPA
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

Re: Docket ID Number OPP-2005-0174
Objections and Request for a Hearing Concerning Sulfuryl Fluoride Tolerances

Dear Director Jones,

This is in response to your letter of June 4, 2005, to Fluoride Action Network and Beyond Pesticides.

Of the issues delineated in your letter, we consider “Issue 9. EPA has failed to protect [certain] subpopulations" relevant to our Objections. We have expanded on our reasons in the attached submission.

We will not pursue issues 1 through 8 as stated in your letter.

Jonathan Fleuchaus suggested to us that EPA would prefer to combine the two “Objections and Request for Hearing” submitted in March 2004 and September 2005. We agree to this.

Due to the fact that we have not received a copy of the Health Risk Assessment that was used to set tolerances in the July 15, 2005, Final Rule, we request that we be given the opportunity to submit more issues, or amend the issues we have identified, that require adjudication.

Having reviewed our 2004 and 2005 appeals and the comments contained in your letter, we are satisfied that the vast bulk and core of the evidence we have presented to the EPA qualifies us for an evidentiary hearing on this matter.

We believe that each of the issues we have identified in the attached submission raises material issues of fact, which, if resolved in our favor would compel revocation of each of the tolerances identified in our objections.

In conjunction with each of these issues we have described our factual contentions in detail. In each instance, our contentions are at odds with the positions of the Agency. We believe that each of these issues can only be resolved by means of an evidentiary hearing as contemplated by FFDCA Section 408(g)(2)(B). At such hearing it is our intention to present factual evidence in the form of documents and expert testimony to support each of the factual contentions identified in this submission.

Sincerely,

Paul Connett, Director
Fluoride Action Network

Richard Wiles, Sr. Vice President
Environmental Working Group
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Jay Feldman, Executive Director
Beyond Pesticides/National Coalition Against the Misuse of Pesticides
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Washington DC 2003

CC:

Jonathan Fleuchaus (2333A)
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Washington, DC 20460-0001

ATTACHMENTS

Submission: Issues for an Evidentiary Hearing Concerning Sulfuryl Fluoride Tolerances

Appendix A. Deaths from fumigation using sulfuryl fluoride “Vikane®”

Appendix B. FAN Drinking Water Analysis #1

Appendix C. FAN Drinking Water Analysis #2

References

Hard copies of references

NOTE: THE COPIES OF THE REFERENCES ARE BEING SENT UNDER SEPARATE MAIL

Issues for an Evidentiary Hearing Concerning Sulfuryl Fluoride Tolerances

Submitted to US EPA by
Fluoride Action Network, Environmental Working Group, and Beyond Pesticides
December 15, 2005

INTRODUCTION

1. History of sufuryl fluoride use and proposed use.

Dow has marketed sulfuryl fluoride (SO_2F_2) as a fumigant in closed structures to control numerous insect pests and rodents since the 1950s. Since receiving approval from EPA in January 2004, Dow AgroSciences (Dow) is now using sulfuryl fluoride as a fumigant on raw and processed foods in warehouses and in food and feed processing plants as an alternative fumigant to methyl bromide (which Dow also manufactures) because of the latter's ozone layer depleting properties.

The following is the timeline for the first-time use of sulfuryl fluoride on food:

June 15, 2001	Notice of Dow's request to EPA for an Experimental Use Permit (EUP) for sulfuryl fluoride. Dow petitions EPA to establish a temporary tolerance for fluoride in/on walnut and sulfuryl fluoride in/on raisins. Dow requests EPA to establish an exemption from the requirement of a tolerance for fluoride in/on raisins (US EPA, 2001a).
September 5, 2001	EPA denies Dow's request for a tolerance exemption for fluoride in/on raisins, and instead propose the following temporary tolerances: fluoride at 30 ppm in/on raisins and 12 ppm in/on walnut, and a tolerance for sulfuryl fluoride in/on walnut at 2 ppm and in/on raisins at 0.004 ppm (US EPA, 2001).
September 19, 2001	Comments submitted to EPA on Sept 5th proposed temporary tolerances (Connett E, 2001).
February 7, 2002	EPA approves temporary tolerances, proposed September 5, 2001, to support Dow's EUP (US EPA, 2002).
February 15, 2002	Dow petitions EPA for tolerances for more than 40 raw and processed food commodities (US EPA, 20002a).
March 18, 2002	FAN submits comments to EPA on Dow's petition of February 15, 2002 (Connett P, Connett E, 2002).
March 27, 2002	EPA approves Dow's request for an EUP (US EPA, 2002b).
April 8, 2002	FAN submits Objections and a Request for Hearing on EPA's February 7, 2002, temporary pesticide tolerances (Connett E, Connett P, 2002).
Jan 23, 2004	EPA establishes the first-time food tolerances for residues of sulfuryl fluoride from post-harvest fumigation. EPA approves the highest food tolerances for fluoride residues in its history. EPA sets a precedent by allowing a dosage of fluoride for infants that is five times higher than for adults. EPA announces that Dow withdrew the EUP because "the California Department of Pesticide Regulation has not issued the necessary state authorization to allow the EUP to proceed..."

	EPA also states that because the EUP has been withdrawn by Dow, the Objections and Request for Hearing submitted by FAN are moot. However, EPA publishes 5 documents in response to FAN's objections (US EPA, 2004).
March 23, 2004	Objections and a Request for Hearing submitted to EPA on the January 2004 tolerances from FAN and Beyond Pesticides (Connett P et al., 2004).
March 4, 2005	Dow petitions EPA for tolerances for over 600 food commodities (US EPA 2005a).
April 19, 2005	FAN submits comments to EPA on Dow's March 4, 2005, petition for tolerances (Connett E, 2005).
June 2, 2005	EPA's first response to the March 2004 Objections and Request for Hearing submitted by FAN and Beyond Pesticides (Jones JJ, 2005).
July 15, 2005	EPA issues new tolerances for 219 processed food commodities, and a 70 ppm fluoride tolerance for all processed food not specifically cited. At this time they issue the highest- ever tolerance for fluoride residues: 900 ppm in/on dried egg (US EPA, 2005).
September 11, 2005	Objections and Request for Hearing submitted to EPA on July 2005 tolerances from FAN, the Environmental Working Group, and Beyond Pesticides (Neurath et al., 2005).

At each and every stage in the process to use sulfuryl fluoride as a food fumigant, FAN has engaged EPA on the problems inherent with increased fluoride exposure. In 2004, Beyond Pesticides joined FAN in submitting Objections and a Request for Hearing, and in September 2005 the Environmental Working Group joined with FAN and Beyond Pesticides in a formal appeal of the tolerances set by EPA.

2. Why FAN has intervened

FAN has intervened because it is concerned about the introduction of a major source of fluoride into the food supply.

Fluoride is the main product of sulfuryl fluoride degradation and that is why EPA has given two tolerances for its use: fluoride and sulfuryl fluoride. In so doing, EPA has set the highest tolerances for residues of fluoride in its history.

Putting another new source of fluoride into the daily lives of Americans is extremely unwise because it is clear that many children, and adults, are already overexposed (see issues 1 & 2), and because, based on a growing body of scientific research, this overexposure can not be considered safe (see issues 3-26).

3. Background on the toxicity of sulfuryl fluoride.

Sulfuryl fluoride is an odorless, colorless gas at room temperature (boiling point –55 ^{o} C) and relatively unreactive chemically. It is slowly hydrolyzed by water to yield the sulfate and fluoride ions. Its stability and its ability to absorb infrared radiation makes it a candidate for a global warming gas. In fact, Californian authorities have stated:

> "It is entirely possible that sulfuryl fluoride has a long or very long atmospheric lifetime and should therefore be considered a greenhouse gas: (CA EPA, 2005 b, page 8)

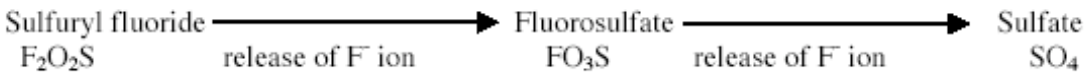
Sulfuryl fluoride is moderately water soluble (0.075 grams per 100 grams) and about ten times more soluble in vegetable oil.

Most of the toxicological studies have been conducted on the inhalation exposure pathway. Little toxicological testing has been done in which animals are given sulfuryl fluoride in their diet.

The most disturbing toxicological finding from the inhalation studies on four different animal species (rats, mice, rabbits, and dogs) is damage to the brain. According to a 2005 Health Risk Assessment on Vikane performed by the California EPA:

> "At non-lethal concentrations, neurotoxicity was observed in rats, mice, rabbits, and dogs. With acute to 2 weeks of exposures, clinical signs observed in these species included tremors, lethargy, respiratory effects, incapacitation, tetany, and convulsion. At the lowest-observed effect level, animals treated with sulfuryl fluoride for two weeks showed tissue damage in the kidney (rats), brain (rabbits, mice), and respiratory tract (rabbits and dogs). After 13 weeks of inhalation exposure, the brain was the primary target for sulfuryl fluoride toxicity in all species studied (rats, mice, rabbits, and dogs). The most common lesion was vacuoles in the cerebrum. Other effects reported were nasal tissue inflammation (rats and rabbits), kidney hyperplasia (rats), lung histiocytosis (rats), thyroid hypertrophy (mice), and fluorosis (rats).
>
> After chronic exposure, the primary target tissue for sulfuryl fluoride was the brain and the respiratory tract in rats, mice, and dogs. As with subchronic exposure, brain vacuoles were observed in the cerebrum ." (CA EPA, 2005, page 3)

It is generally accepted that the main cause of sulfuryl fluoride's toxicity is the generation of fluoride ion when sulfuryl fluoride is metabolized in biological systems or hydrolyzed in water.



A key question is how sulfuryl fluoride enters the brain. It may simply enter because it is more soluble in fat than water; it may enter via an interaction with a protein within the blood barrier, since it is known to have a high affinity for protein or it may enter via the sulfate ion transport mechanism. While it is uncharged (the sulfate ion has two negative charges) it has a very similar size and shape to this essential nutrient. Whatever the mechanism, however, it is clear that sulfuryl fluoride does enter the brain and, when there, can cause problems. Of key concern is that it can introduce the fluoride ion into the brain.

In 1962, Rachel Carson wrote her book 'The Silent Spring" which dealt largely with the problems posed to wildlife and human health by persistent organochlorine pesticides. The upshot of the book was the banning of DDT in 1972, followed by the banning of PCBs in 1979. This signaled a shift in the design of pesticides from long lasting and bio-accumulating substances with a relatively low toxicity to short lived compounds with high toxicity. Generally, this approach has had the result of lowering the long-term impacts on the environment but increased the health damage to applicators and local residents. Sufuryl fluoride seems to combine the worst of both approaches. On the one hand it is highly and acutely toxic, responsible for several deaths, and on the other, it produces not just a *persistent*, but a *permanent*, toxic and bio-accumulating metabolite.

The production of fluoride by sulfuryl fluoride when used as a fumigant for buildings and structures (i.e. as Vikane) has far less significance than when it is applied as a fumigant on food (i.e. as ProFume).

4. Background on the toxicity of fluoride.

It has been known since the first half of the twentieth century that fluoride, while being fairly benign from a chemical perspective (unlike its parent element fluorine), is extremely active biologically. It inhibits enzymes and forms numerous complexes with metal ions. The latter property means it has the potential to interfere with metal ions we need as well as getting toxic metal ions to places where they would not otherwise go. More recently it has been shown that the fluoride ion in the presence of a trace amount of aluminum ion can switch on G-proteins, a key step in the signaling mechanism of many water soluble hormones, neurotransmitters and growth factors (for a review see Li 2003).

While fluoride is still commonly assumed to be an "essential nutrient", the National Academies of Science has confirmed in 1989, 1993 and most recently in 1998, that this is not the case (NAS 1989; NRC 1993; Alberts 1998). Also, while it is still commonly assumed that fluoride's main benefits to teeth come from ingestion, the majority of dental researchers – as acknowledged by CDC in 1999 and 2001 – have confirmed that fluoride's primary, if not only, benefit to teeth comes from topical contact with the surface of the tooth.

Perhaps, however, the most revealing fact about fluoride is its near exclusion from mothers' milk. As noted by Ekstrand (1981), there appears to be a "physiological plasma-milk barrier against fluoride" which limits the transfer of fluoride from the bloodstream into milk. As a result, the level of fluoride in mother's milk is very low (0.005-0.011 ppm; IOM 1997), suggesting that "the newborn is actively protected against fluoride" (Ekstrand 1981). A number of scientists are therefore concerned about exposing infants – via formula made with fluoridated water – to doses of fluoride that greatly exceed (by a factor of 100 to 200) what they would otherwise receive from human milk (Carlsson, 1978; Fomon 2000; Brothwell 2003).

5. Relevant EPA Regulations on Fluoride

The Maximum Contaminant Level Goal (MCLG). The MCLG is a non-enforceable drinking water standard. It is based on the best available science, and robust safety factors, so as to protect against all known or anticipated adverse effects among all members of the population. In 1985, EPA established an MCLG for fluoride of 4 ppm.

The Secondary Maximum Contaminant Level (SMCL). The SMCL is another non-enforceable drinking water standard developed to protect against any adverse "aesthetic" effects. In the case of fluoride, the SMCL was set at 2 ppm because a significant percentage of children drinking water with more than 2 ppm will develop moderate and severe forms of dental fluorosis. (The EPA requires water suppliers to warn their consumers that children should not drink water if it contains more than 2 ppm fluoride.

The Maximum Contaminant Level (MCL). The MCL differs from the MCLG and SMCL in that it is a federally enforceable standard. Unlike the MCLG, the MCL takes into account the economic costs of reducing the concentration of a contaminant to the desired level. A good example of the difference between an MCLG and MCL is the case of arsenic. Because arsenic is a known human carcinogen there is assumed to be no safe level of exposure, thus arsenic's MCLG is set at zero. However, since arsenic occurs naturally in some water supplies, and since it is expensive for communities to filter all of the arsenic out of water, the MCL is set at 10 parts per billion. The MCL, therefore, represents a compromise between health and economics. The MCL for fluoride was set at 4 ppm by the EPA in 1985.

How the MCL is determined. The MCL is established in four steps:

1) First, the lowest observable adverse effect level (LOAEL) is determined for the pollutant from available animal or human studies. In the case of fluoride, the LOAEL was assumed to be 20 mg per day based on evidence of crippling skeletal fluorosis among adult cryolite workers exposed to this dose for 11 to 25 years.

2) After the LOAEL is determined, it is divided by a safety factor to yield a dose not anticipated to cause any known or anticipated effect in any subset of the population. In the case of fluoride, the EPA used a safety factor of 2.5 (rather than the more commonly used factor of 10) to produce a purported safe dose of 8 mg of fluoride per day.

3) After the safe dose is determined, it is divided by the number of liters of tap water humans are assumed to drink. In the case of fluoride, the EPA assumed that people drank two liters of water per day, thus giving an MCL of 4 mg per liter (8 mg/day / 2 Liters = 4 mg/Liter, or 4 ppm).

OPP's Derivation of a Reference Dose for its Risk Assessment of Fluoride Tolerances

Because of the unique statutory requirements under FQPA (Food Quality Protection Act), EPA's Office of Pesticide Programs (OPP) typically develops its own reference dose for a particular chemical, using its own methodology. The OPP, however, chose not to do this with fluoride. Instead, it has opted to derive its reference dose from the Office of Drinking Water's 1985 MCL.

Initially, OPP derived its reference dose from the MCL in the following manner:

- It calculated the dose of fluoride an adult would receive if they consumed 2 liters of water per day with 4 ppm fluoride. They then divided this dose (8 mg/day) by the average weight of an adult (70 kg) in order to express the dose in terms of milligrams per kilogram of bodyweight. The resulting calculation is as follows: 8 mg / 70 kg = 0.114 mg/kg. Hence, OPP's reference dose for fluoride was 0.114 mg/kg/day.

The OPP utilized the 0.114 mg/kg reference dose for all of its risk assessments on fluoride tolerances up until 2004. However, after FAN pointed out to OPP that many children in the US are currently exceeding this reference dose (a fact which typically disenables any further addition of a chemical to food), OPP announced that it was no longer going to use the 0.114 mg/kg reference dose for children. Instead, OPP made the rather incredible announcement that – in the absence of any new evidence - it was increasing the reference dose for children by up to a factor of 5. Hence, for infants (the age group considered to be the most vulnerable to environmental toxins), EPA announced a new reference dose of 0.571 mg/kg.

OPP obtained this new reference dose by changing the starting point of their calculation. Instead of basing the reference dose on the mg/kg dose of an adult drinking 2 liters of 4 ppm water, the OPP now bases its reference dose on the mg/kg dose of a child drinking 1 liter of 4 ppm water.

In making this change to the reference dose, OPP has violated a key component of EPA's drinking water standard for fluoride. As discussed above, the EPA Office of Drinking Water (ODW) recommends that children not consume water containing more than 2 ppm fluoride. EPA's ODW made this recommendation because many children drinking water with >2 ppm will develop moderate and severe dental fluorosis. Moderate/severe dental fluorosis is a disfiguration of teeth (e.g. brown staining, pitting, and erosion of enamel) that a panel of mental health experts concluded would cause an "'impaired self-image' or 'loss of self-esteem'" to the developing child (Federal Register, November 14, 1985, p. 47144.)

As noted by one scientist involved in the establishment of the MCL:

> "You would have to have rocks in your head, in my opinion, to allow your child much more than 2 ppm" (Surgeon General Committee, 1983, p. 416).

Thus, in contrast to EPA's earlier recommendation that children not consume water with more than 2 ppm, OPP has issued a new reference dose based on the assumption that it is safe and acceptable for children to drink 4 ppm fluoride in their water from the first day of life through to adolescence.

6. Criteria needed to qualify issues for an evidentiary hearing on pesticide tolerances.

The criteria, established is in 40 C.F.R. § 178.32(b), for EPA's granting of a public evidentiary hearing, is as follows:

> (1) There is genuine and substantial issue of fact for resolution at a hearing. An evidentiary hearing will not be granted on issues of policy or law.
>
> (2) There is a reasonable possibility that available evidence identified by the requestor would, if established, resolve one or more of such issues in favor of the requestor, taking into account uncontested claims or facts to the contrary. An evidentiary hearing will not be granted on the basis of mere allegations, denials, or general descriptions of positions and contentions, nor if the Administrator concludes that the data and information submitted, even if accurate, would be insufficient to justify the factual determinations urged.
>
> (3) Resolution of the factual issue(s) in the manner sought by the person requesting the hearing would be adequate to justify the action requested. An evidentiary hearing will not be granted on factual issues that are not determinative with respect to the action requested. For example, a hearing will not be granted if the Administrator concludes that the action would be the same even if the factual issues were resolved in the manner sought.

Having reviewed our appeal for an evidentiary hearing on the fluoride tolerances granted by the EPA in January 2004 (Connett P et al., 2004), we are satisfied that the central core and the bulk of our Objections meet the criteria established in 40 C.F.R. § 178.32(b)

In September 2005, a second set of "Objections and Request for Hearing" to new tolerances (US EPA, 2005) was submitted to EPA from FAN, the Environmental Working Group and Beyond Pesticides (Neurath et al., 2005). As noted in our attached letter, we support the combining of these two appeals for one evidentiary hearing.

Below we have merged and amplified the issues presented in our March 2004 and September 2005 appeals for evidentiary hearings. In our view, any one of the 48 issues we have identified should lead to the revocation of the tolerances.

THE FLAWS WITH EPA'S RISK ASSESSMENT

Introduction

The Federal Food and Drug Certification Act (FFDCA) Section 408(b)(2)(A)(ii) requires the EPA, when setting pesticide chemical residues on food, to have a "reasonable certainty that no harm will result". Furthermore, in Section 408(b)(2)(C) this same Act requires that the EPA "give special consideration to exposure of infants and children (US EPA, 2005)."

Again and again in the issues we present below, the EPA fails to provide adequate and factual scientific evidence that they "have certainty that no harm will result" from the sulfuryl fluoride and fluoride tolerances that they have approved.

Further, as far as giving "special consideration to exposure of infants and children" we have shown that the EPA has done the very opposite, and has actually given LESS consideration to children than adults!

A fundamental flaw in the approach of the US EPA in its estimation of the risks posed by fluoride exposure –whether in its derivation of the MCLG or in the HRA used to establish fluoride tolerances on various foodstuffs – is the agency's focus on the impacts of fluoride on the average person and not on sensitive subsets of consumers. Under FIFRA, the agency is supposed to consider the sensitivity of different populations. We will point out, therefore, the failure of EPA to consider more sensitive, or more exposed, subpopulations on each occasion where it occurs.

ISSUE 1) Published data shows that some children are already exceeding the reference dose. There is no room for additional exposures.

Before addressing the glaring problems with the science underpinning EPA's tolerances, we wish to start by emphasizing that – even if one assumes that the method used by the EPA to determine these reference dosages is acceptable, the tolerances for sulfuryl fluoride still need to be rejected because many Americans are already receiving daily doses in excess of the reference dose.

For example, Levy (2003) found that some children aged 3-5 years old living in ≤1 ppm areas already receive more fluoride than EPA's reference dose for this age group. Indeed, Levy found some children of this age to be receiving up to 0.283 mg/kg/day, which is over 50% higher than the new reference dose (0.182 mg/kg/day), and 150% higher than EPA's previous reference dose (0.114 mg/kg/day).

Based on Levy's data, it can be estimated that 1 in 500 children in the general population are already receiving more than EPA's new reference dose. With about 11.8 million children 3-5 years of age in the US, this translates into more than 23,500 children currently receiving more than EPA currently considers safe. (Levy's data also shows that 5-10% of children under the age of 4 are exceeding EPA's previous safe limit of 0.114 mg/kg.)

Because some children are already receiving more fluoride than EPA's new reference dose, there is no safe room for additional exposures. Accordingly, EPA's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 2) EPA's Exposure Analysis has Greatly Underestimated Current Fluoride Exposures

Despite the fact that Levy (2003) was studying children living in ≤ 1 ppm areas (with no exposure to sulfuryl fluoride), 10-25% of the 3 to 5 year olds studied by Levy had fluoride exposures which exceeded EPA's estimates for children of this age consuming water with 2 ppm fluoride.

Levy's study, therefore, indicates that something was wrong with the exposure analysis underlying EPA's risk assessment for sulfuryl fluoride. Indeed, as we will demonstrate below, there are several major errors and non-conservative assumptions that led EPA to greatly underestimate the current extent of fluoride exposure in the US. When these errors and incorrect assumptions are corrected, it becomes apparent (as demonstrated below) that many people in the US are currently exceeding EPA's reference dose.

The two most important errors with EPA's fluoride exposure analysis concern its estimates of fluoride intake from drinking water and toothpaste.

ISSUE 2a) Errors with EPA's Drinking Water Exposure Analysis

As part of the exposure analysis, EPA attempted to determine the average fluoride concentration of US water supplies. EPA's method for deriving an average fluoride concentration was incorrectly weighted leading to an obvious error in EPA's exposure analysis. According to EPA's estimates, only 57 million or just 20% of Americans consume water with > 0.7 ppm fluoride (EPA 2003a; Table c.33). This, of course, is incorrect since, according to the CDC (2005), 170 million Americans drink fluoridated water (0.7-1.2 ppm). EPA's estimate, therefore, of the number of Americans exposed to fluoridated water was off by a factor of 3. This, in turn, led to a significant under-estimation of the average fluoride content of US water supplies. According to EPA, the average fluoride content of US water is 0.4 ppm. Proof that this is incorrect can be found in a recent national analysis of US water supplies by USDA. According to USDA (2004), the average fluoride content of US water supplies (municipal + well) is 0.71 ppm – almost twice as high as EPA's estimate.

In addition to this error, there is another glaring problem with EPA's drinking water exposure analysis. Namely, in only using the chronic exposure model in the DEEM software, EPA was only able to determine the *average* fluoride exposure from water based on the *average* daily intake of water. This is a limitation inherent in the DEEM software. In a recent EPA OPP Dietary Exposure Assessment the output of DEEM-FCID 2.03 is described:

> "For chronic exposure assessments, consumption data are averaged for the entire U.S. population and within population subgroups" (US EPA 2004b).

As FAN has verified using the DEEM software, the chronic exposure model computes only the average exposure for the entire US population and designated subpopulations. The subpopulations are based only on age and sex, not water consumption. Thus, the software and the underlying food consumption database do not allow for any breakdown of exposure by the varying percentiles of water intake. Hence, there is no way to determine the water fluoride intake among the top 25%, top 10%, top 5%, or top 1% of water consumers.

EPA's failure to obtain this vital information represents a major failure of due diligence, and probably the most glaring problem with its exposure analysis. After all, water is one of the most significant sources of fluoride exposure in the US population, and – as highlighted by the Food and Nutrition Board (2004) - its consumption varies greatly across the spectrum of the population. To restrict, therefore, an analysis of water fluoride exposure to simply the average, or 50th percentile, water consumer, provided a fatal blow to EPA's ability to detect the true extent of fluoride exposure in the US among sizeable subsets of consumers.

As is amply documented, there exists a wide variability in both food and water consumption habits among the population. Therefore, the only way to obtain an accurate dietary exposure assessment is to determine the variability in consumption from individual to individual and use the resulting consumption distribution for the population. The FDA has found that, as a rule of thumb, the top 10% consumers of any food eat about twice as much as the average. The top 5% consume about four times as much as average (FDA 1995). In the case of water consumption, numerous studies have documented an even wider range in total water consumption within the US population. The CFSII studies by USDA show a greater than 10-fold range of consumption, from less than 1 liter/day to more than 10 liter/day. When adjusted for body weight, there is still a 7-fold range from lowest to highest consumers.

Had EPA conducted an analysis, therefore, that addressed the intake of high-end water consumers they would have found that many Americans are currently exceeding the reference dose from water sources alone. To demonstrate this fact, we produce below the results of 2 sets of analyses we have recently conducted:

ANALYSIS #1:

Our first set of analyses utilized the 1988-1994 NHANES water intake data as reproduced in Appendix D of the Food and Nutrition Board's 2004 report. Since the NHANES data is divided into percentiles of exposure, it was possible to determine the water intake of the top 1%, top 5%, top 10%, and top 15% of water consumers. We then applied this water intake data to US populations residing in areas with 2 to 4 ppm areas. In order to determine how many people live in such areas, we used the CDC's 1993 Fluoridation Census (which may well be an underestimate of today's population.)

As can be seen in the following table, this analysis indicates that between 1 and 15% of individuals living in 2 to 4 ppm areas in the US will exceed the reference dose from their intake of water. (For more details about this analysis, see Appendix B).

TABLE 1: Populations Exceeding Reference Dose Based on NHANES 1988-1994 Water Intake Data

Water Fluoride	No. of Americans living in area (CDC 1993)	% of People in area exceeding reference dose (8 mg/day)	# of People in area exceeding reference dose (8 mg/day)
2.0 – 2.4 ppm	~565,000	≥1	≥5,650
2.5 - 2.9 ppm	~209,500	≥5	≥10,500
3.0 – 3.4 ppm	~230,000	≥10	≥ 23,000
3.5 – 3.9 ppm	~68,000	≥15	≥10,200
≥ 4 ppm	~210,000	≥15	≥31,500
Total:	~1,282,500	>6%	≥80,850

ANALYSIS #2:

For our second analysis we utilized the DEEM software. We sought to conduct an analysis that would correct the three key problems with EPA's DEEM analysis, namely:

- For all analyses we utilized USDA's (2004) data on the average fluoride level of US water supplies (0.71 ppm) for the non-tap water categories. We used this figure to correct EPA's mistaken 0.4 ppm estimate.
- For the tap water categories, we didn't limit our analysis to only those individuals drinking 2 ppm fluoride in water. We also performed analyses for people drinking water with 1 ppm and at various intervals between 2 and 4 ppm.
- In order to get an indication of fluoride exposure among high-end water consumers, versus simply the average consumer, we utilized DEEM's acute model, rather than the chronic model. We predicated this decision on the assumption that the range of water consumption reported among individuals in the USDA's 2 day survey provides a rough surrogate for the distribution of chronic water consumption across the population.

The results of these DEEM analyses are summarized in Table 2. As with the analysis above, the DEEM analyses clearly show that many high-end water consumers living in 2 to 4 ppm areas will exceed the reference dose. Moreover, the DEEM analyses also indicate that a subset of

individuals living in 1 ppm areas (about 0.25% to 0.5% of the population) will exceed the reference dose as well. With well over a 100 million Americans living in 1 ppm areas, a figure of 0.25-0.5% translates into hundreds of thousands of people. (For the full DEEM analyses, see appendix C).

TABLE 2:
Fluoride Dose by Water Consumption Percentile
(mg/kg-bw/day)

Tap Water F level	90th	95th	99th	99.9th
1.0 ppm	0.037	0.049	0.090	**0.171**
2.0 ppm	0.067	0.088	0.157	**0.338**
2.2 ppm	0.077	0.102	**0.186**	**0.370**
2.7 ppm	0.094	**0.125**	**0.228**	**0.452**
3.2 ppm	0.111	**0.147**	**0.270**	**0.538**
3.7 ppm	**0.128**	**0.170**	**0.316**	**0.622**
4.0 ppm	**0.138**	**0.183**	**0.330**	**0.671**
***Bold** indicates dose exceeds EPA's reference dose.*				

It is therefore clear that, at water fluoride levels, many consumers are exceeding the reference dose simply by drinking their daily mixture of tap water and processed beverages. This fact was obfuscated by EPA, via its decision to focus strictly on the average consumer, and to limit its analysis to only 2 ppm fluoride. Since this method is at fundamental odds with EPAs mandate to protect susceptible subsets of consumers, EPA's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 2b): Errors with EPA's Toothpaste Exposure Analysis

As with its drinking water analysis, EPA also made important errors and unacceptable assumptions in its toothpaste analysis as well.

According to EPA:

> "Despite the variability in the estimates of ingested toothpaste, maximum exposures to fluoride observed in those studies appear to converge to approximately 0.3 mg/day (assuming 2 brushings per day)... The exposure estimates range from 0.004 to 0.04 mg/kg/day and should be considered conservative in nature..." (US EPA 2004a, page 34).

EPA's assertion that 0.3 mg/day fluoride represents the "maximum" exposure from toothpaste is not supported by the scientific literature. Indeed, not only is 0.3 mg/day significantly lower than most reported maximum exposures from toothpaste, it is also lower than many of the reported *average* exposures!

For example, in 1999, Levy compiled data from studies which measured the quantity of toothpaste ingested by children (see Table 3). Levy compiled published data for 11 groupings of children ≤ 5 years old – the age range most susceptible to swallowing excess toothpaste. Of these 11 groups of children, data on maximum intake was presented for 4 groups. All 4 of these maximum intakes (range = 0.66 - 2.55 mg/day) exceed (by a factor of 2 to 9) EPA's purported "conservative" maximum.

Perhaps more notable, however, is the fact that the *average* fluoride exposures in 9 of these 11 groups (range = 0.24 – 0.86 mg/day) also exceed EPA's purported *maximum* exposure (by up to a factor of 3).

Based on this data, it is clear that EPA has made a significant underestimation of the fluoride exposure children receive from toothpaste.

TABLE 3: Comparison of Documented Fluoride Ingestion from Toothpaste with EPA's Purported Maximum Dose (0.3 mg/day)					
	Average F Intake from Toothpaste		Maximum F Intake from Toothpaste		
Age	Intake from 2 Brushings (1,100 ppm F)	% of EPA's Estimated Max Intake	Intake from 2 Brushings (1,100 ppm F)	% of EPA's Estimated Max Intake	Reference
2	0.73 mg	**243%**	n/a	n/a	Levy 1999 *(Naccahe '87)*
2 1/2	0.59 mg	**196%**	1.83 mg	**610%**	Bentley 1999
2-3	0.62 mg	**207%**	n/a	n/a	Levy 1999 *(Simard '84)*
2-4	0.66 mg	**220%**	1.61 mg *(90^{th} percentile)*	**>537%**	Levy 1999 *(Barnhart '76)*
3-6	0.84 mg	**280%**	2.55 mg	**850%**	Levy 1999 *(Hargreaves '75)*
3	0.40 mg	**133%**	n/a	n/a	Levy 1999 *(Naccahe '85)*
4	0.48 mg	**160%**	n/a	n/a	Levy 1999 *(Naccahe '87)*
4	0.86 mg	**287%**	n/a	n/a	Levy 1999 *(Simard '84)*
4	0.29 mg	97%	0.66 mg	**220%**	Levy 1999 *(Ericsson '74)*
5	0.48 mg	**160%**	n/a	n/a	Levy 1999 *(Simard '84)*
5	0.24 mg	80%	n/a	n/a	Levy 1999 *(Naccahe '85)*
5-6	0.59 mg	**197%**	n/a	n/a	Levy 1999 *(Baxter '79)*

Not only did EPA underestimate the amount of toothpaste ingested by children, but – by focusing solely on average-weighted children – it underestimated the body-burden of fluoride exposure experienced by children who weigh less than the average. As can be seen in Table 4, if children weighing less than the average are taken into account, then EPA's reference dose for fluoride can be exceeded by toothpaste ingestion alone. Average weighted children, meanwhile, will exceed the reference dose if other sources of fluoride exposure (e.g. water) are added to their intake from toothpaste.

TABLE 4
Comparison of EPA's estimated Maximum Dose from Fluoride Toothpaste with Maximum Dose Reported in the Literature

	Age	Max Daily Dose from Toothpaste (avg weight child*)	% of EPA Reference Dose (avg wt) (0.182mg/kg)	Max Daily Dose (underweight child**)	% of EPA Reference Dose (0.182mg/kg)
EPA 2004	3	0.0136 mg/kg	7%	n/a	n/a
Hargreaves '75 *(Cited by Levy 99)*	~3	0.181 mg/kg	99%	0.21 mg/kg	114%
Bentley 1999	~3	0.130 mg/kg	71%	0.149 mg/kg	82%
Barnhart '76 *(Cited by Levy 99)*	~3	0.114 mg/kg *(90th percentile dose)*	63%	0.131 mg/kg *(90th percentile dose)*	72%

- Data for the average weight of 3 year old children was obtained from NHANES, the same data source used by EPA. See: http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/charts.htm#Set%201
- Underweight children are defined here as the 10th percentile weight in the age group.

Another way that EPA has underestimated the fluoride exposure problem from toothpaste is to assume that the instructions on the labeling will "significantly limit" ingestion. According to EPA:

> "Regarding exposure to fluoride via dental products, the Agency believes that warning labels on these products provide explicit direction on how to significantly limit dietary exposure to fluoride-containing dental products for children." (US EPA, 2002)

There are two major problems with this assumption.

First, while the instructions warning children not to swallow toothpaste are available in the fine print on the back of the tube, toothpaste manufacturers continue to make child-friendly toothpastes with appealing flavors like bubble-gum and watermelon. Such flavors will undoubtedly tempt kids to use more, and swallow more, of the paste – a fact supported by published research (Levy 1992, as cited in Levy 1999).

Another problem with EPA's assumption: it does not take into consideration the MILLIONS of people who do not have the literacy skills to read the warning label on toothpaste. According to the National Institute for Literacy (NIFL),

> "Almost all adults in Level 1 can read a little but not well enough to fill out an application, **read a food label**, or read a simple story to a child... Between 21 and 23 percent of the adult population or **approximately 44 million people**, according to the National Adult Literacy Survey (NALS), scored in Level 1 (NIFL, 2005)."

Also, we are not aware of any toothpaste sold in the US that have warnings in any language other than English.

Thus, by A) misrepresenting published data on toothpaste ingestion, by B) focusing only on average-weighted children, and by C) assuming that ingestion of toothpaste will not be a problem due to the presence of instructions in fine print, the EPA has greatly underestimated the extent of childhood fluoride exposure from toothpaste. When correcting these problems in EPA's analysis, it becomes clear that some children may come very close, and in some cases exceed, the reference dose from toothpaste use alone. There is therefore no safe margin for additional exposures to fluoride. Accordingly, EPA's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 3: EPA'S altered reference violates FQPA

Because it is commonly accepted that infants and young children are more susceptible to toxic exposure than adults, the Food Quality Protection Act (FQPA), passed into law on August 3, 1996, has mandated that EPA design its regulatory decisions on pesticides to be MORE protective for children. This mandate for extra protection for children, when considering pesticide exposure, is very clearly spelled out in the FQPA. To quote:

> "When setting new tolerances, or reassessing existing tolerances or tolerance exemptions, EPA must now focus explicitly on exposures and risks to children and infants. EPA must, 1) explicitly determine that the tolerance, or exemption from tolerance, is safe for children; 2) consider the need for an additional safety factor of up to ten-fold to account for uncertainty in the data base relative to children unless there is evidence that a different factor should be used; and 3) consider children's special sensitivities and often unique exposure patterns to pesticides. " (US EPA, 1997)

Despite this mandate by FQPA, and the widely acknowledged fact that growing children are more sensitive to toxins than adults, the EPA Pesticide Division took the unusual – and scientifically indefensible – step of deriving a higher reference dosage for children than adults. Despite the fact that EPA had been using a reference dose of 0.114 mg/kg for children up through 2004, and despite the fact that no new evidence was cited to justify a weakening of this standard, EPA announced in 2004 that it was increasing this reference dose to as high as 0.571 mg/kg for infants and 0.308 mg/kg for 1-2 year olds.

In developing its new reference dose, EPA has utilized data derived from adult male workers and applied it directly to children without issuing *any* safety factor.

Further, in increasing the reference dose for children, EPA's Pesticide Division has disregarded EPA's own explicit recommendation (as expressed in the SMCL) that children should not drink water with 4 ppm fluoride, due to the clear risk it presents of developing moderate and severe dental fluorosis (a risk unique to children and not adults). Hence, in contradiction to the clear intent of FQPA, EPA has abandoned a safety factor specifically recommended for children by the Office of Drinking Water. As one scientist involved in the establishment of EPA's MCL stated:

> "You would have to have rocks in your head, in my opinion, to allow your child much more than 2 ppm" (Surgeon General Committee on Non-Dental Health Effects of Fluoride, 1983, p. 416).

By establishing a reference dose, therefore, which is known to produce moderate and severe dental fluorosis in 30-40% of children (Dean 1942; NRC 1993), the burden of proof was on EPA's Pesticide Division to explain with "reasonable certainty" that moderate and severe fluorosis is not associated with any adverse effect on a child's health, including emotional health. EPA did not fulfill this burden.

For example, EPA's Pesticide Division has not demonstrated that severe dental fluorosis (brown and black stained teeth with pitting and crumbling enamel) will not harm the emotional and mental well being of a child (e.g. self esteem, social behavior, etc). Since teeth with widespread brown or

black staining can be anticipated to have an adverse effect on a child's emotional development (a conclusion reached by a panel of experts at the National Institute of Mental Health - *Federal Register, November 14, 1985, p. 47144; Grossman 1990*), it was imperative for EPA to provide evidence showing that this is not the case. EPA Pesticide Division did not do this.
EPA also failed to demonstrate that moderate/severe fluorosis (and the underlying toxic effect on enamel-forming cells) is not associated with any harm to the body – as has been suggested by recent research indicating:

- Severe fluorosis makes teeth more susceptible to caries (Kimm 1984; Manji 1986; Mann 1987, 1990; Cortes 1996; Wondwossen 2004; Cunha-Cruz 2005);
- Cells in other mineralized tissues, e.g. the pinealocytes in the pineal gland, can be impacted in a similar fashion, and at the same time, as the amelobasts (Luke 1997); and
- Children with moderate/severe fluorosis are at an increased risk for bone fracture (Alarcon-Herrera 2001).

Hence, EPA's failure decision to take data derived from adult workers and apply it directly to children without using a safety factor; to increase the reference dose without citing any new data to justify the change; to ignore the safety factor explicitly recommended for children under EPA's SMCL; and to forego proving with "reasonable certainty" that moderate and severe dental fluorosis is safe, represents a clear violation of the goals and mandate of FQPA. Accordingly, EPA's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

Hence, EPA's failure to justify: A) the decision to apply data derived from adult workers to children without applying any safety factor, B) the failure to cite any new data to justify the sudden change in reference dose; C) the decision to ignore the safety factor explicitly recommended for children in EPA's SMCL; and D) the failure to prove with "reasonable certainty" that moderate and severe dental fluorosis is safe, represents a clear violation of the goals and mandate of FQPA. Accordingly, EPA's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

Three Flawed Assumptions Underlying New Reference Dosage

Instead of citing new data, EPA attempted to justify its new reference dosage for children by relying on 3 assumptions that are readily contradicted by available scientific evidence.

Before detailing these 3 flawed assumptions, we start first by quoting EPA's argument:

> "HED has not applied an additional FQPA safety factor to the fluoride assessment. Skeletal fluorosis is an effect that requires chronic (15-20 years) high exposures in order to be manifested. As such, infants and children will not exhibit this effect and an additional factor to account for potential enhanced sensitivity is not necessary" (US EPA 2004a, p 17).

ISSUE 4. Flawed Assumption #1: Skeletal fluorosis requires at least 15 years exposure.

EPA's contention that skeletal fluorosis will only develop after 15 years of exposure is incorrect. According to Roholm (1937), and most other reviewers (NRC 1993, ATSDR 2003), crippling fluorosis can be caused after just 10/11 years, while according to Roholm the earlier stages of clinical fluorosis can be caused after just 2 years of exposure.

The fact that Roholm found clinical fluorosis after just 2 years is particularly significant considering that EPA's new MCL will allow children during their first *5 years* of life a greater daily dosage of fluoride (mg per kg of bodywei ght) than the dosage allowed for adults. Accordingly, EPA's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 5. Flawed Assumption #2: Children do not develop skeletal fluorosis

EPA's contention that children do not develop skeletal fluorosis – a contention based on a study (Roholm 1937) that only examined adults - is also incorrect. Peer reviewed research in the scientific literature has existed for over 20 years demonstrating that debilitating fluorosis can occur in children, as early as the ages of 2 and 4 (Christie 1980; Teotia 1998). Accordingly, EPA's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 6. Flawed Assumption #3: Children's bones are not more sensitive to fluoride than adults

The most important error underlying EPA's alteration of the childhood reference dose is its contention that "an additional factor to account for potential enhanced sensitivity is not necessary."

In contrast to EPA's contention, the scientific evidence does not support the assumption that children's bones react in the same manner to fluoride as adults' bones. Indeed, a Public Health Service (PHS) committee convened at the request of EPA to examine the "non dental health effects of fluoride", concluded that children would be *more* vulnerable to fluoride-induced bone damage than adults, not less (Shapiro 1983a,b; Surgeon General 1983). In fact, because of their concern that fluoride could interfere with bone development during childhood, a majority of the PHS panel members voted to recommend that children not ingest more than 2 ppm fluoride in water before the age of 9 – not just to protect their teeth, but to protect their bones (Shapiro 1983a).

The panel's concern that fluoride may exert its most damaging effect on bone during childhood, directly contradicts OPP's claim that there is no recognized need for a safety factor to protect the skeletal health of children.

Moreover, EPA's contention that rapidly growing bones are no more susceptible to fluoride toxicity than mature bones, runs counter to the recently established fact that children's bones can accumulate a much higher percentage of fluoride than adults – thereby exposing developing bone cells to a significantly higher concentration of fluoride (Teotia 1998; Whitford 1999). For instance, whereas the adult skeleton accumulates roughly 50% of an absorbed dose, the infant skeleton accumulates up to 87% of an absorbed dose (Ekstrand 1994). This fact provides a clear biological basis why it can not be assumed that children's bones will respond to fluoride in an identical manner as adults.

As noted, for instance, by Teotia & Teotia (the scientists who first documented skeletal fluorosis in children):

> "Fluoride toxicity afflicts children more severely and over a shorter period of exposure (about 6 months) as compared to adults. This is because the rapidly growing bones of children are metabolically active and more vascular and thus absorb and accumulate fluoride faster and in greater amounts than older bones, particularly at the sites of bone growth and physiological calcifications" (Teotia 1998).

The Teotia team's conclusion that increased metabolic activity makes children's bones more vulnerable to fluoride is supported by research on animals. According to Johnson 1965:

> "Mottling was the result of the action of fluoride on osteoblasts during bone formation. Young bones undergoing extensive remodeling showed extensive mottling, while old bones with scant remodeling showed little mottling" (Johnson 1965).

Similar to Johnson, Kierdorf (1997, 2000) concluded that an increased rate of growth makes a bone more susceptible to fluoride poisoning. According to Kierdorf:

> "It is concluded that increased fluoride exposure of deer leads to reduced mineral content and mineral density of antler bone and that it is the rapidity of their growth and mineralization that makes antlers especially susceptible to fluoride action" (Kierdorf 1997).

EPA's assumption, therefore, that a child's skeleton – with its more rapid rate of growth and its higher accumulation of fluoride - will respond to fluoride in the same manner as an adult is without scientific basis and thereby devoid of "reasonable certainty." Accordingly**,** the risk assessment supporting the tolerances is scientifically, factually and legally inadequate**.**

ISSUES 7–24. Flawed Assumptions Inherited from 1986 MCLG

There are yet further flawed assumptions underlying EPA's reference dosage for children, but these flawed assumptions arise from the Office of Drinking Water's 1985 MCLG – which the Pesticide Division used uncritically as the foundation for its tolerance risk assessment.

The flawed assumptions underlying the 1986 MCLG include the following:

- 20 mg/day is an adequate LOAEL for all subsets of consumers;
- Skeletal fluorosis is not a problem in the US
- 20 mg/day LOAEL, derived from 1930s' data, is still up to date;
- Crippling fluorosis is only found in other countries at >10 ppm;
- Crippling fluorosis is the only adverse effect that fluoride has on bone;
- Fluoride has no adverse chronic effects on soft tissues.
- A safety factor of 2.5 is adequate to protect all members of society
- People drink only two liters of water per day
- People get no exposure to fluoride other than water

We will now discuss these assumptions one at a time.

ISSUE 7. MCLG Flawed Assumption #1*: 20 mg/day is an adequate LOAEL for all major identifiable sensitive sub groups.*

EPA's 1986 MCLG was based on the assumption that the only way an individual could be harmed by fluoride is if they consumed at least 20 mg/day for at least 10 years. EPA assumed that this 20 mg/day threshold applied equally to every one in the population, irrespective of the presence of factors (e.g. kidney disease, dietary deficiencies, etc) well known to increase an individual's susceptibility to fluoride. Hence, a person with severe kidney disease was assumed to be equally susceptible to fluoride toxicity as an individual with healthy function. This, of course, is an absurd and scientifically indefensible assumption.

It is even more absurd when considering that the study from which the 20 mg/day figure was derived (Roholm 1937; Brun 1941) was based on a small group of adult cryolite workers. Hence, the subset of the population Roholm studied (adult male workers) disallows any conclusions to be drawn about major identifiable sensitive sub groups. It is entirely inappropriate, for instance, for EPA to have applied this 20 mg/day LOAEL, derived from well-nourished adults (with healthy kidney function), to susceptible populations including children, individuals with kidney disease, and individuals with dietary deficiencies.

Another problem with the 20 mg/day LOAEL from Roholm's study is that it only applies to 11 to 25 years of exposure. Since skeletal fluorosis is dependent both on dose *and* duration of exposure, it is not possible - based on Roholm's research - to determine the LOAEL for people exposed to fluoride for longer periods of time than the workers in Roholm's study. It is inappropriate, therefore, for EPA to have based its MCL on a dose that is based on people who had only been exposed for as little as 11 years. Needless to say, humans live for more than 11 years, and as a result, an appropriate MCL would be based on lifetime exposure to fluoride, not

11 years. EPA cannot, therefore, say with reasonable certainty that lifetime doses lower than the 20 mg/day "LOAEL" are safe and that no harm will occur to any major identifiable sensitive sub groups. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 8. MCLG Flawed Assumption #2: *Skeletal fluorosis is not a problem in the US*

One of the arguments utilized by EPA in 1985 to justify the 4 ppm MCLG was the agency's contention that skeletal fluorosis is extremely rare in the US. To quote:

> "The fact that only two cases of crippling skeletal fluorosis have been observed in the US associated with the consumption of drinking water provides convincing evidence that the population at risk at 4 mg/L is negligible" *(Federal Register, November 14,* 1985*, p 47144).*

While there are many problems with this contention, we will focus here on just one: As of 1985, there had yet to be (and still has yet to be) one systematic study in the scientific literature studying the prevalence of fluorosis in the key susceptible group in the population: patients with kidney disease (Groth 1973; Johnson 1979). According, for instance, to Groth (1973):

> "It seems probable that some people with severe or long-term renal disease, which might not be advanced enough to require hemodialysis, can still experience reduced fluoride excretion to an extent that can lead to fluorosis, or aggravate skeletal complications associated with kidney disease... It has been estimated that one in every 25 Americans may have some form of kidney disease; it would seem imperative that the magnitude of risk to such a large sub-segment of the population be determined through extensive and careful study**.** *To date, however, no studies of this sort have been carried out, and none is planned"* (emphasis added).

Thus, EPA's discussion on the prevalence of fluorosis in the US was predicated on data incapable of determining the prevalence among the very population most susceptible to developing the disease. To this date, the absence of systematic research on fluorosis in patients with kidney disease remains one of the most glaring gaps in the literature (Hileman 1988).

Not only did EPA fail to acknowledge this research gap, but it also failed to discuss or even reference a key study – published in 1979 by Mayo Clinic scientists - demonstrating the existence of symptomatic skeletal fluorosis in kidney patients drinking water with less than half of the MCLG (Johnson 1979).

In a group of 4 kidney patients drinking water with just 1.7 – 2.0 ppm, Johnson (1979) found several key indications of fluorosis, including: histological evidence of fluorotic changes to bone; accumulations of fluoride in the bone and blood known to be associated with bone damage in humans and animals; and the successful alleviation of bone pains following the provision of fluoride-free water.

The blood fluoride levels in Johnson's kidney patients were particularly noteworthy. They averaged 10.3 umol/L, and reached as high as 14.3 umol/L in the patient with the severest case of the disease. To put these concentrations in perspective, they exceed:

- The blood fluoride levels (5 - 9 umol/L) found in human populations with skeletal fluorosis (Li 1986, Li 1990; Savas 2001; Singla 1976);
- The blood fluoride levels (7.6 umol/L) found to increase bone osteoid volume in rats (Turner 1996, see figure 5).
- The blood fluoride levels (9-10.6 umol/L) found to reduce bone strength in Turner's animal studies (Turner 1995, 1996, 2001; see also: Dunipace 1995, 1998);

- The blood fluoride levels (10 umol/L) which Pak (1989) considers toxic to bone mineralization in short term exposures (< 5 years), especially in the absence of major calcium supplementation.

Based on their findings, Johnson (1979) concluded that 2 ppm fluoride in water presents a probable risk to the bones of people with advanced kidney disease and that the effect may also be experienced in 1 ppm areas as well. To quote:

> "The available evidence suggests that some patients with long-term renal failure are being affected by drinking water with as little as 2 ppm fluoride... The finding of adverse effects in patients drinking water with 2 ppm of fluoride suggests that a few similar cases may be found in patients inbibing 1 ppm, especially if large volumes are consumed, or in heavy tea drinkers and if fluoride is indeed a cause" (Johnson 1979).

In light of Johnson's findings, and in light of EPA's mandate under the Safe Drinking Water Act "to protect the most sensitive subgroup of the population", it amazes us that EPA could have established an MCL**G** of 4.0 ppm in 1985.

EPA, in fact, actually acknowledged that the MCLG could not be relied on to protect the most sensitive subgroup of the population. To quote:

> "The Agency feels that this RMCL provides an adequate margin of safety ***except*** in those very extreme cases involving severely renally impaired individuals who consume unusually high levels of fluoride due in part to polydipsia and other confounding factors" (emphasis added; *Federal Register, Nov 14, 1985, p. 47152*).

"Except" is the key word here, as it openly contradicts EPA's mandate to protect "the most sensitive subgroup of a population " (*Federal Register, Nov 14, 1985, p. 47151*). Further, EPA's attempt to downplay this contradiction by highlighting the "unusual" amounts of water consumed, obfuscates the fact that excessive thirst (polydipsia) is a common medical feature of kidney disease. Thus, the argument that excessive thirst is an unusual confounding factor that somehow relieves the EPA of having to protect individuals with kidney disease, is an invalid argument and a violation of EPA's mandate under the Safe Drinking Water Act to protect the most sensitive subsets of consumers.

Research, meanwhile, published since 1985 has raised yet further concerns about the safety of the MCLG for people with kidney disease.

Of particular concern are a series of studies showing that dialysis patients have an extremely impaired ability to clear fluoride from their body (Warady 1989; Huraib 1993; Tanimura 1994; Takahashi 1995; Cohen-Solal 1996; Al-Wakeel 1997; Usuda 1997; Torra 1998 Marumo 2001; Cohen-Solal 2002; Ng 2004).

Even when the dialysis unit filters the fluoride content to less than 0.05 ppm (as most now do), dialysis patients have still been found to accumulate strikingly high fluoride levels in their bones and blood – presumably from the fluoride in their drinking water and food.

For example, Torra (1998) found that a dialysis patient living in a 0.2 ppm area had a blood fluoride level of 185 ppb. This exceeds the concentration of fluoride found in humans with skeletal fluorosis (Li 1986, Li 1990; Savas 2001; Singla 1976) and the fluoride concentration found to weaken the bones of animals (Turner 1996).

Because of the marked inability of dialysis patients to excrete fluoride, researchers such as Usuda (1997) have advised that:

> "HD (hemodialysis) patients need to practice dietary control for the restriction of oral F intake. Namely, they should not take F-rich foodstuffs such as tea or marine products."

Torra (1998) made a similar recommendation, advising that:

> "it is important to control the intake of this element and the prolonged use of fluoridated dental products in the subjects with chronic renal insufficiency, to avoid a risk of fluorosis."

In light of these findings and recommendations, and the fact that over 400,000 Americans are on dialysis (NIH 2004), we find it completely unacceptable that EPA is continuing to rely on a LOAEL that has never taken into account individuals with kidney disease.

To further underscore the problem of assuming a 20 mg/day LOAEL for kidney patients, we have reproduced recent comments from Dr. Georges Boivin, a noted bone researcher from France who spent nearly two decades studying the impact of fluoride on bone:

> CONNETT: In the US, they've created this safe standard of 10 milligrams a day for life. This is from the age of 8 through for the rest of your life. Do you think that for a kidney patient, what would you say about 10 milligrams a day for a kidney patient?
>
> BOIVIN: For a patient with bad kidney function?
>
> CONNETT: Yes.
>
> BOIVIN: It is 10 milligrams of fluoride ion?
>
> CONNETT: Yes, per day.
>
> BOIVIN: Ah, it is too much. It is definitely too much. During all the life? I would be very surprised if you do not obtain skeletal fluorosis after some years of treatment with such a dose in patients suffering from a bad, a poor renal function.
>
> CONNETT: So you think that's too high a level for the kidney patients?
>
> BOIVIN: Absolutely. 1 milligram is perhaps correct, but 10 milligram is too much. It is half the therapeutic dose, and the therapeutic dose is for two years only...
>
> CONNETT: Even getting it from little bits each day, not in one bolus dose?
>
> BOIVIN: I think that a total of 10 milligrams per day is too much, whatever the source, whether it is one source or multiple sources. I think it is too much.
>
> CONNETT: Do you think it is too much for just the everyday person, not just the kidney patient?
>
> BOIVIN: It is too much because in the population you can not

> say what patient is, or will be, suffering from renal insufficiency in the future. *(Video-taped interview with Michael Connett, October 7, 2005).*

The fact that doses lower than 20 mg/day can not – with reasonable certainty – be considered safe for individuals with kidney disease underscores the inadequacy of the 20 mg/day LOAEL, and its corresponding reference dose, for susceptible subsets of consumers. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 9. MCLG Flawed Assumption #3: *The 20 mg/day LOAEL, based on 1930's data, is still up to date*

A further problem with EPA's use of the 20 mg/day LOAEL in deriving its 1985 MCL, was the fact that the 20 mg/day LOAEL was already outdated by the time EPA wrote the standard.

The scientist who had derived the 20 mg/day LOAEL from Roholm's research was Harold C. Hodge, a prominent pro-fluoridation scientist (Hodge 1950). Hodge first published this estimate in 1950, and repeated it continuously throughout the 1950s, 1960s, and 1970s. In 1979, however, Hodge revised his estimate, conceding that doses as low as 10 mg/day could cause crippling fluorosis (Hodge 1979).

Although Hodge revised his estimate in 1979, 6 years before EPA issued its MCL, the EPA chose to use Hodge's original estimate from 1950.

Data published since 1985 supports Hodge's 1979 estimate.

In 2003, Cao published a careful analysis of the doses causing crippling skeletal fluorosis in Tibet. According to Cao's analysis, the average dose causing crippling fluorosis was just 12 mg/day. A more recent study from Sun (2005) found advanced fluorosis among Chinese brick tea drinkers who consumed an average of just 6.4 mg fluoride a day.

While nutritional factors likely amplify the toxicity of fluoride in Tibet, India, and China, it should be born in mind that there are many malnourished individuals living in the US as well (NCCNHR 2000; USDA 2003), and their susceptibility may be quite similar to the situations in some of the Asian communities studied. As noted, for instance, in a recent review of malnourishment in elderly populations of the US:

> "the level of malnutrition and dehydration in some American nursing homes is similar to that found in many poverty-stricken developing countries where inadequate food intake is compounded by repeated infections" (NCCNHR 2000).

Further, the findings from Asia are consistent with the 1993 estimates from the National Research Council. In 1993, the NRC estimated that crippling skeletal fluorosis may be caused by exposure to as little as 10 mg/day.

Based on this data, it is completely inappropriate for the EPA in 2004 to still be using 20 mg/day as the LOAEL for crippling fluorosis. Accordingly, EPA's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 10. MCLG Flawed Assumption #4: *Crippling fluorosis is only found in communities with >10 ppm fluoride in water.*

In EPA's January 20, 2004 risk assessment, they stated: "the typical 100x factor used by the HED to account for inter- and intra-species variability have been removed due to the large amounts of human epidemiological data surrounding fluoride and skeletal fluorosis" (US EPA, 2004a; p. 16).

The problem with this assertion by EPA is that it is based again on incorrect assumptions made in 1985 – namely the ODW's demonstrably incorrect characterization of epidemiological data on skeletal fluorosis.

In its November 14, 1985 Final Rule, EPA's ODW made a profoundly incorrect assumption about the epidemiological data on skeletal fluorosis. To quote:

> "EPA notes that crippling skeletal fluorosis, rheumatic attack, pain and stiffness have been observed in a large number of individuals in other countries chronically exposed to fluoride in drinking water at levels of 10 mg/L to 40 mg/L" (*Federal Register, Nov 14, 1985, p. 47144*).

ODW's contention that crippling fluorosis was only found in other countries when the water supply exceeded 10 ppm fluoride, while fitting conveniently with EPA's desired 4 ppm MCLG + 2.5 safety factor, was incorrect.

Prior to 1985, there were at least 6 studies, published in the peer-reviewed literature, documenting crippling fluorosis in communities with less than 10 ppm fluoride (see Table5). 2 of these 6 studies were from the U.S.

TABLE 5: Documented Cases, Prior to 1985, of Crippling Skeletal Fluorosis in Humans Consuming Water with < 10 ppm Fluoride

Study	Water F Content Mean, ppm (range)	Crippling Skeletal Fluorosis?	Country
Singh 1961	1.2 & 1.3	Yes	India
Siddiqui 1970	1.35	Yes	India
Sauerbrunn 1965	(2.2-3.5)	Yes	U.S.
Krishnamachari 1973	(3.5-6.0)	Yes	India
Goldman 1971	(4.1-8.0)	Yes	U.S.
Siddiqui 1955	5.2	Yes	India

It is puzzling and unacceptable, therefore, for EPA to have concluded in 1985 that the minimum water fluoride level producing crippling fluorosis was 10 ppm. Indeed, one of the most thorough and widely-cited studies on fluorosis in India, conducted by a scientific advisor to the WHO (Jolly), clearly showed crippling fluorosis to occur at levels well below 10 ppm. Jolly published this data in 1970 (see Table 6), and thus there is little excuse for the EPA to have ignored it in 1985 - and for other EPA agencies to perpetuate this oversight. Indeed, the burden is on EPA pesticide's division to clearly show why this information is not relevant.

TABLE 6: Relation between Water Fluoride & Skeletal Fluorosis in Punjab, India (1970)					
	Fluoride Content of Water		Skeletal Fluorosis		
Village	Mean (ppm)	Range (ppm)	Individuals Examined	Skeletal Fluorosis %	Crippling Fluorosis
Gharachon	1.4	0.9-2.5	82	2.4	No
Laluwala	2.4	1.0-5.5	74	23.0	No
Dhapai	3.0	1.1-5.5	107	19.6	No
Bhodipura	**3.0**	**1.3-5.2**	64	42.2	**Yes**
Rajthai	3.3	0.5-6.5	160	10.0	No
Bhikti	**3.3**	**1.0-5.9**	160	45.6	**Yes**
Sanghera	**3.6**	**1.1-5.8**	154	33.1	**Yes**
Ramuana/ Ganjigulab	**5.0**	**1.5-11.5**	90	60.0	**Yes**
Singh	**8.5**	**3.7-14.0**	56	58.9	**Yes**
Khara	**9.7**	**6.0-16.2**	232	80.7	**Yes**
SOURCE: Jolly SS. (1970). Fluoride in Medicine. Hans Huber, Bern. pp. 116					

If there was no justification for EPA to cite a 10 ppm threshold for crippling fluorosis in 1985, there is even less justification to do so today since more data is now available confirming that crippling fluorosis does indeed occur in communities with less than 10 ppm (see Tables 7 and 8). The EPA Pesticide Division's vague reference, therefore, to a large body of epidemiological data to support the MCLG is extremely misleading. Being that much of this epidemiological data contradicts the premise of EPA's MCLG, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

TABLE 7: Documented Cases, Post-1985, of Crippling Skeletal Fluorosis in Humans Consuming Water with < 10 ppm Fluoride			
Study	Water F Content Mean, ppm (range)	Crippling Skeletal Fluorosis?	Country
Misra 1988	**2.4**	**Yes**	India
Cao 2003*	**(3.2-4.5)**	**Yes**	Tibet
Fisher 1989	**3.9**	**Yes**	Mexico
Haimanot 1990	**(4.0-7.0)**	**Yes**	Ethiopia
Misra 1988	**5.5**	**Yes**	India
Misra 1988	**7.0**	**Yes**	India
Brouwer 1988	**7.4**	**Yes**	Senegal
*Cao's data refers to the F content of brick tea, the sole significant source of F (99% of total intake) in the area studied.			

TABLE 8: Relation between Water Fluoride & Skeletal Fluorosis in Rajasthan India (2001)					
	Fluoride Content of Water		Skeletal Fluorosis		
District/ Village	Mean (ppm)	Range (ppm)	Individuals Examined	% w/ Skeletal Fluorosis	Crippling Fluorosis?
Banswara					
Deolya	1.5	1.0-2.8	132	6.1%	No
Isarwada	1.6	1.2-2.1	108	6.5%	No
Gangertalai	1.9	1.2-3.0	102	14.7%	No
Vassioda	2.6	2.2-2.9	122	18.9%	No
Mangala	**3.3**	**2.7-4.1**	126	24.6%	**Yes**
Borda	**3.5**	**2.6-4.2**	120	30%	**Yes**
Chhotipadel	**3.7**	**2.9-4.6**	116	32.8%	**Yes**
Dungarpur					
Fatehpura	1.5	1.0-2.3	105	9.5%	No
Mewadi	1.6	1.1-1.8	112	8.9%	No
Jhariyana	1.8	1.7-2.0	104	19.2%	No
Indora	2.4	1.1-3.1	105	25.7%	No
Deotalab	**2.8**	**1.5-4.1**	98	39.8%	**Yes**
Dad	**3.1**	**2.8-3.9**	96	42.7%	**Yes**
Bokedsal	**3.2**	**2.9-3.5**	102	39.2%	**Yes**
Udaipur					
Matasula	1.5	1.2-1.7	103	6.8%	No
Amlu	1.6	1.3-1.6	94	8.5%	No
Dagar	1.9	0.2-3.0	90	15.6%	No
Thada	2.6	0.2-5.1	102	19.6%	No
Bhabrana	**3.0**	**2.6-3.5**	114	21.1%	**Yes**
Dhamodar	**3.8**	**3.0-4.7**	110	33.6%	**Yes**
Jhalara	**4.0**	**3.5-4.7**	142	36.6%	**Yes**
SOURCE: Choubisa SL. (2001). Endemic fluorosis in Southern Rajasthan, India. Fluoride 34: 61-70.					

While it is true that nutritional deficiencies, and elevated water consumption, in India and China can exacerbate the impact of waterborne fluoride, these conditions can also be found in the US as well (NCCNHR 2000; USDA 2003). It would not be surprising therefore if malnourished individuals in the US exhibit a similar susceptibility to fluoride toxicity as found in India and elsewhere. This possibility, in fact, was articulated by the Surgeon General's 1983 panel reviewing – at the request of the EPA - the "Non-Dental Health Effects of Fluoride." To quote:

> DR. KLEEREKOPER: The reports outside of the United States, taking everything into consideration, do get clinically observable adverse effects certainly at four (ppm) or above. There are plenty of papers.
>
> DR. SPENCER: I don't believe that we can compare a report in India which is a tropical country, where you don't know how much water you take in, where the nutritional status is very poor, where they don't have any milk and little meat; therefore, no calcium, no phosphorus and magnesium and one cannot compare this to the high fluoride areas in this country.
>
> DR SMITH: I think you are going to find some populations of that sort in this country too.

> DR. SPENCER: Then we should see more pathologic indication of myelopathy and fluorosis in this country. Why don't we see it in the areas of four ppm?
>
> DR. KLEEREKOPER: I think that you have to conclude that we haven't looked for it and we really don't know. (Surgeon General, 1983, p 412-413).

Thus, given the established fact that dietary deficiencies increase an individual's susceptibility to fluoride toxicity, and given the fact that there has yet to be any systematic study to examine the relationship between malnourishment, fluoride exposure, and fluorosis in the US, EPA can not state with reasonable certainty that susceptible subsets of consumers will not be harmed at doses lower than the 20 mg/day LOAEL, and its respective reference dose. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 11. MCLG Flawed Assumption #5: Crippling fluorosis is the only adverse effect fluoride has on bone.

Yet another incorrect assumption made by ODW was their assumption that crippling fluorosis is the only adverse effect fluoride can have on bone. As we will demonstrate below, this assumption is blatantly incorrect. Fluoride can cause other adverse effects on bone and it produces these effects before it produces crippling fluorosis. Two key pre-crippling bone effects ignored by EPA are:

- Arthritic symptoms
- Bone fracture

We will discuss these effects one at a time.

ISSUE 11a. MCLG Flawed Assumption #5 (continued). *Arthritic Symptoms: A pre-crippling effect of fluoride ignored by EPA*

One of the most significant errors made by EPA in 1985, was their conclusion that the pre-crippling clinical stages of skeletal fluorosis (osteosclerotic changes in bone structure) are not associated with any adverse symptoms. To quote:

> "the Agency can find no evidence that fluoride induced increases in bone density, osteosclerosis, result in bodily harm or impaired functioning of the body. No new evidence or argument on this point was received in public comment. Therefore, the EPA reaffirms its conclusion that fluoride induced osteosclerosis is not an adverse health effect within the meaning of the SDWA" (EPA 1985).

EPA's contention that the pre-crippling, osteosclerotic phase of fluorosis is asymptomatic, is incorrect.

According to the US Public Health Service (1991), fluoride-induced osteosclerosis can cause, depending on its severity, "sporadic pain", "stiffness of joints," "chronic joint pain," and "arthritic symptoms." Further, the PHS concluded that these arthritic effects occur before the crippling stage of fluorosis.

This ability of the pre-crippling osteosclerotic stage of fluorosis to cause joint pains should have been well known by EPA in 1985, as all of the studies cited by the Public Health Service were published prior to 1980.

While not everyone with pre-crippling clinical fluorosis will experience arthritic pain (Franke 1975), the evidence is clear that some people *will* (Singh 1963; Singh & Jolly 1970; Vischer 1970; Cook 1971; Schlegel 1974; Franke 1975; Teotia 1976; Czerwinski 1977; Boillat 1980; Carnow 1981; Czerwinski 1988; PHS 1991; Roschger 1995; Savas 2001; Eichmiller 2005).

Thus, if skeletal fluorosis is EPA's endpoint of concern, it is imperative that EPA set its MCLG to protect against the arthritic symptoms encountered in the pre-crippling, clinical stage of the disease. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 11b. MCLG Flawed Assumption #5 (continued). *Bone fracture: A pre-crippling effect of fluoride ignored by EPA*

In addition to its ability to produce arthritic symptoms in the pre-crippling phase of fluorosis, fluoride can also reduce the strength of bone thereby increasing the risk of fracture. This is another issue that EPA ignored when setting its 1985 standard, although to be fair to EPA's ODW, most of the research on fluoride and fracture has been published after 1985. While this fact may excuse ODW's 1985 staff, it raises serious questions about the due diligence employed by the Pesticide Division in 2004 when they chose to rely on crippling fluorosis as the sole endpoint of concern.

Indeed, based on the scientific research published after 1985, the evidence on fluoride and bone fracture is amply clear that fluoride can cause bone fracture well before it causes a crippled skeleton.

There are three lines of evidence supporting this conclusion: human clinical trials, epidemiological studies of communities with varying levels of waterborne fluoride, and animal studies. We'll discuss each in turn.

Fluoride & Bone Fracture: Clinical Trials

Since 1985, a series of well-controlled clinical trials - including the much anticipated NIH-sponsored 4 year double-blind trial (Riggs 1990) - have reported that osteoporotic patients treated with fluoride experience a higher rate of bone fractures, particularly hip fracture and other types of non-vertebral fracture (Dambacher 1986; Hedlund 1989; Bayley 1990; Orcel 1990; Riggs 1990; Schnitzler 1990; Haguenauer 2000; Gutteridge 2002). Two studies published before 1985, including a double-blind trial – had also found this effect (Inkovaara 1975; Gerster 1983).

Of particular interest are the clinical trials of Inkovaara (1975), Gerster (1983), Hedlund (1989); Bayley (1989), Orcel (1990), and Gutteridge (2002), as the doses used in these trials ranged from just 21 to 25 mg per day. Perhaps more important, however, was the short duration of these trials, and the fact that fractures were seen in some patients within just 8 and 11 months of exposure (Inkovaara 1975; Gerster 1983). Thus, at doses virtually identical to EPA's LOAEL, clear evidence of toxicity was experienced in less than a year of exposure – much less than the 10-year minimum duration necessary to cause an adverse effect according to EPA.

While EPA attempted to dismiss the relevance of these trials by pointing out that the doses greatly exceed the current LOAEL of 20 mg/day, EPA's argument was based on the elementary error of failing to convert the dose of sodium fluoride into the respective dose of fluoride ion. Hence, EPA stated that the doses used by Hedlund (1989), Bayley (1990), and Gutteridge (2002) ranged from 50 to 60 mg/day, when in fact they ranged from 21 to 25 mg/day – or just a hair higher than the LOAEL.

EPA's dismissal also overlooked the fact that the fractures in these trials occurred before crippling fluorosis developed, and developed over a notably shorter duration. Hence, it is simply not appropriate for EPA to continue pretending that 1) crippling fluorosis is the first adverse effect that

fluoride can have on bone, and that 2) an adverse effect on bone requires at least 10 to 15 years of exposure. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

Fluoride & Bone Fracture: Epidemiology

Just as most clinical research reporting increased fracture rates in fluoride-treated patients was published after 1985, the same is true for epidemiological studies finding an increased fracture rate in communities with elevated fluoride in water. Indeed, all of the important studies on waterborne fluoride and fracture have been published since 1985.

A year after EPA issued its MCL, Sowers (1986) reported a statistically significant increase in bone fractures in a 4 ppm community versus a control community with 1 ppm. In 1991, Sowers updated her findings, and noted that in addition to an increase in bone fractures, there was also a statistically significant reduction in bone mass in the 4 ppm community.

A year earlier, Phipps (1990) reported the results of a separate study which also looked at bone mass in a 4 ppm community. As with Sowers, Phipps found that the 4 ppm community had significantly less bone density than the 1 ppm community in the bone that she measured (the forearm).

While Phipps' study did not investigate bone fracture rates, a later study by Li (2001) did. As with Sowers, Li found a statistically significant increase in bone fracture rates, particularly hip fractures, in communities with excess fluoride. In a community with 4.3-8 ppm, Li found that the hip fracture rate was 3 times higher than the hip fracture rate in the control 1 ppm community. Li also found a doubling of hip fractures at 1.5+ ppm, however, this effect was not statistically significant at the 95% confidence interval.

Following closely on Li (2001), a study by Alarcon-Herrera (2001) showed that, in a high endemic area for fluoride in Mexico (1.5 – 5.5 ppm), bone fractures in children increased linearly with the severity of dental fluorosis. Of note with Alarcon-Hererra's study, is the fact that an increase in fracture rate was present in the group of children exhibiting only mild fluorosis. According to the CDC(2005) dental fluorosis now impacts over 30% of American children, and not all of it in its very mild form. However, no attempt has been made in the US to see if this correlation exists among American children.

A more recent study by Sowers (2005), again looking at a 4 ppm versus 1 ppm community, has again reported significantly higher osteoporotic fractures in the 4 ppm area, although the significance of this finding was lost when the authors controlled for other covariates, including bone density.

When taken together as a whole, the studies by Sowers (1986, 1991, 2005), Phipps (1990), Li (2001), Alarcon-Herrera (2001) as well as Arnala (1985) disallow the EPA from having any semblance of "reasonable certainty" that fracture rates are not increased at the 4 ppm MCLG.

It is, therefore, completely unacceptable that the EPA Pesticide Division continues to rely on ODW's 1985 outdated assumption that crippling fluorosis is the only adverse effect of fluoride on bone. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate

Fluoride & Bone Fracture: Animal Studies

In addition to the clinical and epidemiological studies on fluoride/fracture, a series of well conducted animal studies finding that fluoride reduces bone strength have also been published since 1985 (Mosekilde 1987; Turner 1992, 1993, 1995, 1996, 1997, 2001; Lafage 1995; Sogaard 1995).

One of the important observations from these studies is that fluoride was able to reduce the strength of bone before any evidence of fluorosis was detectable on the microscopic level (Fratzl 1996; Turner 1995, 1997). This finding again underscores the negligence of EPA's continued focus on crippling fluorosis as the only bone effect to protect against.

Another important result from the animal studies is Turner's 1996 finding of increased osteomalacia and reduced bone strength in rats with kidney disease drinking water with the estimated human equivalent concentration of 3 ppm fluoride (Turner 1996). Further, the blood fluoride levels (9-10.8 umol/L) consistently associated with reduced bone strength in Turner's studies (Turner 1995, 1996, 2001; see also: Dunipace 1995, 1998), are blood fluoride levels known to occur in humans with kidney disease living in communities with less than 2 ppm fluoride in water (Johnson 1979; Waterhouse 1980; Warady 1989; Torra 1998).

Turner's repeated finding that fluoride reduces bone strength at blood fluoride levels seen in humans with kidney disease drinking less than <2 ppm, further undermines the premise that the MCLG is safe for all susceptible subsets of consumers. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUES 12-21. MCLG Flawed Assumption #6: Fluoride has no chronic adverse effects on soft tissues.

In a similarly egregious manner as the EPA MCLG ignores all bone effects except crippling fluorosis, the EPA MCLG also ignores all soft tissue effects. Indeed, EPA's standard is based on the assumption that an intake of 20 mg/day of fluoride for an entire lifetime will not produce any adverse effect on any soft tissue in the body.

Even if one were to accept that the evidence supported this assumption in 1985, it is simply no longer possible to maintain this assumption today – as there now exists an overwhelming body of evidence showing that fluoride can damage soft tissues, sometimes at remarkably low concentrations. This fact makes the 1985 MCLG yet more obsolete and antiquated.

Non-skeletal tissues and functions impacted by fluoride include:

- Brain
- Kidney
- Insulin Secretion
- Endocrine disruption (reproductive system, g-proteins, pineal gland, thyroid gland)

EPA cannot state with certainty that fluoride does not affect soft tissues. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 12: Fluoride's Impact on the Brain

- *Brain Damage in Animals.*

When the EPA issued its MCLG in 1985, there was hardly any research yet available on fluoride and the brain. This is no longer the case. Starting with a 1986 study from Guan, there have been over 30 studies indicating that fluoride can damage animal brain. In some cases brain damage has been caused at very low doses. For example, Varner et al. (1998) fed rats with 1 ppm fluoride in doubly distilled and de-ionized water (1 ppm is the same level used in water fluoridation programs) for 1 year and showed kidney damage, brain damage and uptake of aluminum into the brain. In addition, the studies by Dr. Guan and colleagues (Guan 1998; Long 2002; Shen 2004) have consistently found neurotoxic effects among rats drinking water with 30 ppm fluoride in water. When considering that blood fluoride levels are typically 5 times lower in rats than in

humans when exposed to the same dose of fluoride (Turner 1992), the Guan studies are probably more indicative of human exposure to ~6 ppm fluoride in water.

- *Fluoride crosses the blood brain barrier*

Research has shown that fluoride is able to pass through the blood brain barrier. While some, such as Whitford have questioned whether it can accumulate in the tissue, it is now abundantly clear that – at the very least - the fluoride circulating in the bloodstream will enter the brain. (Zhai et al. 2003; Inkielewicz & Krechniak 2003; Vain and Reddy 2000; Long 2002; Guan et al 1998; Mullenix et al. 1995; Gerents et al. 1986; Tomomatsu 1981).

- *Fluoride and the hippocampus.*

Several published papers on fluoride's effect on the hippocampus should raise concern (Zhai JX et al. 2003; Bhatnagar et al. 2002; Shivarajashankara YM et al. 2002; Chen J et al. 2002; Zhang Z et al. 2001; van der Voet et al. 1999; Varner et al. 1998; Mullenix et al. 1995; Kay et al. 1986). Damage to the hippocampus usually results in profound difficulties in forming new memories and affects access to memories prior to the damage. In Alzheimer's disease, the hippocampus becomes one of the first regions of the brain to suffer attack; causing memory problems and disorientation

- *Lowering of IQ in children.*

There have been several studies from China indicating a lowering of IQ associated with exposure to fluoride. Some of these studies have not controlled for some key variables, but the latest study by Xiang et al. (2003 a and b) did control for both lead and iodine exposure, and found a lowering of IQ children estimated to occur at 1.8 ppm fluoride. Of added concern is the potential for fluoride to exacerbate the neural developmental effects on the fetus in situations where the pregnant woman has low iodine intake (Lin Fa-Fu, 1991). The ability of fluoride to exacerbate the neurological lesions induced by iodine deficiency (a major cause of low IQ) has since been established in repeated animal experiments (Zhao 1998; Wang 2004a,b; Ge 2005).

- *Pre-natal effects: fluoride crosses the placenta.*

The placenta does not prevent the passage of fluoride from maternal blood to the fetus (WHO 2002). As a result, pre-natal exposure to fluoride may present risks to the child. According to a 1992 paper (Du) presented results of an examination of brains of 15 aborted fetuses at 5-8th gestation month from an endemic fluorosis area compared with those from a non-endemic area. Fetal brains from the endemic fluorosis area revealed a significant reduction in the density of mitochondria and a reduction in the mean volume of neurons.

- *Fluoride helps aluminum cross the blood-brain barrier*

Fluoride elevates the aluminum level in brain (Varner et al. 1998, Isaacson et al. 1997) and the formation of beta amyloid deposits (Varner 1998) which are the classic brain abnormality of Alzheimers' disease. Varner et al. (1998) discussed the reason why rats in the NaF group had detectable levels of aluminum in their brain. They postulated that fluoride enables the aluminum in the rat chow to cross the blood brain barrier.

- *Fluoride ions are well-known activators of G-proteins.*

G-proteins are considered the most important signal transducing molecules in cells. Fluoride's interaction with G-proteins is thought to explain its well done activation of adenylate cyclase. In neurons, adenylate cyclases are located next to calcium ion channels for faster reaction to Ca2+ influx; they are suspected of playing an important role in learning processes. Recent data (Borasio et al. 2004) suggest a NaF-sensitive G protein "involvement of the inhibitory regulatory

subunit of the cAMP system in inducing presynaptic inhibition by interaction with calcium-sensitive structures."

EPA cannot state with certainty that fluoride will cause no harm to the brain of vulnerable age groups, such as the fetus, infant, child, and elderly. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 13: Fluoride's Impact on the Kidney

With the exception of the pineal gland, the kidney accumulates more fluoride than all other soft tissues in the body (Hongslo 1980; Ekstrand 1996; Whitford 1996). It is well known that high doses of fluoride can damage the kidney after short periods of exposure, e.g. anesthesia (Mazze 1977). There is also evidence that low doses of fluoride, taken over longer periods of time, can also damage the kidney. For example, both Varner (1998) and Ramseyer (1957) found kidney damage in rats drinking water with just 1 ppm. Manocha (1975) found kidney damage in monkeys drinking water with just 5 ppm F, while Borke & Whitford (1999) found kidney damage in rats drinking water with just 10 ppm. In the latter study, the average blood fluoride levels of the rats with kidney damage was just 38 ppb – a concentration commonly exceeded in people living in < 4 ppm areas (Parkins 1974; Johnson 1979; Warady 1989; Jackson 1997; Torra 1998; Sowers 2005).

Complementing this animal research, many studies have found kidney disease to be a common feature of human skeletal fluorosis (Ando 20001; Derryberry 1963; Jolly 1980; Kumar 1963; Lantz 1987; Reggabi 1984; Shortt 1937; Siddiqui 1955; Singh 1963; Singla 1976).

Also, and perhaps most significantly, a recent human study from China, has found a dose-dependent relationship between fluoride ingestion and kidney damage in children (Liu 2005). The study found evidence of kidney damage among children drinking water with as little as 2.6 ppm. This is well below EPA's MCLG.

EPA cannot state with certainty that fluoride will cause no harm to the kidney. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 14: Fluoride's Impact on the Insulin Secretion

A new study published this year (Menoyo 2005) has confirmed earlier animal, human, and in-vitro findings (Rigalli 1990, 1995; Trivedi 1993) that fluoride can impair the secretion of insulin at remarkably low levels. The concentration of fluoride repeatedly found capable of inhibiting the secretion of insulin was only 5 umol/L (95 ppb), with a non-significant reduction found study at a concentration as low as 2 umol/L (Rigalli 1995; see Table 1).

Based on this research, spanning over 15 years, (Rigalli 1990, 1995), the authors conclude that:

> "The overall information afforded by present experiments indicate that extracellular concentrations of fluoride above 5 umol/L [95 ppb] affect the insulin excretion. The results suggest that fluoride affects some stage of insulin secretion situated below the cascade of events that include the participation of calmodulin, protein-kinase C and cyclic AMP" (Menoyo 2005).

What's remarkable about this finding is that 5 umol/L is a concentration of fluoride that many individuals with kidney disease, even those living in ≤1 ppm areas, will attain in their bloodstream (Johnson 1979; Waterhouse 1980; Warady 1989; Torra 1998). Even some individuals without kidney disease living in <4 ppm areas will attain this concentration (Parkins 1974; Singer 1979; Jackson 1997; Sowers 2005).

With published evidence repeatedly finding that fluoride can inhibit insulin secretion at concentrations produced in humans by drinking water with ≤ 4 ppm fluoride, EPA can not state with reasonable certainty that the MCLG is safe for all subsets of consumers. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 15: Fluoride's Impact on the Endocrine System

Dow AgroSciences makes the incorrect claim that there is no evidence that fluoride causes any damage to the endocrine system (US EPA 2001a, 2002a, 2005a). In fact, there is a substantial body of scientific literature indicating that fluoride impacts the male reproductive system; interacts with G-proteins; accumulates in the pineal gland and lowers thyroid function. We discuss each of these in more detail below.

EPA did not correct this false assertion by Dow, which was published three times in the Federal Register (US EPA 2001a, 2002a, 2005a), the most accessible document to the public on pending tolerance issues. However, EPA did state in a docket document,

> "… The Agency is aware of potential endocrine effects of fluoride being noted in the open literature. From a preliminary review of this literature (Baetcke, et al., 2003), there does not appear to be a sufficient science foundation to permit confident conclusions regarding the ability of fluoride to produce endocrine effects… The National Academy of Sciences is currently in the process of reviewing the toxicological data for fluoride. When their review is available, EPA will reexamine this conclusion." (US EPA, 2004a, page 18)

The public deserves more than a "preliminary review" from EPA on this important issue. In stating that the "Agency is aware of potential endocrine effects of fluoride" EPA was negligent not to wait for the National Academy of Sciences review (if that is who they were relying on to resolve this issue) before issuing the tolerance. EPA cannot state with certainty that no harm will be done by fluoride to the endocrine system. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 16: Fluoride's Impact on the Male Reproductive System:

There is a substantive body of published papers that detail fluoride's adverse effects on the male reproductive system (see Neurath et al., 2005a). The predominant effect reported in animal studies is fluoride's potential to affect male fertility.

Sperm abnormalities
Pushpalatha et al. 2005; Chinoy et al. 2004; Chinoy & Sharma 2000; Chinoy et al. 1997; Kumar & Susheela 1995; Kumar & Susheela 1994; Song K et al. 1991; Chinoy, Sequeira , Narayana 1991; Chinoy & Rao et al. 1991; Pati & Bhunya 1987. (See attachment: Table 6)

Decrease in Sperm Count
Pushpalatha et al. 2005; Ghosh et al. 2002; Zhu XZ et al. 2000; Chinoy & Sharma 2000; ; Narayana & Chinoy 1994; Chinoy & Sequeira 1992; Chinoy, Pradeep & Sequeira 1992; Chinoy, Sequeira , Narayana 1991; Chinoy & Rao et al. 1991. (See attachment: Table 6)

Decrease in Sperm Motility:
Pushpalatha et al. 2005; ; Zhu XZ et al. 2000; Chinoy & Sharma 2000; Chinoy & Sharma 1998; Chinoy et al. 1997; Chinoy, Reddy, Michael 1994; Narayana & Chinoy 1994; Chinoy & Narayana 1994; Chinoy & Sequeira 1992; Chinoy, Sequeira , Narayana 1991. (See attachment: Table 6)

Decline in Testosterone Levels:
Chinoy et al. 2004; Susheela & Jethanandan 1996; Chubb 1985; Kanwar et al. 1983; Araibi

et al. 1989. (See attachment: Table 6)

Decrease in Fertility:
Elbetieha et al. 2000; Chinoy & Sharma 2000; Chinoy & Sharma 1998; Pinto et al. 1998; Chinoy et al. 1995; Chinoy, Reddy, Michael 1994; Chinoy & Sequeira 1992; Chinoy, Pradeep & Sequeira 1992; Araibi et al. 1989.

Leydig cell damage:
Susheela & Kumar 1997; Narayana & Chinoy 1994.

Effects on spermatogenesis:
Jiang CX et al. 2005; Chinoy, Tewari, Jhala 2004; Song K et al. 1991; Susheela & Kumar 1991; Chinoy, Rao et al. 1991; Shashi 1990; Kour & Singh 1980.

Fluoride accumulation in rodent testis:
Kiang CX et al. 2005; Inkielewicz & Krechniak 2003; Krasowska & Wlostowski 1996; Tomomatsu 1991)

With the numerous studies that demonstrate an effect on the male reproductive system, EPA cannot state with reasonable certainty that no harm will be done. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 17: Biological Plausibility of a Fluoride/Endocrine Effect:

In doing a weight of analysis of whether a pollutant has an undesired effect on a tissue it is always important to see if a biological mechanism of action can be proffered to help resolve mixed animal and human findings. With respect to fluoride's potential for impacting the endocrine system its activation of G-proteins demands careful attention. G-proteins are involved in transmitting signals across membranes from water soluble messengers at the outside of the cell in order to activate an enzyme or some other process inside the cell. Such water soluble messengers include many hormones.

There are thousands of biochemical experiments which document fluoride's ability in the presence of a trace amount of aluminum ion to activate G-proteins in the absence of the messenger. This offers a general mechanism whereby fluoride, if it reaches a sufficient concentration, could interfere with MANY hormonal systems. Of particular concern would be at the interface of soft and hard tissues.

EPA scientists did not respond to concerns of fluoride's impact on G-proteins. Everything is in its biological place for potential harm to occur from G-proteins when the fluoride enters the body. This important issue needed to be resolved prior to granting the tolerance. EPA cannot state with a reasonable certainty that harm will not occur via a G-protein mechanism. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 18: Fluoride's Impact on the Pineal Gland

Another place where fluoride concentrations are such that they could interfere with G-proteins, as well as enzymes, is the pineal gland.

In the 1990s, Jennifer Luke from the UK discovered that the human pineal gland accumulates fluoride. This gland, which is a calcifying tissue like the teeth and the bones, produces concentrations (average 9000 ppm) in the calcium hydroxy apatite crystals which is higher than either found in tooth enamel or the bone, except for those with crippling skeletal fluorosis (Luke, 2001).

In her PhD thesis Luke showed that the accumulation of fluoride in the pineal gland can reduce the gland's synthesis of melatonin, a hormone that helps regulate the onset of puberty. Fluoride-treated animals were found to have reduced levels of circulating melatonin and an earlier onset puberty than untreated animals (Luke, 1997). Luke concluded:

> "The safety of the use of fluorides ultimately rests on the assumption that the developing enamel organ is most sensitive to the toxic effects of fluoride. The results from this study suggest that the pinealocytes may be as susceptible to fluoride as the developing enamel organ (Luke 1997, page 7)."

The fact that fluoride's impact on the pineal gland was never studied, or even considered, before the 1990s, highlights a major gap in knowledge underpinning current policies on fluoride and health.

The fact that Luke found in her animal studies that fluoride lowered melatonin levels AND shortened the time the animals took to reach puberty, puts into interesting light a finding from the Newburgh-Kingston fluoridation trial. The authors reported that on average the girls in Newburgh started menstruation 5 months earlier than the girls in the non-fluoridated city of Kingston. However, they did not consider the result significant at the time (Schlesinger et al. 1956)

One of the risks we may be taking by exposing our whole population to fluoride is interfering with delicate regulatory timing processes, from the onset of puberty to the aging process.

In every comment we submitted to EPA (E Connett 2001, 2002, 2005a; P Connett 2002, 2004; Neurath 2005) on sulfuryl fluoride we noted our concerns of fluoride's potential to accumulate in the pineal gland. (In October 2001 we sent Luke's thesis to EPA's Dennis McNeilly who was then coordinating responses to the tolerances.) While EPA dismisses these concerns, it cannot dismiss the scientific plausibility that fluoride's ability to concentrate in the pineal has the potential to cause adverse effects. At the very least the EPA should have flagged this issue and directed Dow to do an analysis of the fluoride levels in the pineal glands of rats used in the developmental neurotoxicity studies. Also, EPA should have initiated a study to analyze archived human (including fetal) pineal glands for the levels of fluoride. Without such elementary data, EPA cannot say with certainty that more human fluoride exposure from these tolerances will do no harm. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 19: Fluoride's Impact on the Thyroid Gland:

For a long period in Europe (from the 1930s through to the 1970s) doctors used sodium fluoride to lower the activity of the thyroid gland of patients who suffered from hyperthyroidism. The doses used were remarkably low - 2-10 mg fluoride /day (Galletti and Joyet, 1958).

The response by promoters of fluoridation has been that while fluoride lowers the activity of the thyroid gland of patients with hyperthyroidism it has no effect on those with normal thyroid function.

For example, in 1970, Demole dismissed concerns about water fluoridation and its impact on the thyroid gland. He argued, based largely on animal studies, that fluoride, like some other drugs "which act upon the sick organism" is "inactive in the healthy organism."

However, Bachinskii et al. (1985) showed that normal thyroid function was lowered at 2.3 ppm fluoride in drinking water. This Russian study was not referenced by the EPA in 1986 or the National Research Council in 1993.

Meanwhile, in September 2005, at the 26th conference of the International Society for Fluoride Research, Dr. Alma Ruiz-Payan from the University of South Texas, presented her findings of a

study conducted in Mexico. This researcher found a significant reduction in thyroid function in adolescents drinking water at 1 ppm (Ruiz-Payan et al., 2005).

Lastly, research – in both animals and humans - has shown that fluoride's impact on the thyroid and brain is exacerbated when coupled with an iodine deficiency (Guan 1998; Li-Lu 1991; Wang 2004a,b, Ge 2005) – a fact that may explain some of the contradictory findings in the literature on fluoride and thyroid. The CDC has recently estimated that 12% of the US population has an iodine deficiency (CDC 1998). This represents an extremely large subset of consumers that are potentially at increased risk from fluoride exposure.

Considering the significant problem of hypothyroidism in the United States, and the widespread and increasing exposure to fluoride, this issue needs urgent attention. Being that no research has ever been conducted in the US to examine the combined impact of fluoride exposure and iodine deficiency, EPA can not state with reasonable certainty that individuals with iodine deficiency will be not be harmed by current fluoride exposures. Accordingly, the risk assessment supporting the tolerances are scientifically, factually and legally inadequate.

ISSUE 20: Fluoride and Osteosarcoma in Boys

EPA's failure to consider the evidence that fluoride may cause osteosarcoma represents a major problem with its risk assessment. In light of the acknowledged biological plausibility of a fluoride osteosarcoma connection (NTP 1990), and in light of new epidemiological research (Bassin 2001) finding a statistically significant, "remarkably robust", and age-specific association between fluoride and osteosarcoma in young males, it is simply not possible for EPA to claim "reasonable certainty" that fluoride does not cause osteosarcoma. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

(For an extensive review of the scientific literature on fluoride/osteosarcoma, we refer EPA to our recent two-part submission submitted to the National Research Council earlier this year. We have included copies of this submission with the attached documentation (P Connett et al, 2005 a, b).

ISSUE 21: Fluoride's Teratogenic Effects

The possibility that fluoride is a teratogen is supported by at least four published studies showing that it can reduce crown-rump length (one study referred to it as head-tail length). This effect was found in FOUR species exposed to either sulfuryl fluoride (rat and rabbit) or to sodium fluoride (frog and screech owl).

FROG: In 2003, Gof & Neff published the most definitive study and concluded that fluoride "is a direct acting teratogen on developing embryos" The authors stated:

> ... The most prominent malformations caused by sodium fluoride are **reduction in the head-tail lengths** and dysfunction of the neuromuscular system of the tadpoles. The values for LC50, EC50, and minimal concentration to inhibit growth (MCIG) of sodium fluoride met the limits established for a teratogen in frog embryos, **showing that sodium fluoride is a direct acting teratogen on developing embryos.** Since FETAX has a high degree of success in identifying mammalian teratogens, the observed teratogenic action of sodium fluoride on frog embryos would indicate **a strong possibility that sodium fluoride may also act directly on developing mammalian fetuses to cause malformation** (Goh & Neff, 2003).
>
> Note: Dow's studies for teratogenicity were performed in 1980 and 1981.

RAT: 2001: Collins & Sprando et al. reported

> The single **statistically significant decrease in crown-rump length of F2 females** at 175 ppm [sodium fluoride] was considered random. (Collins et al. August 2001)

RAT: 1989: TR Hanley and other Dow Chemical scientists reported:

> Groups of 35-36 bred rats were exposed via inhalation to sulfuryl fluoride for 6 hr/day on Days 6 through 15 of gestation and exposed to levels of 25, 75, and 225 ppm. "Mean fetal body weights and **crown-rump lengths among litters exposed to 225 ppm were statistically elevated** when compared to controls; however these values were only 3.7 and 1.5% above the control values, respectively, and were not considered toxicologically significant . (Hanley et al. 1989)

RABBIT: 1989: TR Hanley and other Dow Chemical scientists reported:

> Groups of 28-29 inseminated rabbits were exposed via inhalation to sulfuryl fluoride for 6 hr/day on days 6 through 18 of gestation and exposed to levels of 25, 75, and 225 ppm. "At 225 ppm, the average body weight was significantly lower (14%) than in the control group, and there was a **trend toward decreased fetal crown-rump length**." (Hanley et al. 1989)

SCREECH OWL: 1985: Researchers at the Patuxent Wildlife Research Center reported:

> The effects on reproduction in screech owls (Otus asio) of chronic dietary sodium fluoride administration of 0, 40, and 200 ppm were examined. Fluoride at 40 ppm resulted in a significantly smaller egg volume, while 200 ppm also resulted in lower egg weights and lengths. Day-one hatchlings in the 200 ppm group weighed almost 10% less than controls and had **shorter crown-rump lengths**. (Hoffman et al. 1985)

Fetal growth is critical to a person's eventual height. Before birth, the key measure is the crown-rump length. The teratogenic effect found in the four species cited above has a distinct possibility of translating to the human in the following, but not exclusive, way. Ruiz-Payal et al. (2005) reported the results of a study of 201 adolescents exposed to chronic exposure to various water fluoride concentrations (0.3, 1.0, 5.3 mg/L) in three communities in northern Mexico. The authors stated,

> In Villa Ahumada [water fluoride average of 5.3 mg/L] **a significant inverse relationship was found between urine fluoride levels and stature**; this association suggests that fluoride exposure may affect the teeth but also the growth of adolescents… These findings show that high fluoride ingestion has a definite relationship with the prevalence of dental fluorosis, decrease of stature, and decrease of thyroid hormone secretion…

EPA has not adequately assessed fluoride's potential for inducing teratogenic effects. EPA cannot state with a reasonable certainty that no harm will occur. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 22. MCLG Flawed Assumption #7. A safety factor of 2.5 is adequate to protect major identifiable sensitive sub groups.

The EPA should have used the standard safety factor of 10 to allow for the range of vulnerability in a human population to any toxic substance (intra-species variation). This was an especially serious error because the data used to derive the 20 mg/day LOAEL (Roholm 1937) was based on a small sample of otherwise healthy industrial workers. One needs a safety factor, therefore, to cover the extra vulnerability of the very young, the very old, the malnourished, and those with

kidney dysfunction. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 23. MCLG Flawed Assumption #8. People only drink 2 Liters of Water a Day.

EPA's assumption that people only drink 2 liters of tap water a day ignores the fact that - according to EPA's own data (EPA 2004c) - 10% of the population drink more than 2 liters of tap water a day.

Moreover, EPA's MCLG incorrectly assumes that tap water is the only source of water intake. According to data cited by FNB (2004), tap water comprises less than 50% of an individual's total water intake – a fact that is confirmed when comparing the difference between total water intake and total tap-water intake in the CSFII database.

EPA's failure to account for other sources of water intake besides tap water is significant because most non-tap water beverages in the US now contain elevated fluoride levels due to the widespread practice of water fluoridation. Hence, an individual drinking 2 liters of tap water in a 4 ppm community will exceed the reference dose the moment they drink any additional processed beverage. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 24. MCLG Flawed Assumption #9. There are no other sources of fluoride besides water.

Just as EPA's MCLG incorrectly assumes that tap water is the only source of water intake, it also incorrectly assumes that tap water is the only source of fluoride (USDA 2004).

Hence, if a person living in a 4 ppm area consumes 2 liters of water a day, they will exceed the reference dose as soon as they drink one cup of tea, one can of soda, or consume any other additional source of fluoride (which may now include certain fluorinated pharmaceuticals that metabolize into fluoride ion – see: Rimoli 1991; Pradhan 1995).

EPA's failure to account for other sources of fluoride besides tap water was a terrible omission. What EPA should have done was subtract from their reference dose (8 mg/day) their best estimate of exposure from all other sources (X mg/day). The safe drinking water standard would then have been derived as follows (for the sake of this specific argument we will use the EPA's inaccurate assumption that no one drinks more than 2 liters of tap water per day):

$8 - X / 2 \text{ liters} = < 4 \text{ ppm}$.

If EPA had accounted for other sources of fluoride in such a manner, it might have been possible to protect individuals drinking water at the MCLG from exceeding the reference dose when they are exposed to additional sources of fluoride. But EPA didn't do this and thus the fluoride tolerances must be rescinded, otherwise people drinking 2 liters of water at the MCLG will exceed the reference dose the moment they get their first bite of sulfuryl fluoride fumigated food. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 25. EPA's attempt to use a new reference dose of 10 mg/day is not scientifically based.

In response to FAN's critique that the 1985 MCLG is an outdated and inadequate standard on which to derive a safe reference dose, EPA has suggested it may use the Institute of Medicine's "Tolerable Upper Intake Level" of 10 mg/day as an alternative reference dose. The Institute of Medicine's (IOM) standard, however, is as scientifically indefensible as EPA's MCLG, and thus not an acceptable alternative.

According to IOM's standard, it is safe for every individual in society (regardless of any health condition they may have, such as kidney disease) to ingest 10 mg of fluoride *every day of life from 8 years of age to death*. This is not a scientifically defendable statement. As noted, for instance, by Dr. Boivin in Issue 8 above, 10 mg/day can not be considered safe for people with kidney disease.

Furthermore, as detailed in section 12 of our September 2005 submission, the IOM issued an "uncertainty factor" of 1, despite the fact that a key author of the IOM report (Gary Whitford) had one year earlier stated that a dose of 10 mg/day could cause crippling fluorosis (Whitford 1996). The fact that a dose of 10 mg/day could go from a dose estimated to cause crippling fluorosis in 1996 to a dose assumed to be safe for every single member of the population in 1997 – without ANY new data published in the interim period – is a disgrace to science.

Underscoring the uncertainty of Whitford's and IOM's "certainty" in the safety of 10 mg/day for every member of the population, is the WHO's recent assessment that bone damage may occur at daily doses of 6 mg/day (WHO 2002). To quote:

> "studies from China and India indicate that for a total intake of 14 mg/day, there is a clear excess risk of skeletal adverse effects; and ***there is suggestive evidence of an increased risk of effects on the skeleton at total fluoride intakes above about 6 mg/day"*** (emphasis added, WHO 2002).

For these reasons, the use of 10 mg/day as a potential new reference dose for EPA's risk assessment is scientifically, factually and legally inadequate.

DIETARY EXPOSURE TO FLUORIDE FROM NEW FOOD COMMODITY TOLERANCES

ISSUE 26. ACUTE EXPOSURE. The US EPA has failed to consider any acute toxic health effects, resulting from exposure to the new tolerances, besides death (US EPA 2005a, 2005).

The EPA lists sub-lethal acute health effects such as vomiting but then cites only those dosages associated with death. For example, they extrapolate from the Certainly Lethal Dose by dividing by four to get what they call a "safely tolerated dose" (8-16mg/kg-bw), meaning it is unlikely to cause death. However, not only is the EPA's "safely tolerated dose" higher than the dose (5 mg/kg) estimated to cause death in some people (Whitford 1987, 1990, 1996), it is also far higher than the doses documented to produce gastrointestinal distress (e.g. nausea and vomiting). Doses as low as 0.1 to 0.3 mg/kg-bw can result in acute gastrointestinal symptoms (Akiniwa 1997, Gessner et al. 1994). Such symptoms may not be life threatening but it is certainly unacceptable for a pesticide residue to result in vomiting for many people consuming average portions of the fumigated food

Thus the EPA cannot claim that they are proceeding with "A reasonable certainty that no harm will result" and that they are giving "special consideration to exposure of infants and children" if they have not examined these non-lethal but acute affects. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ACUTE EXPOSURE.
The EPA's failure to examine non-lethal acute effects, can be shown to be serious.

FAN will demonstrate how the new fluoride tolerance residues will lead to such acute poisoning episodes (see ISSUES 41-44). We shall take the examples of dried eggs and wheat flour, both commonly consumed items in most people's diets. The fluoride tolerance for dried eggs is 900 ppm and for wheat flour is 125 ppm (FAN 2005, Table 1).

ISSUE 27. ERROR. The US EPA, in a response to comments has apparently made a mistake in their calculations of how many milligrams of F would be contained in one reconstituted dried egg made up from 900 ppm dried egg powder (US EPA 2005b). We do not know where their mistake arose, but we note they used recipes supposedly based on teaspoons and may have confused these with tablespoons. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 28. ACUTE EXPOSURE. FAN's correction of EPA's calculations on the risks posed by powdered egg consumption.

We used recipes and conversion factors from several sources, including the American Egg Board and the USDA to determine how many grams of dried egg is mixed with water to make one egg equivalent. Both sources gave conversions by weight, not by volume, so there was no possibility of errors when converting volumes and densities to weights. Using both of these independent conversion factors returned the same result which provides reassurance that the methods are correct. We here document and reference all our calculations. In contrast, the EPA does not reference any of their calculations and makes many unsubstantiated claims in their assessment of the likely exposure levels from consuming fumigated dried eggs.

Our calculations for acute fluoride dose from dried eggs:

- F residue level in dried eggs: 900 ppm or 900 mg/kg
- Average weight of one large fresh egg: 50 g (American Egg Board 2005)
- Conversion factor from dried egg to fresh egg: 1 part by weight dried egg to 3 parts by weight water (USDA 2003; American Egg Board 2005)
- USDA standard serving size: 2 eggs
- 90^{th} percentile large serving: 4 eggs (FDA 1995; 90^{th} percentile is double the mean)

12.5 g dried egg mixed with 37.5 g water gives 50 g reconstituted egg

12.5 g X 900 mg/kg X 0.001 kg/g = 11.25 mg per fresh egg equivalent

2 egg equivalents X 11.25 mg/egg equivalent = 22.5 mg fluoride per serving

4 egg equivalents X 11.25 mg/egg equivalent = 45 mg fluoride per meal

This is based on whole dried eggs. These are the types of eggs most likely to be used as a direct replacement for fresh eggs in recipes like scrambled eggs and omelets.

We note that the EPA has calculated a much lower dose of only 3.1 mg/egg equivalent (US EPA 2005b). Since they do not reference their conversion factors it is not possible to determine where their mistake is made. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 29. UNCERTAINTY. EPA assumes a limitation of use of sulfuryl fluoride on powdered eggs but it has no provision for enforcing this limitation.

The EPA has no provision for enforcing a restriction on the number of times a year a processing facility will be fumigated (40 CFR Part 180.145; US EPA 2005). Therefore, without better supporting evidence for the number of times fumigations will take place using ProFume and the amount of food fumigated (PCT), there can not be a reasonable assurance that the exposure assessment is sufficiently conservative to reduce the chance of acute exposure a RfD exceedance. The EPA has still not provided their HRA supporting the July 2005 ruling so we can not assess the strength of their information underlying their PCT assumptions.

A higher real world PCT would also produce higher chronic exposures which would increase the number of people who would then exceed the chronic RfD. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 30. ACUTE EXPOSURE. EPA incorrectly assumes that an individual will only consume one egg equivalent of powdered egg at any one meal.

In the EPA's response to the issue of dried egg tolerances, the EPA claims that it is highly unlikely for any individual to ever consume more than a single egg's worth of dried eggs (US EPA 2005b). They base this on their claim that dried eggs will only be used in mixes such as baking mixes. They apparently don't realize that dried eggs are a standard USDA food item supplied to schools, Indian Reservations, prisons, food banks, disaster relief agencies, and other low budget end-users where they may frequently be used instead of fresh eggs to prepare dishes such as scrambled eggs or omelets (USDA 2005). The USDA purchased 4 million pounds of dried eggs in 2003 (USDA 2004). Dried eggs are also commonly found in lightweight foods for campers. Approximately 1/3 of all eggs consumed in the US are dried eggs. (American Egg Board 2005a)

Moreover, two eggs is considered a single serving of eggs by the USDA. Almost everyone would consume at least a single serving, and many would consume two servings worth or four eggs. As shown above, a four-egg meal prepared with 900 ppm residue dried eggs would give an acute dose of 45 mg F. Depending on the weight of the individual, this could range from 1.5 mg/kg-bw for a 30 kg child to 0.5 mg/kg-bw for a large adult weighing 90 kg. These dosages range from 2x to 15x greater than the dosages found to cause acute gastrointestinal symptoms including vomiting.

As a check on the reasonableness of these calculations, we can compare this outcome to the fluoride overdose warning on toothpaste. This warning is mandated by the Food and Drug Administration (FDA 1997). Fluoridated toothpastes contain between 1000 and 1500 ppm fluoride so they have only a slightly greater concentration than may be found in fumigated dried eggs. The FDA warning states that if a child ingests more than a pea-sized portion of toothpaste that a poison control center should be contacted immediately. A pea sized portion of dried eggs, or even several pea sized portions of dried eggs, would represent not even a single mouthful of scrambled eggs. This independently derived determination of the acute toxicity of fluoride ingestion by the FDA reinforces the accuracy of our calculations. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 31. ACUTE EXPOSURE. Many acute poisonings will ensue with a tolerance level of 900 ppm on powdered eggs.

An acute poisoning scenario could occur in as many as 1% of meals prepared from dried eggs even if EPA is correct in assuming only 1% of all dried eggs will be fumigated. We have not been able to determine the total number of institutional meals where scrambled eggs made from dried eggs will be served per year in the US. However, the 4 million pounds of USDA dried eggs purchased each year (USDA 2003) represents 36 million four-egg servings per year. If 1% of these servings were made from 900 ppm egg powder that could result in 360,000 acute poisoning cases per year. In USDA pesticide residue surveys, typically 0.3% of all tested samples exceed the legal tolerance (USDA 2003a [PDP 2003]). A European Union wide pesticide residue testing program has found that more than 5% of all tested samples exceeded the legal tolerances (European Commission 2004). Therefore, even if we assume that most fumigated dried eggs will contain less than 900 ppm, it is probable that 0.1 to 1% will contain the full tolerance level. This translates into 400 to 4000 very likely cases of acute fluoride poisoning per year. The USDA has never tested for fluoride pesticide residues in foods so no better estimates can be made.

It is clearly unacceptable for even a small number of institutions to have poisoning incidents about once every 100 days of serving egg dishes. At each such incident people consuming even a single serving could be vomiting from the fluoride they ingested.

But in fact, the situation is likely to be worse. Dried eggs are commonly sold in bulk containers up to 200 lbs. An institution might well purchase up to a year's supply of dried eggs which have a long shelf life. One out of a hundred such purchases would be of a batch which was fumigated. For this school, prison, nursing home, or food bank, every egg meal made from this fluoride contaminated batch would produce widespread acute illness. Even if this scenario only plays out in a few dozen institutions a year in the US, affecting only several thousand people, this is clearly unacceptable.

Conclusion. The failure of the EPA to do justice to the full potential of harm from acute exposure to these fluoride tolerances undermines their claim that they are proceeding with "A reasonable certainty that no harm will result". As we have shown above some Americans will be exposed to levels of fluoride (from ProFume) from consumption of dried egg which will exceed a dose at which we can anticipate acute effects.

As an independent check on our acute exposure analysis, we have employed the same DEEM software and food consumption database as used by EPA for their chronic exposure assessment. As noted earlier, EPA did not consider any sub-lethal acute health effect endpoints for fluoride. The results of the DEEM acute model analysis confirm our findings above. The acute DEEM Monte Carlo analysis model, using as assumed normal distribution of fluoride residues in dried eggs, with a mean of 300 ppm, found that Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 32. ACUTE EXPOSURE The EPA was remiss in failing to consider sub-lethal doses of fluoride resulting from the tolerances on other commonly consumed foods.

The above analysis considered fluoride exposure from only a single commodity, dried eggs. At this time we are unable to expand the analysis to consider all foods which will be fumigated because the list includes all processed foods. Even using DEEM software, the ability to do a full assessment is hampered by the difficulty in defining every category of processed food and its individual exposure contribution. But difficulty in performing an analysis does not relieve EPA from the requirement to perform an acute toxicity analysis taking into account exposures from all food items with tolerances. A failure to do so indicates that they cannot sustain the claim that they are proceeding with "A reasonable certainty that no harm will result" The omitted analysis should have included all processed foods with tolerances of 70 ppm, wheat and other grains with tolerances from 40 ppm to 125 ppm, and a wide range of commonly consumed fruits, vegetables, nuts, dairy, and meat products. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 33. ACUTE EXPOSURE. In addition, the ProFume pesticide label approved by US EPA on July 15, 2005 (Dow 2005) has been changed so that a 1:10 diluting of fumigated food products with non-fumigated products (blending) is no longer required. It is possible the EPA exposure assessment was based on the earlier labeling requirement (Dow 2004) rather than the current label. If this is the case then the EPA would underestimate the acute levels of exposure by a factor of 10. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 34. EXPOSURE. The US EPA's health risk assessment for F residues may further underestimate chronic doses of fluoride, because not all foods are considered.

The July 15, 2005, Final Rule for fluoride tolerances (US EPA 2005) appears to address only some of the food tolerances requested by Dow in March 2005 (US EPA 2005a). On July 15, 2005, EPA approved tolerances for processed foods and a small number of raw agricultural commodities. The current EPA exposure may be based solely on these food tolerances and may fail to account for the exposures that will result if Dow receives tolerances for the Raw Agricultural Commodities (RAC) that are pending (FAN 2005, Table 3). These RAC foods include Group 16

(grains, forage etc.) and Group 17 (both Groups with proposed tolerances of 130 ppm F); animal feed at 130 ppm; and flour, post harvest at 98 ppm. By incrementally approving sets of tolerances, all for the same residues, EPA has failed to account for the total potential residues from all foods which are likely to be treated. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 35. EXPOSURE. Changes in labeling requirements lead to an EPA underestimate of fluoride exposure from fluoride tolerances.

It is not clear whether EPA's underestimates has used the most current pesticide label requirements on which to base their exposure assumptions. The label for ProFume was just changed as of July 15, 2005 (Dow 2005). The changes in conditions of use were substantial. Three pages of specific restrictions were removed. Requirements for blending after fumigation to dilute concentrations of fluoride are eliminated. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 36. EXPOSURE. Eliminating blending requirements leads to another underestimate of exposure by EPA.

It may be relevant to note that the only comment on the pesticide petition received by the EPA other than those opposed to the petition was from the North American Millers' Association representing 95% of the industry. Their one request was to alter the ProFume registration by eliminating the blending requirement:

> "The current label for sulfuryl fluoride requires that wheat flour that is exposed to the compound must be blended into flour that has not been fumigated in a 10:1 ratio. This restriction severely limits or, depending on the location, could prevent its use as a tool to ensure that milled grain products are produced in a sanitary environment." (Bair 2005)

They strongly requested the EPA to eliminate this label restriction and the EPA seems to have complied, without any explanation or request for public input.

If the EPA based their exposure assessment on the pre July 15, 2005 label (Dow 2004) requirements, then they would have severely underestimated the possible levels and amounts of food affected. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 37 UNCERTAINTY. Health Risk Assessment used to set tolerances in July 15, 2005, was not made public.

The failure of the EPA to make the FULL Health Risk Assessment and supporting documents used in the July 15 Final Rule (US EPA 2005) publicly available prior to issuing the Final Rule does not give us confidence that the EPA is proceeding with "A reasonable certainty that no harm will result". If they can't or won't make a final HRA freely available to the public we, and other independent observers, have no way of checking their assumptions or methods which makes the Final Ruling incomplete.

This failure of the EPA to make the FULL Health Risk Assessment used in the July 15 Final Rule (US EPA 2005) publicly available prior to issuing the Final Rule, partially explains the uncertainties inherent in issues 45-50.

The Final Rule for these tolerances should be rescinded, at least until such time as the EPA can resolve these uncertainties. Any claim they make about the safety of these tolerances is moot until they have done so. With these uncertainties still in place the EPA cannot claim that they are proceeding with "A reasonable certainty that no harm will result. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 38. EXPOSURE. The failure of the EPA to require ProFume's registration label to specifically prohibit fumigation of any quantity of flour because of the risks of residue accumulation (as is required in the UK).

The label for ProFume use in the United Kingdom in food processing facilities specifically prohibits fumigation of any flour that will be used for human or animal consumption. Any incidentally fumigated flour must be destroyed and the non-fumigated flour must be run through the equipment to flush out remaining fumigated material. This flush material must also be discarded. The UK label says this requirement is to prevent the risk of ProFume residue accumulation in food.

The UK decided the risks of allowing fumigated flour to be consumed was too great. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 39. EXPOSURE. The failure of the EPA to require that the first run out of the equipment following fumigation of flour must be discarded and that the succeeding 50 minutes of run must be blended 10:1 with unfumigated flour (Dow 2005a). This failure will lead to further unacceptable exposure to fluoride.

This label requirement in the 2004 label was dropped in the current label (Dow 2005a). Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 40. EXPOSURE. The EPA also failed to take into account those significant sub-populations which will receive the highest exposures.

This is a result of the EPA's failure to even consider the highest exposure groups. The EPA has only considered age and sex groups, not diet groups. In particular, those who consume high amounts of particular food types. The US FDA (FDA 1995) has found that the 90th percentile of heavy consumers of a food type eat twice as much as the average consumer. The highest 95th percentile typically eats four times as much. The EPA only considered the average consumer. This leads to an underestimate of exposure of half in about 10% of the population, and of four in about 5% of the population. The 99th percentile and the 99.9th percentile are likely to consume considerable more. Considering the entire population of the US, even the 99.9th percentile is a very large number of people: 300,000. For the EPA to not consider the many-fold higher exposure to this large subpopulation reveals that their HRA has no assurance of protecting these people from harm. This failure again undermines the EPA's claim that they are proceeding with "A reasonable certainty that no harm will result" from these tolerances. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 41. EXPOSURE. The EPA's use of a "processing factor" in its analysis of exposure to the tolerance levels on wheat is non-conservative and thus underestimates the potential for exposure to fluoride from this important source of fluoride exposure.

We believe that application of this "processing factor" is not likely to be protective of a significant portion of the American population. Increasing numbers of people are consuming more whole grain products based on medical findings of significant health benefits from eating whole grains. In fact, the USDA recommends that Americans switch to whole grains as much as possible (USDA 2005b). This trend is exemplified by General Mills Corporation's recent announcement that it plans to change the recipe of all it's cereals to whole grain over the next few years (USA Today 2004). It would be ironic if people switching to whole grains for their established health benefits would be faced with the prospect of consuming unacceptably high fluoride residues due to fumigation by sulfuryl fluoride. This is analogous to the difficult trade-off between health

benefits of eating fish while trying to avoid excessive mercury exposure. However, it is much easier to solve by simply preventing the use of sulfuryl fluoride as a food fumigant.

The use of this non-conservative "processing factor" again undermines the EPA's claim that they are proceeding with "A reasonable certainty that no harm will result" from these tolerances. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 42. EPA made a gross mathematical error in their response to public comments.

While trying to explain their estimates for the percentage of food items that might be fumigated twice, they state: "about 5% of 1% fumigated products could be fumigated twice or 0.0005% of foods" (US EPA 2005b, p. 7). They are off by a factor of 100x! Five percent of 1% equals 0.05%, not 0.0005%. If this error was used in the EPA's exposure analysis it would lead to a gross underestimate of chronic exposure to these food tolerances. In any case, if this error is indicative of the lack of care with which EPA prepared their health risk assessment, then it raises concerns they have made errors elsewhere.

With such gross errors it again puts into question the EPA's claim that they are proceeding with "A reasonable certainty that no harm will result" from these tolerances and the problems which arise when Final Rulings are made prior to the final HRA being made available to the public. Often public and independent scrutiny reveals errors which in-house review does not.

Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 43. EXPOSURE. Chronic exposure to tolerances becomes much worse if EPA had considered major identifiable sensitive sub groups.

For food exposure, the critical sub-population is those who consume more than the average quantity of wheat and grain products. The FDA has found that a good approximation can be made to determine the 90^{th} and 95^{th} percentile of food consumption for most categories of food. They find that the upper 10% of consumers eat about twice as much of a food type as the average. They have also found that the top 5% eat about 4 times the average (FDA 1995). For the US population 10% represents about 30 million people, and 5% represents about 15 million. These are very large subpopulations which certainly qualify as "significant" by anyone's definition. They are larger than some of the subpopulations which the EPA considered.

Therefore, 30 million Americans are likely to eat larger than average portions of bread, pasta, and other grain products. EPA's failure to account for these populations makes its risk assessment supporting the tolerances scientifically, factually and legally inadequate.

ISSUE 44. EXPOSURE. EPA failed to correct the "processing factor" for dried fruit, including raisins, even after FAN pointed this out in our submission of 2004.

As acknowledged in their "Corrected" HRA, EPA did apply the correction to the fluoride residues from cryolite. However, they did not apply the correction to fluoride residues from ProFume use. Drying fruits results in a 5 or more fold increase in concentration of fluoride per unit weight due to the removal of water. Therefore, the EPA's HRA's exposure assessment will underestimate exposure from raisins and other dried foods by a factor of approximately 5 fold. The subgroup of the population which are heavy consumers of raisins and other dried foods are likely to consume many fold more of these items than the average. The corrected exposure from dried foods will lead to particularly high exposures to this subgroup, enough to potentially push some of them over the RfD when aggregate exposure from all sources is considered.

ISSUE 4 The July 2005 tolerance decision granted tolerances to hundreds of food items under the catch-all heading “processed foods”. This is everything from Cheerios to Hamburger Helper to Macaroni and Cheese. Yet only a tiny fraction of these food items have had even a minimal number of residue tests conducted on them. If the properties of the commodity itself are what largely determine the amount of residues which are absorbed from fumigation, then there can be no reasonable assurance that EPA has sufficient data from real testing of a wide variety of these food products to vouch for the accuracy of the assumed residue levels in the HRA. For example, one of the very few foods which apparently has had residue tests conducted on it is dried eggs. Apparently, these tests produced extraordinarily high residue levels of fluoride as the tolerance was set at 900 ppm.

We can not know what the test results actually were because, as mentioned at the outset, the full HRA and it’s supporting documents for the July 2004 decision have yet to be made publicly available.

If dried eggs absorb massive quantities of fluoride from fumigation, ostensibly because of their high protein or fat content, then it is reasonable to expect other processed foods to similarly exhibit very high residue levels.

Without substantially more residue data from a wide variety of food storage and processing facilities and a wide range of food commodities, the safety of the tolerances can not be established. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 45. EXPOSURE. Deficiencies with Residue Data

The HRA of October 2004 states that the pesticide applicant has supplied only marginally sufficient residue data from fumigation trials to allow for tolerances to be set. It lists six “residue chemistry deficiencies” on page 4. To date, none of these deficiencies have been remedied to our knowledge. Any one of them is significant enough that the granted tolerance residues could be underestimated to a degree that significant numbers of Americans could be put above the EPA’s RfD. When the actual data upon which the tolerances were determined is examined in detail it can be seen that it is not even marginally sufficient to be assured that the limited data will adequately reflect real world fumigation practices and resulting residues. For example, for the critical commodity wheat flour, the range of fluoride residues found was 15 ppm to 82 ppm and most of this data was not from fumigation at the approved application rate. All this data is from a single flour mill facility, so there is no way to know how residues will vary under the unique fumigation conditions found at each facility. Fumigation is a complicated process involving many variables of temperature, ventilation rates, building leakage rates, fumigant injection sites, outside wind, shielding foods from exposure, etc. To base tolerances on data from only a single site is highly presumptuous. Even within this single facility the HRA reports there was “a fairly high degree of variability across treatment replicates” [EPA HRA Oct. 2004 p 13]. The HRA goes on to state there was even more variability due to the properties of the food commodities themselves. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 46. EXPOSURE. EPA has failed to account for increased exposure from deboned meat.

One of the six residue chemistry deficiencies cited in the HRA is the lack of livestock feeding studies to assess the degree to which secondary residues, through eating the meat, will increase human exposures [HRA p. 4]. The HRA states that no such studies have been provided. Yet there is a strong probability that this route of exposure will be significant. The HRA notes that cereal grain commodities are a major portion of livestock feed. Tolerances as high as 125 ppm fluoride were granted to cereal grain commodities. Fluoride bioconcentrates very aggressively in animals. In humans approximately 50% of all ingested fluoride becomes sequestered in the bones and calcified tissues. The bone concentrations are known to increase steadily throughout

the lifetime of animals, reaching levels of thousands of parts per million. The bones and possibly other tissues of animals fed high levels of fluoride contaminated feed will increase rapidly, reaching higher levels by the time of slaughter. Studies show that mechanically de-boned meat already contains high levels of fluoride (Field 1976; Dolan 1978; Fein 2001). If ProFume treated grain products are fed to animals the levels in these frequently consumed meat products are likely to raise significantly higher. By not considering this exposure pathway, the HRA significantly underestimates exposures to the population. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 47. EXPOSURE. EPA OPP has failed to properly validate the analytical chemistry methods for measuring levels of sulfuryl fluoride and fluoride in cereal grain commodities.

Cereal grain commodities dominate the exposure source in most people's diets due to the relatively high levels of residues and the high consumption rates of these foods. The OPP recommended that the methods have validation studies conducted using radioisotope labeling because of concern that the methods may not be able to measure "incurred fluoride". To quote:

> "The petitioner has not demonstrated that either method is capable of extracting incurred residues from cereal grain commodities." [EPA Oct 2004 HRA Corrected p. 20]

The HRA goes on to paradoxically state that the EPA's Analytical Chemistry Branch recommended:

> "Both methods have been reviewed by the Agency's Analytical Chemistry Branch, which recommended that (1) the petitioner radiovalidate both methods and (2) OPP accept the analytical methods without a laboratory validation based on the submitted data" (Method Review Memorandum, D.Wright, D282408, 8/14/03).

This self-contradictory recommendation to both validate the methods and to skip validation has resulted in these methods never being properly validated.

Therefore the methods can not be considered reasonably certain to provide accurate levels of residues. Furthermore, the concern by OPP is that they may specifically underestimate the levels. These analytical chemisty methods are the foundation of the HRA's exposure assessment. All trial fumigation interpretations and all future monitoring and regulatory enforcement depends on the ability to accurately determine residue levels in foods. If the trial fumigation results under-measured the actual residue levels, then all the input levels into the DEEM model are suspect. The final output of the model would likewise underestimate the true exposure people would receive. Without an acceptable validation of the methods, the tolerances must be rejected, as the methods by which they were determined can not be reasonably certain of accuracy. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 48. EPA's failure to obtain ORAL Developmental Neurotoxicity (DNT) Studies on sulfuryl fluoride and fluoride before issuing its Final Rule on the tolerances.

There is a dearth of oral exposure animal studies for sulfuryl fluoride and a significant lack of data from the few studies that were performed. Yet, EPA set first-time tolerances for sulfuryl fluoride on the most common foods consumed by the American public. And when they set these tolerances, EPA approved the highest fluoride residues for food in its history. For example, in July 2005, EPA set a fluoride tolerance of 70 ppm for **all** processed foods not otherwise specifically cited, and a sulfuryl fluoride tolerance of 2.0 ppm for this category.

The animal studies available to the public are inhalation studies. This is of some convenience to Dow, as the majority of these studies were performed for the non-food fumigation uses of sulfuryl

fluoride. The brain was a major target organ in all the inhalation animal studies performed. All these studies were performed by Dow, and some are quite dated.

EPA behaved unscientifically by not directing Dow to perform, at a minimum, three developmental neurotoxicity (DNT) studies, prior to the granting of any tolerance for sulfuryl fluoride. The DNT studies that needed to be performed before tolerances were approved:

1. An oral DNT for fluoride
2. An oral DNT for sulfuryl fluoride
3. An oral DNT for simutaneous fluoride + sulfuryl fluoride exposure.

EPA has only directed Dow to perform an inhalation DNT study for sulfuryl fluoride. This study should have been performed years ago as sulfuryl fluoride has been used as a structural fumigant in the US since at least 1959. A more poignant reason why this study should have been conducted years ago comes from a 1998 study on structural fumigation workers. The authors state:

> "Occupational sulfuryl fluoride exposures may be associated with subclinical effects on the central nervous system, including effects on olfactory and some cognitive functions. However, no widespread pattern of cognitive deficits was observed... " (Calvert 1988).

This study is an example for the need for the right study at the right time. For food consumers, the right study are oral DNT studies, and the right time was before tolerances were granted.

By not ordering Dow to perform the appropriate DNT studies, and by not waiting for the results of these studies that would have allowed an informed decision as to tolerances (especially in regards to children, with significant ongoing brain development) EPA cannot, with any reasonable certainty, say that no harm will occur. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

CONCLUSION

We believe that each of the issues we have identified in this submission raises material issues of fact, which, if resolved in our favor would compel revocation of each of the tolerances identified in our objections. In conjunction with each of these issues we have described our factual contentions in detail. In each instance, our contentions are at odds with the positions of the Agency. We believe that each of these issues can only be resolved by means of an evidentiary hearing as contemplated by FFDCA Section 408(g)(2)(B). At such a hearing it is our intention to present factual evidence in the form of documents and expert testimony to support each of the factual contentions identified in this submission.

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ATTACHMENTS

Appendix A. Deaths from fumigation using sulfuryl fluoride “Vikane®”

Appendix B. FAN Drinking Water Analysis #1

Appendix C. FAN Drinking Water Analysis #2

References

Hard copies of references

APPENDIX A
Fluoride Action Network Pesticide Project
December 2005.

Deaths from fumigation using sulfuryl fluoride "Vikane®"

March 10, 2005 CALIFORNIA Newspaper report	Excerpt from newspaper report: … An employee of D&S Fumigation had returned to the 30-unit complex around 2 p.m. to check toxicity levels around the building when he heard someone screaming for help and noticed a rustling inside the tent. The employee found Williams and pulled her out, D&S owner Dawn Charrette said. Williams, the mother of five children, **died later that day at a San Diego hospital.** ... State officials said it was apparently the third such death in recent years… Ref. Green K (2005). Fault is disputed in death, gassing. Woman was inside a tented building. The San Diego Union-Tribune (California). March 10. **Update:** In August 2005, the California San Diego Medical Examiner's Office stated **cause of death as pesticide poisoning.** Residential/commercial fumigation. Manner of death accidental. Ref: Ellen Connett's telephone inquiry to the San Diego Medical Examiner's Office, California, on December 12, 2005. See • County of San Diego (California) (2005). Office of the Medical Examiner. Toxicology Report. Name: Williams, Linh Da. March 29. • County of San Diego (California) (2005). Office of the Medical Examiner. Investigative Report. Name: Williams, Linh Da. July 12. • County of San Diego (California) (2005). Office of the Medical Examiner. Amended Autopsy Report. Linh Da Willams. August 23.
From Minutes of a Structural Pest Control Board meeting in Austin, TEXAS. 2002	(page 15) ... Otis Woods, Pioneer Pest Services. " I have a pest control business here or in San Juan up in Dallas, but the situation coming that's up right now about fumigation**, we lost a guy who was using Sulfuryl Fluoride,** Vikane. It is very dangerous. (page 23) … Mr. Burnett: Otis, you had mentioned you "lost a guy**". He is deceased?** **Mr. Woods: Yes.** Mr. Burnett: If I could ask some follow-up questions to you with that. What kind of training had the deceased received? Mr. Woods: Really the training that he had was just for putting the tarps up. Knowing how to roll the tarps, you know, and sealing the house. He didn't deal with the gases at all. Mr. Burnett: Okay, and how long had this person been on this type of work?

	Mr. Woods: Couple of years. Mr. Burnett: Couple of years. Mr. Woods: About two years I believe. Ref: Structural Pest Control Board (2002). Meeting minutes. Joe C. Thompson Conference Center, Austin, Texas. February 12.
2002 GERMANY From newspaper report.	On 14 October 2002 in St. Vitus village church in Ursensollen, Southern Germany**, a seeming routine fumigation resulted in the tragic death of a 39 year old man.** A company from Munich was using a subcontractor from Frankfurt to treat woodworm in the roof. Two families (eleven people in total) in an adjacent house were not evacuated in advance of the fumigation and had no reason to suspect anything was amiss as sulfuryl fluoride, the highly toxic gas used, is odourless and colourless. The only person to have remained at home throughout the duration of the fumigation started to feel ill by the evening, experiencing nausea, vomiting, diarrhoea, and itchiness**. The 39 year old father of three was admitted to hospital the following day but after three hours stopped breathing and died of heart failure shortly after.** The remaining ten people who had been in the adjacent building all experienced poisoning symptoms… Ref: Pesticide News 68 (UK) (2005). Sulfuryl fluoride kills bystander. June. Page 23.
Cited in 1991 U.S.A	**A 25 year old man** with postmortem blood alcohol level of 0.156% was found lifeless in a residence that had been fumigated with sulfuryl fluoride under canvas. Ref: Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 2. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991. Page 564. Source: Hazardous Substances Data Bank at Toxnet
September 25, 1986 VIRGINIA	Fatalities Resulting From Sulfuryl Fluoride Exposure After Home Fumigation -- Virginia. Two fatalities occurred when the owners of a home re-entered after the dwelling had been fumigated with 250 pounds of sulfuryl fluoride. The concentration to which the occupants were exposed was not determined. **The man died within 24 hr, and the woman expired 6 days after exposure.** Signs of intoxication included severe dyspnea, cough, generalized seizure, cardiopulmonary arrest (in the male), and weakness, anorexia, nausea, repeated vomiting, and hypoxemia; ventricular fibrillation and diffuse pulmonary infiltration were also reported in the female. References: • MMWR, Sept. 18, 1987 and • American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1471 (Source: Hazardous Substances Data Bank at Toxnet)

Information on the number of human deaths as a result of fumigation with Vikane® is not accessible to the public. Nor is any information available to the public on the number of people who became sick, but didn't die, from exposure to sulfuryl fluoride. It is also unknown to the public if there is any long-term follow-up with workers involved in sulfuryl fluoride fumigation.

APPENDIX B

FAN's ANALYSIS #1 – Drinking Water Exposure Analysis; NHANES/USDA/CDC Data

ANALYSIS A – Water Fluoride Exposure in ≥ 4 ppm Areas.

Facts Underlying Analysis – Population Size:

Fact #1: 210,000 people live in communities identified by CDC Fluoridation Census (1993) as ≥4 ppm fluoride in the water.

Facts Underlying Analysis – Water Intake

Fact #2: According to the FNB (2004, p. 496-97):

- Approximately 15% of the population consumes ≥ 4.15 Liters/day

Fact #3: According to data cited by FNB (2004, p.86), water intake comes from 3 sources:

- 28% comes from plain water;
- 28% comes from food;
- 44% comes from processed beverages.

Assumptions Underlying Analysis:

Assumption #1: The fluoride concentration of the 3 water-intake sources are assumed as follows:

- F Content of Plain Water = F content of town water supply.
- F Content of Water from Food = F content of town water + processed beverages / 2.
- F Content of Processed Beverages = 0.71 ppm (average F content of water in US, USDA 2004).

Results of Analyses for ≥ 4ppm areas

Based on Facts 1 & 2: 31,500 people in ≥ 4 ppm areas will be consuming ≥4.15 Liters/day.

Based on Fact #4, and Assumption #1:

> Plain Water: 28% of 4.15 Liters/day = 1.16 Liters/day = 4.64 mg/day (at 4 ppm)
> Foods: 28% of 4.15 Liters/day = 1.16 Liters/day = 2.73 mg/day (at 2.35 ppm)
> Processed Beverages: 44% of 4.15 Liters/day = 1.83 Liters/day = 1.3 mg/day (at 0.71 ppm)
> **Total Intake from WATER = ≥ 8.67 mg/day**

Conclusions of Analysis:

>15% of the population living in ≥ 4 ppm areas -- or 31,500 people in the US -- are consuming 8.7 mg/day of fluoride from water sources. This exceeds the EPA's reference dose of 8 mg/day.

ANALYSIS B – Water Fluoride Exposure in 3.5-3.9 ppm Areas.

Facts Underlying Analysis – Population Size:

Fact #1: 67,974 people live in communities identified by CDC Fluoridation Census (1993) as having 3.5-3.9 ppm fluoride in the water.

Facts Underlying Analysis – Water Intake

Fact #2: According to the FNB (2004, p. 496-97).

- 15% of the population consumes $\geq$ 4.15 Liters/day

Fact #3: According to data cited by FNB (2004, p.86), water intake comes from 3 sources:

- 28% comes from plain water;
- 28% comes from food;
- 44% comes from processed beverages.

Assumptions Underlying Analysis:

Assumption #1: The fluoride concentration of the 3 water-intake sources are as follows:

- F Content of Plain Water = 3.7 ppm (median of 3.5-3.9 ppm range)
- F Content of Water from Food = F content of town water + processed beverages / 2.
- F Content of Processed Beverages = 0.71 ppm (average F content of water in US, USDA 2004).

Results of Analyses for 3.5-3.9 ppm areas

Based on Facts #1 & #2: 10,196 people in 3.5-3.9 ppm areas will be consuming $\geq$ 4.15 Liters/day.

Based on Fact #3, and Assumption #1:

> Plain Water: 28% of 4.15 Liters/day = 1.16 Liters/day = 4.29 mg/day (at 3.7 ppm)
> Foods: 28% of 4.15 Liters/day = 1.16 Liters/day = 2.55 mg/day (at 2.2 ppm)
> Processed Beverages: 44% of 4.15 Liters/day = 1.83 Liters/day = 1.3 mg/day (at 0.71 ppm)
> **Total Intake from WATER = $\geq$ 8.14 mg/day**

Conclusions of Analysis:

15% of the population living in 3.5-3.9 ppm areas -- or 10,196 people -- are consuming at least 8.1 mg/day of fluoride from water sources. This exceeds the EPA's reference dose of 8 mg/day.

ANALYSIS C – Water Fluoride Exposure in 3.0-3.4 ppm Areas.

Facts Underlying Analysis – Population Size:

Fact #1: 230,132 people live in communities identified by CDC Fluoridation Census (1993) as having 3.0-3.4 ppm fluoride in the water.

Facts Underlying Analysis – Water Intake

Fact #2: According to the FNB (2004, p. 496-97).

- 10% of the US population consumes more than 4.66 Liters/day

Fact #3: According to data cited by FNB (2004, p.86), water intake comes from 3 sources:

- 28% comes from plain water;
- 28% comes from food;
- 44% comes from processed beverages.

Assumptions Underlying Analysis:

Assumption #1: The fluoride concentration of the 3 water-intake sources are as follows:

- F Content of Plain Water = 3.2 ppm (median of 3.0-3.4 ppm range)
- F Content of Water from Food = F content of town water + processed beverages / 2.
- F Content of Processed Beverages = 0.71 ppm (average F content of water in US, USDA 2004).

Results of Analyses for 3.0-3.4 ppm areas

Based on Facts #1 & #2: 23,013 people in 3.0-3.4 ppm areas will be consuming $\geq$ 4.15 Liters/day.

Based on Fact #3, and Assumption #1:

Plain Water: 28% of 4.66 Liters = 1.3 Liters = 4.16 mg/day
Foods: 28% of 4.66 Liters = 1.3 Liters = 2.54 mg/day (at 1.95 ppm)
Processed Beverages: 44% of 4.66 Liters = 2.05 Liters = 1.46 mg/day (at 0.71 ppm)
Total Intake from Water = 8.16 mg/day

Conclusions of Analysis:

10% of the population living in 3.0-3.4 ppm areas -- or 23,000 people -- are consuming at least 8.1 mg/day of fluoride from water sources. This exceeds the EPA's reference dose of 8 mg/day.

ANALYSIS D – Water Fluoride Exposure in 2.5-2.9 ppm Areas.

Facts Underlying Analysis – Population Size:

Fact #1: 209,467 people live in communities identified by CDC Fluoridation Census (1993) as having 2.5-2.9 ppm fluoride in the water.

Facts Underlying Analysis – Water Intake

Fact #2: According to the FNB (2004, p. 496-97).

- 5% of the US population consumes more than 5.4 Liters/day

Fact #3: According to data cited by FNB (2004, p.86), water intake comes from 3 sources:

- 28% comes from plain water;
- 28% comes from food;
- 44% comes from processed beverages.

Assumptions Underlying Analysis:

Assumption #1: The fluoride concentration of the 3 water-intake sources are as follows:

- F Content of Plain Water = 2.7 ppm (median of 2.5-2.9 ppm range)
- F Content of Water from Food = F content of town water + processed beverages / 2.
- F Content of Processed Beverages = 0.71 ppm (average F content of US water, USDA 2004).

Results of Analyses for 2.5-2.9 ppm areas

Based on Facts #1 & #2: 10,473 people in 2.5-2.9 ppm areas will be consuming 5.4 Liters/day.

Based on Fact #3, and Assumption #1:

Plain Water: 28% of 5.4 Liters = 1.51 Liters = 4.08 mg/day
Foods: 28% of 5.4 Liters = 1.51 Liters = 2.57 mg/day (at 1.7 ppm)
Processed Beverages: 44% of 5.4 Liters = 2.4 Liters = 1.68 mg/day (at 0.71 ppm)
Total Intake from Water = 8.33 mg/day

Conclusions of Analysis:

5% of the population living in 2.5-2.9 ppm areas -- or 10,473 people -- are consuming at least 8.3 mg/day of fluoride from water sources. This exceeds the EPA's reference dose of 8 mg/day.

ANALYSIS E – Water Fluoride Exposure in 2.0--2.4 ppm Areas.

Facts Underlying Analysis – Population Size:

Fact #1: 565,000 people live in communities identified by CDC Fluoridation Census (1993) as having 2.0-2.4 ppm fluoride in the water.

Facts Underlying Analysis – Water Intake

Fact #2: According to the FNB (2004, p. 496-97).

- 1% of the US population consumes more than 7.25 Liters/day

Fact #3: According to data cited by FNB (2004, p.86), water intake comes from 3 sources:

- 28% comes from plain water;
- 28% comes from food;
- 44% comes from processed beverages.

Assumptions Underlying Analysis:

Assumption #1: The fluoride concentration of the 3 water-intake sources are as follows:

- F Content of Plain Water = 2.2 ppm (median of 2.0-2.4 ppm range)
- F Content of Water from Food = F content of town water + processed beverages / 2.
- F Content of Processed Beverages = 0.71 ppm (average F content of US water, USDA 2004).

Results of Analyses for 2.0-2.5 ppm areas

Based on Facts #1 & #2: 5,650 people in 2.0-24 ppm areas will be consuming 7.24 Liters/day.

Based on Fact #3, and Assumption #1:

Plain Water: 28% of 7.24 Liters = 2.03 Liters = 4.47 mg/day
Foods: 28% of 7.24 Liters = 2.03 Liters = 2.94 mg/day (at 1.45 ppm)
Processed Beverages: 44% of 7.24 Liters = 3.19 Liters = 2.26 mg/day (**at 0.71 ppm**)
Total Intake from Water = 9.7 mg/day

Conclusions of Analysis:

1% of the population living in 2.0-2.4 ppm areas -- or 5,650 people -- are consuming at least 9.7 mg/day of fluoride from water sources. This exceeds the EPA's reference dose of 8 mg/day.

APPENDIX C: FAN'S ANALYSIS #2 – DEEM, DRINKING WATER

2-day exposures at various tap water fluoride concentrations. Other water is 0.71 ppm F.
Exposures (mg/kg-bw/day) at selected percentiles for several subpopulations.

Residue file for 1.0 ppm tap water and 0.71 ppm other water showing the 8 forms of water available in DEEM.

Sample Residue File

Chris Neurath Ver. 2.15
DEEM-FCID Acute analysis for FLUORIDE
Residue file name: C:\Documents and Settings\HP_Owner\My Documents\CN docs\DEEM docs CN\DEEM tap water 1o0 ppm.R98
Analysis Date 12-15-2005 Residue file dated: 12-13-2005/05:01:41/88
Reference dose (aRfD) = 0.114 mg/kg bw/day
Comment: 1.0 ppm tap water, 0.71 ppm other; EPA PADs 2-day

EPA Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
86011000	O	Water, direct, tap	1.000000	1.000	1.000	
86012000	O	Water, direct, bottled	0.710000	1.000	1.000	
86013000	O	Water, direct, other	0.710000	1.000	1.000	
86014000	O	Water, direct, source-NS	0.710000	1.000	1.000	
86021000	O	Water, indirect, tap	1.000000	1.000	1.000	
86022000	O	Water, indirect, bottled	0.710000	1.000	1.000	
86023000	O	Water, indirect, other	0.710000	1.000	1.000	
86024000	O	Water, indirect, source-NS	0.710000	1.000	1.000	

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE Analysis for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 1o0 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:05:32 Residue file dated: 12-13-2005/05:01:41/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "1.0 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"

1.0 ppm

% of PAD

high percentiles

Summary calculations--users:

	95th Percentile Exposure	95th Percentile % aPAD	99th Percentile Exposure	99th Percentile % aPAD	99.9th Percentile Exposure	99.9th Percentile % aPAD
U.S. Population:						
	0.046743	41.00	0.082788	72.62	0.170613	149.66
All infants:						
	0.181129	31.72	0.259086	45.37	0.375902	65.83
Nursing infants (<1 yr old):						
	0.125683	22.01	0.234622	41.09	0.297112	52.03
Non-nursing infants (<1 yr old):						
	0.186572	32.67	0.268599	47.04	0.375925	65.84
Children 3-5 yrs:						
	0.066974	36.80	0.098739	54.25	0.194416	106.82
Children 6-12 yrs:						
	0.044501	44.50	0.071688	71.69	0.101497	101.50
Youth 13-19 yrs:						
	0.034395	25.86	0.061155	45.98	0.112592	84.66
Adults 20-49 yrs:						
	0.044082	38.67	0.069462	60.93	0.104499	91.67
Adults 50+ yrs:						
	0.038639	33.89	0.055533	48.71	0.092705	81.32
Custom demographics 1: All over age 18:						
	0.041547	36.44	0.065908	57.81	0.103514	90.80

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE Analysis for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 1o0 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:05:32 Residue file dated: 12-13-2005/05:01:41/88
Acute Reference Dose (aRfD) = 0.114000 mg/kg body-wt/day
Two-Day Average Results Reported
Run Comment: "1.0 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"

U.S. Population — 2-Day Avg Exposure Analysis /a (mg/kg body-weight/day)

	per User
Mean	0.019677
Standard Deviation	0.016674
Standard Error of mean	0.000118
Percent of aRfD	17.26

Percent of Individuals that are Users (over two days) = 99.26%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Percent of aPAD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
10.00	0.005699	5.00	90.00	0.035749	31.36
20.00	0.008644	7.58	95.00	0.046743	41.00
30.00	0.011108	9.74	97.50	0.060583	53.14
40.00	0.013467	11.81	99.00	0.082788	72.62
50.00	0.015997	14.03	99.50	0.102663	90.05
60.00	0.018951	16.62	99.75	0.130754	114.70
70.00	0.022402	19.65	99.90	0.170613	149.66
80.00	0.027353	23.99			

a/ Analysis based on all two-day participant records in CSFII 1994-98 with 2 days of valid drinking water records.

1.0 ppm

% of PAD

all percentiles

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE PLOT FILE for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 1o0 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:05:32 Residue file dated: 12-13-2005/05:01:41/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "1.0 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"
==========

1.0 ppm

mg/kg-bw/day

all percentiles
all subpops

Number of populations included in this file: 10
Populations:

1 = U.S. Population
2 = All infants
3 = Nursing infants (<1 yr old)
4 = Non-nursing infants (<1 yr old)
5 = Children 3-5 yrs
6 = Children 6-12 yrs
7 = Youth 13-19 yrs
8 = Adults 20-49 yrs
9 = Adults 50+ yrs
10 = Custom demographics 1: All over age 18

Pops: ,	1,	2,	3,	4,	5,	6,	7,	8,	9,	10,
Means:,	0.019677,	0.074266,	0.038979,	0.082713,	0.027321,	0.018818,	0.014253,	0.018322,	0.019318,	0.018568,
PAD: ,	0.114000,	0.571000,	0.571000,	0.571000,	0.182000,	0.100000,	0.133000,	0.114000,	0.114000,	0.114000,
Pctl(Users)										
10.00,	0.005699,	0.009728,	0.003755,	0.015238,	0.007178,	0.005380,	0.003507,	0.005454,	0.007767,	0.005938,
20.00,	0.008644,	0.022135,	0.006759,	0.035738,	0.011528,	0.008164,	0.005481,	0.008220,	0.010618,	0.008928,
30.00,	0.011108,	0.037644,	0.010774,	0.050169,	0.015471,	0.010485,	0.007183,	0.010486,	0.012860,	0.011268,
40.00,	0.013467,	0.052411,	0.017310,	0.062553,	0.018963,	0.013033,	0.009139,	0.012835,	0.015047,	0.013500,
50.00,	0.015997,	0.066001,	0.022130,	0.073453,	0.023074,	0.015592,	0.011474,	0.015327,	0.017299,	0.015864,
60.00,	0.018951,	0.077393,	0.030565,	0.086977,	0.027234,	0.018896,	0.013871,	0.017952,	0.019831,	0.018578,
70.00,	0.022402,	0.096073,	0.044749,	0.103516,	0.032420,	0.022324,	0.016632,	0.021251,	0.022829,	0.021689,
80.00,	0.027353,	0.116625,	0.066308,	0.122050,	0.039383,	0.026878,	0.020108,	0.025790,	0.026795,	0.026123,
90.00,	0.035749,	0.145928,	0.087384,	0.152775,	0.051790,	0.035497,	0.027825,	0.033720,	0.032812,	0.033224,
95.00,	0.046743,	0.181129,	0.125683,	0.186572,	0.066974,	0.044501,	0.034395,	0.044082,	0.038639,	0.041547,
97.50,	0.060583,	0.214540,	0.172187,	0.221723,	0.079297,	0.055384,	0.044631,	0.055773,	0.045807,	0.051506,
99.00,	0.082788,	0.259086,	0.234622,	0.268599,	0.098739,	0.071688,	0.061155,	0.069462,	0.055533,	0.065908,
99.50,	0.102663,	0.298434,	0.254666,	0.314438,	0.116106,	0.085479,	0.071601,	0.082076,	0.065472,	0.078712,
99.75,	0.130754,	0.372445,	0.296926,	0.372911,	0.135643,	0.093381,	0.096049,	0.096926,	0.072141,	0.091213,
99.90,	0.170613,	0.375902,	0.297112,	0.375925,	0.194416,	0.101497,	0.112592,	0.104499,	0.092705,	0.103514,
100.00,	0.378972,	0.378972,	0.297236,	0.378972,	0.212575,	0.109824,	0.160587,	0.207213,	0.135614,	0.207213,

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE Analysis for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 2o0 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:39:02 Residue file dated: 12-15-2005/10:31:40/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "2.0 ppm tap water, 0.71 ppm other water; EPA PADs 2-day"

Summary calculations--users:

	95th Percentile Exposure	95th Percentile % aPAD	99th Percentile Exposure	99th Percentile % aPAD	99.9th Percentile Exposure	99.9th Percentile % aPAD
U.S. Population:						
	0.088332	77.48	0.157344	138.02	0.337515	296.07
All infants:						
	0.340351	298.55	0.497586	436.48	0.749559	657.51
Nursing infants (<1 yr old):						
	0.211294	37.00	0.471827	82.63	0.593546	103.95
Non-nursing infants (<1 yr old):						
	0.345920	60.58	0.514639	90.13	0.749390	131.24
Children 1-6 yrs:						
	0.128927	113.09	0.201469	176.73	0.312153	273.82
Children 7-12 yrs:						
	0.078047	68.46	0.120967	106.11	0.189796	166.49
Youth 13-19 yrs:						
	0.066347	49.89	0.113163	85.09	0.224298	168.65
Adults 20-49 yrs:						
	0.081606	71.58	0.132719	116.42	0.208308	182.73
Adults 50+ yrs:						
	0.075194	65.96	0.108143	94.86	0.186093	163.24
Custom demographics 1: All over age 18:						
	0.079215	69.49	0.126546	111.01	0.207012	181.59

2.0 ppm

% of PAD

high percentiles

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE Analysis for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 2o0 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:39:02 Residue file dated: 12-15-2005/10:31:40/88
Acute Reference Dose (aRfD) = 0.114000 mg/kg body-wt/day
Two-Day Average Results Reported
Run Comment: "2.0 ppm tap water, 0.71 ppm other water; EPA PADs 2-day"

2.0 ppm

% of PAD

all percentiles

U.S. Population	2-Day Avg Exposure Analysis /a (mg/kg body-weight/day) per User
Mean	0.035506
Standard Deviation	0.032079
Standard Error of mean	0.000227
Percent of aRfD	31.15

Percent of Individuals that are Users (over two days) = 99.26%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Percent of aPAD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
10.00	0.008890	7.80	90.00	0.067211	58.96
20.00	0.013989	12.27	95.00	0.088332	77.48
30.00	0.018597	16.31	97.50	0.114593	100.52
40.00	0.022987	20.16	99.00	0.157344	138.02
50.00	0.027990	24.55	99.50	0.196634	172.49
60.00	0.033557	29.44	99.75	0.248665	218.13
70.00	0.040672	35.68	99.90	0.337515	296.07
80.00	0.050195	44.03			

a/ Analysis based on all two-day participant records in CSFII 1994-98 with 2 days of valid drinking water records.

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE PLOT FILE for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 2o0 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:39:02 Residue file dated: 12-15-2005/10:31:40/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "2.0 ppm tap water, 0.71 ppm other water; EPA PADs 2-day"
==========

2.0 ppm

mg/kg-bw/day

all percentiles
all subpops

Number of populations included in this file: 10
Populations:

1 = U.S. Population
2 = All infants
3 = Nursing infants (<1 yr old)
4 = Non-nursing infants (<1 yr old)
5 = Children 1-6 yrs
6 = Children 7-12 yrs
7 = Youth 13-19 yrs
8 = Adults 20-49 yrs
9 = Adults 50+ yrs
10 = Custom demographics 1: All over age 18

Pops: ,	1,	2,	3,	4,	5,	6,	7,	8,	9,	10,
Means:,	0.035506,	0.128796,	0.066851,	0.143624,	0.049591,	0.032270,	0.025706,	0.033064,	0.035106,	0.033615,
PAD: ,	0.114000,	0.114000,	0.571000,	0.571000,	0.114000,	0.114000,	0.133000,	0.114000,	0.114000,	0.114000,
Pctl(Users)										
10.00,	0.008890,	0.014864,	0.005200,	0.023535,	0.011238,	0.008334,	0.005608,	0.008384,	0.011816,	0.009224,
20.00,	0.013989,	0.032086,	0.010027,	0.049406,	0.017865,	0.012691,	0.008933,	0.013513,	0.017017,	0.014446,
30.00,	0.018597,	0.054703,	0.016834,	0.069940,	0.024373,	0.017524,	0.012478,	0.018025,	0.021527,	0.018877,
40.00,	0.022987,	0.073554,	0.025217,	0.095182,	0.031622,	0.021573,	0.015805,	0.021899,	0.026063,	0.023095,
50.00,	0.027990,	0.103056,	0.036049,	0.119830,	0.039061,	0.025595,	0.019608,	0.026248,	0.030626,	0.027932,
60.00,	0.033557,	0.134289,	0.050080,	0.149907,	0.047724,	0.031519,	0.024186,	0.031878,	0.035732,	0.033000,
70.00,	0.040672,	0.164669,	0.068106,	0.187746,	0.058994,	0.038798,	0.029808,	0.038627,	0.041782,	0.039826,
80.00,	0.050195,	0.209826,	0.102112,	0.225752,	0.073665,	0.046960,	0.036738,	0.046743,	0.050132,	0.048236,
90.00,	0.067211,	0.272268,	0.154110,	0.283668,	0.099177,	0.063587,	0.051952,	0.063750,	0.062985,	0.063337,
95.00,	0.088332,	0.340351,	0.211294,	0.345920,	0.128927,	0.078047,	0.066347,	0.081606,	0.075194,	0.079215,
97.50,	0.114593,	0.417661,	0.346270,	0.418974,	0.161009,	0.099140,	0.084710,	0.105215,	0.089431,	0.100111,
99.00,	0.157344,	0.497586,	0.471827,	0.514639,	0.201469,	0.120967,	0.113163,	0.132719,	0.108143,	0.126546,
99.50,	0.196634,	0.574872,	0.507066,	0.575184,	0.232564,	0.148145,	0.131636,	0.162874,	0.127246,	0.152544,
99.75,	0.248665,	0.627042,	0.592157,	0.629923,	0.272162,	0.159192,	0.193257,	0.179725,	0.140920,	0.177342,
99.90,	0.337515,	0.749559,	0.593546,	0.749390,	0.312153,	0.189796,	0.224298,	0.208308,	0.186093,	0.207012,
100.00,	0.749621,	0.749621,	0.594471,	0.749621,	0.425149,	0.191035,	0.321174,	0.414427,	0.271227,	0.414427,

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE Analysis for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 2o2 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:14:45 Residue file dated: 12-13-2005/04:23:53/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "2.2 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"

Summary calculations--users:

	95th Percentile Exposure	95th Percentile % aPAD	99th Percentile Exposure	99th Percentile % aPAD	99.9th Percentile Exposure	99.9th Percentile % aPAD
U.S. Population:	0.096950	85.04	0.172886	151.65	0.370443	324.95
All infants:	0.373793	65.46	0.545117	95.47	0.822437	144.03
Nursing infants (<1 yr old):	0.231202	40.49	0.516282	90.42	0.653683	114.48
Non-nursing infants (<1 yr old):	0.379174	66.41	0.569512	99.74	0.822708	144.08
Children 3-5 yrs:	0.139896	76.87	0.205144	112.72	0.425597	233.84
Children 6-12 yrs:	0.094312	94.31	0.155390	155.39	0.223130	223.13
Youth 13-19 yrs:	0.072599	54.59	0.124479	93.59	0.246726	185.51
Adults 20-49 yrs:	0.089261	78.30	0.145674	127.78	0.229152	201.01
Adults 50+ yrs:	0.082589	72.45	0.119031	104.41	0.204860	179.70
Custom demographics 1: All over age 18:	0.086969	76.29	0.139172	122.08	0.227801	199.83

2.2 ppm

% of PAD

high percentiles

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE Analysis for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 2o2 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:14:45 Residue file dated: 12-13-2005/04:23:53/88
Acute Reference Dose (aRfD) = 0.114000 mg/kg body-wt/day
Two-Day Average Results Reported
Run Comment: "2.2 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"

U.S. Population — 2-Day Avg Exposure Analysis /a (mg/kg body-weight/day) per User

Mean	0.038672
Standard Deviation	0.035284
Standard Error of mean	0.000250
Percent of aRfD	33.92

Percent of Individuals that are Users (over two days) = 99.26%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Percent of aPAD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
10.00	0.009312	8.17	90.00	0.073642	64.60
20.00	0.014929	13.10	95.00	0.096950	85.04
30.00	0.019972	17.52	97.50	0.125378	109.98
40.00	0.024879	21.82	99.00	0.172886	151.65
50.00	0.030397	26.66	99.50	0.215596	189.12
60.00	0.036469	31.99	99.75	0.273094	239.56
70.00	0.044331	38.89	99.90	0.370443	324.95
80.00	0.054870	48.13			

a/ Analysis based on all two-day participant records in CSFII 1994-98 with 2 days of valid drinking water records.

2.2 ppm

% of PAD

all percentiles

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE PLOT FILE for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 2o2 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:14:45 Residue file dated: 12-13-2005/04:23:53/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "2.2 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"
==========

2.2 ppm

mg/kg-bw/day

all percentiles
all subpops

Number of populations included in this file: 10
Populations:

1 = U.S. Population
2 = All infants
3 = Nursing infants (<1 yr old)
4 = Non-nursing infants (<1 yr old)
5 = Children 3-5 yrs
6 = Children 6-12 yrs
7 = Youth 13-19 yrs
8 = Adults 20-49 yrs
9 = Adults 50+ yrs
10 = Custom demographics 1: All over age 18

Pops: ,	1,	2,	3,	4,	5,	6,	7,	8,	9,	10,
Means:,	0.038672,	0.139701,	0.072425,	0.155806,	0.053609,	0.037081,	0.027996,	0.036012,	0.038263,	0.036625,
PAD: ,	0.114000,	0.571000,	0.571000,	0.571000,	0.182000,	0.100000,	0.133000,	0.114000,	0.114000,	0.114000,
Pctl(Users)										
10.00,	0.009312,	0.015820,	0.005644,	0.024794,	0.012151,	0.009025,	0.005962,	0.008910,	0.012377,	0.009755,
20.00,	0.014929,	0.034408,	0.010808,	0.052078,	0.019289,	0.014043,	0.009441,	0.014474,	0.017957,	0.015290,
30.00,	0.019972,	0.056903,	0.017285,	0.072513,	0.026819,	0.019210,	0.013329,	0.019564,	0.023242,	0.020227,
40.00,	0.024879,	0.077662,	0.027477,	0.100666,	0.034419,	0.023913,	0.016892,	0.023743,	0.028285,	0.025067,
50.00,	0.030397,	0.109624,	0.038177,	0.128349,	0.042012,	0.028841,	0.021197,	0.028416,	0.033239,	0.030331,
60.00,	0.036469,	0.143602,	0.053774,	0.163417,	0.052202,	0.036215,	0.026433,	0.034597,	0.039109,	0.035931,
70.00,	0.044331,	0.180456,	0.071469,	0.205151,	0.063646,	0.043792,	0.032476,	0.042188,	0.045809,	0.043560,
80.00,	0.054870,	0.230300,	0.111732,	0.248322,	0.079533,	0.053354,	0.040410,	0.051222,	0.055058,	0.052792,
90.00,	0.073642,	0.298916,	0.170317,	0.312917,	0.106270,	0.073137,	0.057046,	0.070041,	0.069192,	0.069513,
95.00,	0.096950,	0.373793,	0.231202,	0.379174,	0.139896,	0.094312,	0.072599,	0.089261,	0.082589,	0.086969,
97.50,	0.125378,	0.457557,	0.378895,	0.459056,	0.167814,	0.119003,	0.092925,	0.115743,	0.098335,	0.108996,
99.00,	0.172886,	0.545117,	0.516282,	0.569512,	0.205144,	0.155390,	0.124479,	0.145674,	0.119031,	0.139172,
99.50,	0.215596,	0.632415,	0.560389,	0.635926,	0.243623,	0.188538,	0.144799,	0.177852,	0.138816,	0.167863,
99.75,	0.273094,	0.693808,	0.653330,	0.697089,	0.279489,	0.207315,	0.212581,	0.197709,	0.154461,	0.195152,
99.90,	0.370443,	0.822437,	0.653683,	0.822708,	0.425597,	0.223130,	0.246726,	0.229152,	0.204860,	0.227801,
100.00,	0.824583,	0.824583,	0.653919,	0.824583,	0.467664,	0.241614,	0.353292,	0.455870,	0.298350,	0.455870,

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE PLOT FILE for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 2o7 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/09:22:50 Residue file dated: 12-13-2005/04:26:47/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "2.7 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"
==========

2.7 ppm

mg/kg-bw/day

all percentiles
all subpops

Number of populations included in this file: 11
Populations:

1 = U.S. Population
2 = All infants
3 = Nursing infants (<1 yr old)
4 = Non-nursing infants (<1 yr old)
5 = Children 1-2 yrs
6 = Children 3-5 yrs
7 = Children 6-12 yrs
8 = Youth 13-19 yrs
9 = Adults 20-49 yrs
10 = Adults 50+ yrs
11 = Custom demographics 1: All over age 18

Pops: ,	1,	2,	3,	4,	5,	6,	7,	8,	9,	10,	11,
Means:,	0.046586,	0.166966,	0.086361,	0.186261,	0.069343,	0.064562,	0.044690,	0.033722,	0.043383,	0.046157,	0.044149,
PAD: ,	0.114000,	0.571000,	0.571000,	0.571000,	0.308000,	0.182000,	0.100000,	0.133000,	0.114000,	0.114000,	0.114000,
Pctl(Users)											
10.00,	0.010546,	0.017507,	0.006396,	0.026632,	0.012395,	0.013732,	0.010481,	0.006833,	0.010021,	0.013738,	0.010945,
20.00,	0.017165,	0.038533,	0.013157,	0.054819,	0.021599,	0.022004,	0.016336,	0.010789,	0.016593,	0.020255,	0.017632,
30.00,	0.023322,	0.062029,	0.018710,	0.078629,	0.030624,	0.030641,	0.022734,	0.015325,	0.022676,	0.027276,	0.023724,
40.00,	0.029478,	0.085120,	0.031650,	0.110591,	0.042274,	0.040566,	0.027775,	0.019877,	0.028046,	0.033565,	0.029788,
50.00,	0.036060,	0.124260,	0.043175,	0.150542,	0.054262,	0.050104,	0.034699,	0.025481,	0.034064,	0.040243,	0.035936,
60.00,	0.044025,	0.173053,	0.061533,	0.198400,	0.067624,	0.062961,	0.043507,	0.031747,	0.041807,	0.047411,	0.043436,
70.00,	0.053801,	0.219586,	0.085800,	0.244527,	0.085739,	0.077399,	0.052470,	0.039490,	0.051093,	0.055674,	0.052833,
80.00,	0.066630,	0.281344,	0.131444,	0.303017,	0.105089,	0.096876,	0.064728,	0.048897,	0.062284,	0.067421,	0.064372,
90.00,	0.089882,	0.363590,	0.209242,	0.376852,	0.140919,	0.130107,	0.089397,	0.069692,	0.085676,	0.084696,	0.085190,
95.00,	0.118208,	0.457915,	0.284043,	0.463239,	0.179613,	0.170141,	0.115677,	0.089205,	0.108997,	0.101186,	0.105733,
97.50,	0.153271,	0.558983,	0.465491,	0.560417,	0.234279,	0.205451,	0.145118,	0.113947,	0.141859,	0.120171,	0.131710,
99.00,	0.211623,	0.671245,	0.634277,	0.694518,	0.295914,	0.251904,	0.190569,	0.152952,	0.178123,	0.145902,	0.171098,
99.50,	0.264491,	0.774656,	0.688465,	0.775510,	0.358217,	0.299296,	0.229500,	0.177920,	0.214492,	0.170820,	0.204770,
99.75,	0.334434,	0.845882,	0.802348,	0.850098,	0.386335,	0.343359,	0.252389,	0.258621,	0.242963,	0.190072,	0.237595,
99.90,	0.452307,	1.011442,	0.802461,	1.011499,	0.421332,	0.522856,	0.274324,	0.303163,	0.281602,	0.249594,	0.280117,
100.00,	1.011988,	1.011988,	0.802536,	1.011988,	0.477079,	0.573951,	0.296526,	0.433585,	0.559476,	0.366157,	0.559476,

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE PLOT FILE for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 3o2 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/09:49:01 Residue file dated: 12-13-2005/04:27:35/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "3.2 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"
==========

3.2 ppm

mg/kg-bw/day

all percentiles
all subpops

Number of populations included in this file: 10
Populations:

1 = U.S. Population
2 = All infants
3 = Nursing infants (<1 yr old)
4 = Non-nursing infants (<1 yr old)
5 = Children 3-5 yrs
6 = Children 6-12 yrs
7 = Youth 13-19 yrs
8 = Adults 20-49 yrs
9 = Adults 50+ yrs
10 = Custom demographics 1: All over age 18

Pops: ,	1,	2,	3,	4,	5,	6,	7,	8,	9,	10,
Means:,	0.054501,	0.194231,	0.100297,	0.216716,	0.075515,	0.052300,	0.039448,	0.050754,	0.054051,	0.051673,
PAD: ,	0.114000,	0.571000,	0.571000,	0.571000,	0.182000,	0.100000,	0.133000,	0.114000,	0.114000,	0.114000,
Pctl(Users)										
10.00,	0.011606,	0.017477,	0.006797,	0.028808,	0.014603,	0.011631,	0.007544,	0.011119,	0.014833,	0.012036,
20.00,	0.019293,	0.040673,	0.014701,	0.057267,	0.024205,	0.018578,	0.012243,	0.018933,	0.022696,	0.019714,
30.00,	0.026475,	0.065823,	0.021573,	0.082832,	0.034426,	0.025384,	0.017507,	0.025759,	0.031267,	0.027050,
40.00,	0.034054,	0.093780,	0.036059,	0.120090,	0.046881,	0.032183,	0.022412,	0.032466,	0.039274,	0.034490,
50.00,	0.042000,	0.139768,	0.050685,	0.175166,	0.058733,	0.040259,	0.029283,	0.039603,	0.047123,	0.042028,
60.00,	0.051755,	0.201093,	0.067766,	0.232601,	0.073756,	0.050839,	0.037200,	0.048919,	0.055648,	0.050979,
70.00,	0.063212,	0.259658,	0.096143,	0.288803,	0.091090,	0.061992,	0.046433,	0.059819,	0.065755,	0.062078,
80.00,	0.078686,	0.331338,	0.153999,	0.358790,	0.114938,	0.076148,	0.057892,	0.073566,	0.079568,	0.075859,
90.00,	0.106102,	0.429442,	0.247891,	0.443033,	0.153961,	0.105823,	0.082700,	0.101419,	0.100323,	0.100690,
95.00,	0.139621,	0.543398,	0.336509,	0.549817,	0.201092,	0.136867,	0.105103,	0.129072,	0.120112,	0.125035,
97.50,	0.181386,	0.661984,	0.551472,	0.664445,	0.243550,	0.172930,	0.134628,	0.166562,	0.142484,	0.154698,
99.00,	0.248908,	0.796551,	0.751434,	0.824320,	0.297747,	0.225807,	0.181787,	0.211484,	0.172815,	0.202014,
99.50,	0.312576,	0.919266,	0.815632,	0.920449,	0.356989,	0.273975,	0.210212,	0.252789,	0.202034,	0.242064,
99.75,	0.395185,	1.003788,	0.950687,	1.008977,	0.405627,	0.301262,	0.308616,	0.287085,	0.224804,	0.283675,
99.90,	0.537530,	1.192325,	0.950967,	1.193743,	0.617675,	0.325958,	0.358187,	0.332742,	0.298155,	0.331134,
100.00,	1.199393,	1.199393,	0.951154,	1.199393,	0.680239,	0.351438,	0.513879,	0.663083,	0.433964,	0.663083,

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE Analysis for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 3o7 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/09:55:32 Residue file dated: 12-13-2005/04:24:51/88
Acute Reference Dose (aRfD) = 0.114000 mg/kg body-wt/day
Two-Day Average Results Reported
Run Comment: "3.7 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"

3.7 ppm

% of PAD

all percentiles

U.S. Population 2-Day Avg Exposure Analysis /a
(mg/kg body-weight/day)

	per User
Mean	0.062415
Standard Deviation	0.059686
Standard Error of mean	0.000423
Percent of aRfD	54.75

Percent of Individuals that are Users (over two days) = 99.26%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Percent of aPAD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
10.00	0.012571	11.03	90.00	0.122429	107.39
20.00	0.021309	18.69	95.00	0.161076	141.29
30.00	0.029758	26.10	97.50	0.209042	183.37
40.00	0.038563	33.83	99.00	0.285490	250.43
50.00	0.048001	42.11	99.50	0.361186	316.83
60.00	0.059269	51.99	99.75	0.456982	400.86
70.00	0.072641	63.72	99.90	0.621744	545.39
80.00	0.090590	79.46			

a/ Analysis based on all two-day participant records in CSFII 1994-98
with 2 days of valid drinking water records.

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE PLOT FILE for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 3o7 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/09:55:32 Residue file dated: 12-13-2005/04:24:51/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "3.7 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"
==========

3.7 ppm

mg/kg-bw/day

all percentiles
all subpops

Number of populations included in this file: 10
Populations:

1 = U.S. Population
2 = All infants
3 = Nursing infants (<1 yr old)
4 = Non-nursing infants (<1 yr old)
5 = Children 3-5 yrs
6 = Children 6-12 yrs
7 = Youth 13-19 yrs
8 = Adults 20-49 yrs
9 = Adults 50+ yrs
10 = Custom demographics 1: All over age 18

Pops: ,	1,	2,	3,	4,	5,	6,	7,	8,	9,	10,
Means:,	0.062415,	0.221495,	0.114233,	0.247171,	0.086468,	0.059909,	0.045174,	0.058125,	0.061945,	0.059196,
PAD: ,	0.114000,	0.571000,	0.571000,	0.571000,	0.182000,	0.100000,	0.133000,	0.114000,	0.114000,	0.114000,
Pctl(Users)										
10.00,	0.012571,	0.019055,	0.006888,	0.031170,	0.015538,	0.012681,	0.008143,	0.012075,	0.015744,	0.013042,
20.00,	0.021309,	0.043739,	0.015839,	0.059844,	0.026695,	0.020712,	0.013427,	0.020949,	0.024917,	0.021785,
30.00,	0.029758,	0.068136,	0.024062,	0.088917,	0.038056,	0.028150,	0.019839,	0.029068,	0.035390,	0.030452,
40.00,	0.038563,	0.099328,	0.040428,	0.132248,	0.052784,	0.036431,	0.025547,	0.036835,	0.044859,	0.039193,
50.00,	0.048001,	0.152722,	0.057454,	0.200242,	0.067110,	0.045564,	0.033649,	0.045317,	0.054209,	0.048124,
60.00,	0.059269,	0.228864,	0.072315,	0.269670,	0.084804,	0.057971,	0.042601,	0.056194,	0.064034,	0.058712,
70.00,	0.072641,	0.296161,	0.104841,	0.333794,	0.105097,	0.071335,	0.052941,	0.068572,	0.075907,	0.071361,
80.00,	0.090590,	0.382947,	0.177150,	0.412815,	0.132473,	0.087833,	0.066683,	0.084733,	0.091729,	0.087579,
90.00,	0.122429,	0.493668,	0.285158,	0.514074,	0.177907,	0.122368,	0.095499,	0.116948,	0.115858,	0.116274,
95.00,	0.161076,	0.627722,	0.390969,	0.635118,	0.232562,	0.158278,	0.121562,	0.149088,	0.139008,	0.144480,
97.50,	0.209042,	0.764011,	0.640721,	0.766217,	0.281665,	0.200071,	0.155711,	0.191806,	0.164196,	0.178974,
99.00,	0.285490,	0.917448,	0.873045,	0.959059,	0.344253,	0.261247,	0.210256,	0.244619,	0.199956,	0.233721,
99.50,	0.361186,	1.063173,	0.938250,	1.060298,	0.412856,	0.316976,	0.243133,	0.292396,	0.233855,	0.280083,
99.75,	0.456982,	1.167700,	1.095623,	1.173899,	0.469105,	0.348545,	0.356947,	0.332065,	0.260212,	0.328230,
99.90,	0.621744,	1.383806,	1.098113,	1.384541,	0.714338,	0.375133,	0.414281,	0.384876,	0.345116,	0.383143,
100.00,	1.386798,	1.386798,	1.099772,	1.386798,	0.786526,	0.406351,	0.594173,	0.766690,	0.501771,	0.766690,

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE Analysis for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 4o0 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:00:13 Residue file dated: 12-13-2005/04:28:23/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "4.0 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"

4.0 ppm

% of PAD

high percentiles

Summary calculations--users:

	95th Percentile Exposure	95th Percentile % aPAD	99th Percentile Exposure	99th Percentile % aPAD	99.9th Percentile Exposure	99.9th Percentile % aPAD
U.S. Population:	0.174087	152.71	0.309580	271.56	0.670958	588.56
All infants:	0.678818	118.88	0.995059	174.27	1.499012	262.52
Nursing infants (<1 yr old):	0.423782	74.22	0.936949	164.09	1.187948	208.05
Non-nursing infants (<1 yr old):	0.686978	120.31	1.029962	180.38	1.491863	261.27
Children 3-5 yrs:	0.251184	138.01	0.370515	203.58	0.776316	426.55
Children 6-12 yrs:	0.170920	170.92	0.282389	282.39	0.405858	405.86
Youth 13-19 yrs:	0.131672	99.00	0.227159	170.80	0.450246	338.53
Adults 20-49 yrs:	0.160820	141.07	0.263801	231.40	0.414159	363.30
Adults 50+ yrs:	0.149956	131.54	0.215280	188.84	0.371503	325.88
Custom demographics 1: All over age 18:	0.156012	136.85	0.251566	220.67	0.416485	365.34

Chris Neurath Ver. 2.15
DEEM-FCID ACUTE PLOT FILE for FLUORIDE (1994-98 data)
Residue file: DEEM tap water 4o0 ppm.R98 Adjustment factor #2 NOT used.
Analysis Date: 12-15-2005/10:00:13 Residue file dated: 12-13-2005/04:28:23/88
Acute Pop Adjusted Dose (aPAD) varies with population; see individual reports
Two-Day Average Results Reported
Run Comment: "4.0 ppm tap water, 0.71 ppm other; EPA PADs 2-day"
"
==========

4.0 ppm

mg/kg-bw/day

all percentiles
all subpops

Number of populations included in this file: 10
Populations:

1 = U.S. Population
2 = All infants
3 = Nursing infants (<1 yr old)
4 = Non-nursing infants (<1 yr old)
5 = Children 3-5 yrs
6 = Children 6-12 yrs
7 = Youth 13-19 yrs
8 = Adults 20-49 yrs
9 = Adults 50+ yrs
10 = Custom demographics 1: All over age 18

Pops: ,	1,	2,	3,	4,	5,	6,	7,	8,	9,	10,
Means:,	0.067164,	0.237854,	0.122594,	0.265444,	0.093040,	0.064475,	0.048610,	0.062547,	0.066681,	0.063711,
PAD: ,	0.114000,	0.571000,	0.571000,	0.571000,	0.182000,	0.100000,	0.133000,	0.114000,	0.114000,	0.114000,
Pctl(Users)										
10.00,	0.013113,	0.020164,	0.007172,	0.031969,	0.016048,	0.013386,	0.008410,	0.012657,	0.016291,	0.013563,
20.00,	0.022473,	0.045358,	0.016222,	0.060898,	0.028065,	0.021860,	0.014225,	0.022113,	0.026435,	0.023055,
30.00,	0.031642,	0.069997,	0.025823,	0.092496,	0.040534,	0.030080,	0.021154,	0.031076,	0.037818,	0.032414,
40.00,	0.041371,	0.103402,	0.041664,	0.139895,	0.056330,	0.039020,	0.027141,	0.039463,	0.048228,	0.041974,
50.00,	0.051604,	0.163566,	0.059554,	0.215598,	0.072389,	0.048742,	0.036165,	0.048600,	0.058425,	0.051713,
60.00,	0.063925,	0.246256,	0.076988,	0.289662,	0.091417,	0.062357,	0.045873,	0.060426,	0.069153,	0.063343,
70.00,	0.078290,	0.318753,	0.112515,	0.360117,	0.113514,	0.077201,	0.057003,	0.073866,	0.081963,	0.076864,
80.00,	0.097699,	0.414060,	0.192018,	0.447087,	0.142501,	0.094777,	0.071754,	0.091404,	0.098961,	0.094428,
90.00,	0.132285,	0.534568,	0.308199,	0.553499,	0.191792,	0.132082,	0.102725,	0.126012,	0.125443,	0.125677,
95.00,	0.174087,	0.678818,	0.423782,	0.686978,	0.251184,	0.170920,	0.131672,	0.160820,	0.149956,	0.156012,
97.50,	0.225780,	0.826957,	0.694496,	0.830203,	0.303446,	0.215706,	0.169229,	0.207582,	0.178151,	0.193827,
99.00,	0.309580,	0.995059,	0.936949,	1.029962,	0.370515,	0.282389,	0.227159,	0.263801,	0.215280,	0.251566,
99.50,	0.391466,	1.148357,	1.016996,	1.150072,	0.444383,	0.341133,	0.264240,	0.314644,	0.254253,	0.301159,
99.75,	0.493131,	1.253942,	1.186456,	1.260685,	0.509806,	0.375155,	0.384094,	0.360905,	0.281322,	0.353261,
99.90,	0.670958,	1.499012,	1.187948,	1.491863,	0.776316,	0.405858,	0.450246,	0.414159,	0.371503,	0.416485,
100.00,	1.499241,	1.499241,	1.188943,	1.499241,	0.850298,	0.439298,	0.642349,	0.828854,	0.542455,	0.828854,

REFERENCES:
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• Abou-Issa H, Reichert LE Jr. (1978). Properties of particulate and detergent-solubilized adenylate cyclase of rat testis. Effects of follitropin stimulation. Biochim Biophys Acta 526(2): 613-25. October 12.

• Adelung D, Bossmann K, Rossler D (2001). The distribution of fluoride in some Antartic seals. In: Canadian Water Quality Guidelines for the Protection of Aquatic Life: Inorganic Fluorides. Environment Canada, August 2001. □

+ Agency for Toxic Substances & Disease Registry [ATSDR] (2003). Toxicological profile for Fluorides, Hydrogen Fluoride, and Fluorine. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Pages 19-20.

§ Akiniwa, Kenji (1997). Re-examination of acute toxicity of fluoride. Fluoride 30(2): 89-104. □

•§ Alarcon-Herrera MT et al. (2001). Well Water Fluoride, Dental fluorosis, Bone Fractures in the Guadiana Valley of Mexico. Fluoride 34(2): 139-149.

+ Alberts B, Shine K. (1998). Letter to Albert Burgstahler, from Bruce Alberts, President, National Academy of Sciences, and Kenneth Shine, President, Institute of Medicine. November 18.

• Alhava EM et al. (1980). The effect of drinking water fluoridation on the fluoride content, strength and mineral density of human bone. Acta Orthopaedica Scandinavica 51: 413-420.

+ Al-Wakeel JS et al. (1997). Serum ionic fluoride levels in haemodialysis and continuous ambulatory peritoneal dialysis patients. Nephrol Dial Transplant 12:1420-4.

§ American Egg Board (2005) Egg Products web page at:
http://www.aeb.org/proc/egg_products.html - equivalents

§ American Egg Board (2005a) Liquid Egg Product Statistics web page at:
http://www.aeb.org/proc/stats/liquid-use.html

• Andersen PH, Klysner R, Geisler A (1984). Fluoride-stimulated adenylate cyclase activity in rat brain following chronic treatment with psychotropic drugs. Neuropharmacology 23(4): 445-7. April. □

§ Ando M et al. (2001). Health effects of fluoride pollution caused by coal burning. Science of the Total Environment 271(1-3): 107-16.

• Angmar-Mansson B, Whitford GM (1982). Plasma fluoride levels and enamel fluorosis in the rat. Caries Research 16: 334-9.

• Angmar-Mansson B, Whitford GM (1984). Enamel fluorosis related to plasma F levels in the rat. Caries Research 18: 25-32.

§ Anon (1978). Nonskeletal fluorosis. Fluoride 12(3): 111-114.

§ Aoba T, Fejerskov O (2002). Dental fluorosis: chemistry and biology. Critical Reviews of Oral Biology and Medicine 13(2): 155-70.

•§ Apetri AC, Surewicz WK (2003). Atypical effect of salts on the thermodynamic stability of human prion protein. The Journal of Biological Chemistry 278(25): 22187-22192. June 20.

•§ Araibi AA, Yousif WH, Al-Dewachi OS (1989). Effect of high fluoride on the reproductive

performance of the male rat. J BIOL SCI RES; 20 (1): 19-30.

• Arnala I et al. (1985). Effects of fluoride on bone in Finland. Histomorphometry of cadaver bone from low and high fluoride areas. Acta Orthopaedica Scandinavica 56(2): 161-6.

• Arnold CM et al. (1997). The effect of water fluoridation on the bone mineral density of young women. Canadian Journal of Public Health 88(6): 388-91.

•§ Bachinskii PP et al. (1985) Action of the body fluorine of healthy persons and thyroidopathy patients on the function of hypophyseal-thyroid the system. Probl Endokrinol (Mosk) 31(6): 25-9. [English translation.]

§ Bair J (2005). Letter to US EPA on behalf of the North American Millers' Association in response to new pesticide tolerances for sulfuryl fluoride. Federal Register Docket No. OPP-2005-0067-0018. April 19.

• Barot VV (1998). Occurrence of endemic fluorosis in human population of North Gujarat, India: human health risk. Bulletin of Environmental Contamination and Toxicology 61: 303-10.

§ Bassin EB (2001). Association Between Fluoride in Drinking Water During Growth and Development and the Incidence of Osteosarcoma for Children and Adolescents. Doctoral Thesis, Harvard School of Dental Medicine. Boston, Massachusetts. Pages 3, 68-83, 92-100.

• Baud CA et al. (1978). Value of the bone biopsy in the diagnosis of industrial fluorosis. Virchows Archiv A. Pathological Anatomy and Histology 380(4): 283-97.

•§ Bayley TA et al. (1990). Fluoride-induced fractures: relation to osteogenic effect. Journal of Bone and Mineral Research 5(Suppl 1): S217-22.

§ Begley S (2005). Fluoridation, cancer: did researchers ask the right question? Wall Street Journal. Page B1. July 22.

§ Beltrán-Aguilar ED, Griffin SO, Lockwood SA (2002). Prevalence and trends in enamel fluorosis in the United States from the 1930s and 1980s. Journal of the American Dental Association 133:157--66.

• Bentley EM et al. (1999). Fluoride ingestion from toothpaste by young children. British Dental Journal 186(9): 460-2.

• Berkowitz L, Nyquist SE (1986). Dolichol kinase activity in the developing rat testis. Biology of Reproduction 34(3): 518-26.

•§ Bhatnagar M, Rao P, Sushma J, Bhatnagar R (2002). Neurotoxicity of fluoride: neurodegeneration in hippocampus of female mice. Indian J Exp Biol. 40(5): 546-54. May.

• Bo Z et al. (2003). Distribution and risk assessment of fluoride in drinking water in the West Plain region of Jilin Province, China. Environmental Geochemistry and Health 25: 421-431.

• Bogdanow NA, Gembizkij EW. Proiswodstwennyj Fljuoros [Industrial Fluorosis] [Russian]. Medizina, Leningrad 1975, 95 pp. In: Book Review, Fluoride 1979; 12(4): 209-210.

+ Boillat MA et al. (1980). Radiological criteria of industrial fluorosis. Skeletal Radiology 5: 161-165.

• Boivin G et al. (1993). Relationship between bone fluoride content and histological evidence of calcification defects in osteoporotic women treated long term with sodium fluoride. Osteoporosis

International 3(4): 204-8.

§ Bolea S, Avignone E, Berretta N, Sanchez-Andres JV, Cherubini E (1999). Glutamate Controls the Induction of GABA-Mediated Giant Depolarizing Potentials Through AMPA Receptors in Neonatal Rat Hippocampal Slices. J Neurophysiol 81: 2095-2102.

§ Borasio PG, Cervellati F, Pavan B, Pareschi MC (2004). "Low" concentrations of sodium fluoride inhibit neurotransmitter release from the guinea-pig superior cervical ganglion. Neuroscience Letters 364(2): 86-9. July 1.

•§ Borke JL, Whitford GM (1999). Chronic fluoride ingestion decreases 45Ca uptake by rat kidney membranes. Journal of Nutrition 129: 1209-13.

§ Breakwell NA, Behnisch T, Publicover SJ, Reymann KG (1995). Attenuation of high-voltage-activated Ca2+ current run-down in rat hippocampal CA1 pyramidal cells by NaF. Exp Brain Res. 106(3): 505-8.

• Brostrom MA, Brostrom CO, Breckenridge BM, Wolff DJ (1978). Calcium-dependent regulation of brain adenylate cyclase. Advances in Cyclic Nucleotide Research 9: 85-99.□

+ Brothwell D, Limeback H (2003). Breastfeeding is protective against dental fluorosis in a nonfluoridatd rural area of Ontario, Canada. Journal of Human Lactation 19(4): 386-390.

+ Brouwer ID et al. (1988). Unsuitability of World Health Organisation guidelines for fluoride concentrations in drinking water in Senegal. Lancet 1(8579):223-5.

• Brun G, Buchwald H, Roholm K (1941). [The excretion of fluorine in the urine of cryolite workers with chronic fluorine poisoning]. Acta Medica Scandinavica 106: 261-273.

+ Burger SG, Kayser-Jones J, BellJP (2000). Malnutrition and dehydration in nursing homes: key issues in prevention and treatment. National Citizens' Coalition for Nursing Home Reform.

§ Burgstahler AW et al. (1997). Fluoride in California wines and raisins. Fluoride 30(3): 142-146.

• Buzalaf MA et al. (2002). Correlation between plasma and nail fluoride concentrations in rats given different levels of fluoride in water. Fluoride 35(3): 185-192.

+ CA EPA (2005). Sulfuryl fluoride (Vikane ®). Risk Characterization Document. Volume I. Health Risk Assessment. Final Draft. Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency. June 1, 2005.

+ CA EPA (2005a). Sulfuryl fluoride (Vikane ®). Risk Characterization Document. Volume I!. Exposure Assessment. Final Draft. Worker Health and Safety Branch, California Environmental Protection Agency. June 1, 2005.

+ CA EPA (2005b). Sulfuryl fluoride (Vikane ®). Risk Characterization Document. Volume III. Environmental Fate. Final Draft. Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency. July 5, 2005.

+ CA EPA (2005c). Sulfuryl fluoride (Vikane ®). Risk Characterization Document. Volume IV DPR Responses to Comments. Final Draft. Medical Toxicology Branch, Worker Health and Safety Branch, Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency. June 1, 2005.

• Calderon J et al. (2000). Influence of fluoride exposure on reaction time and visuospatial organization in children. Epidemiology 11(4): S153.

+ Calvert GM et al (1998). Health effects associated with sulfuryl fluoride and methyl bromide exposure among structural fumigation workers. American Journal of Public Health 88(12): 1774-80. December.

+ Carlsson A (1978). Current problems of the pharmacology and toxicology of fluorides]. [Article in Swedish]. Lakartidningen 75(14): 1388-92. April 5.

• Cao J et al. (2003). Brick tea fluoride as a main source of adult fluorosis. Food and Chemical Toxicology 41: 535-42.

• Cao J et al. (2003). Prevention and control of brick-tea type fluorosis-a 3-year observation in Dangxiong, Tibet. Ecotoxicology and Environmental Safefy 56: 222-7.

§ Carnow BW, Conibear SA (1981). Industrial fluorosis. Fluoride 14(4): 172-181.

• Carton RJ (1991). Editorial: National Toxicology Program - Critique of Peer Review Draft Report. Fluoride 24(3): 85-89.

§ Carton RJ, Hirzy JW (1998). Applying the NAEP Code of Ethics to the Environmental Protection Agency and the Fluoride in Drinking Water Standard.

• Caverzasio J, Palmer G, Bonjour JP (1998). Fluoride: mode of action. Bone 22(6): 585-589. June.

+ Centers for Disease Control and Prevention (CDC, 1998). Decrease of iodine intake found in Americans. October 1.

+ Centers for Disease Control and Prevention (CDC, 1999)

§ Centers for Disease Control and Prevention (CDC, 2002). Prevalence of self-reported arthritis and chronic joint symptoms among adults. MMWR 51: 948-950.

§ Centers for Disease Control and Prevention (CDC, 2005). Surveillance for dental caries, dental sealants, tooth retention, edentulism, and enamel fluorosis--United States, 1988-1994 and 1999-2002. MMWR Surveill Summ 54(3): 1-43.

+ Centers for Disease Control and Prevention (CDC, 2005a). ADA and CDC celebrate 60th anniversary of community water fluoridation. Press Release. National Center for Chronic Disease Prevention and Health Promotion. January 21.

• Chan AW, Minski MJ, Lai JC (1983). An application of neutron activation analysis to small biological samples: simultaneous determination of thirty elements in rat brain regions. Journal of Neuroscience Methods 7(4): 317-28. April.

• Charen J et al. (1979). Bone fluoride concentrations associated with fluoridated drinking water. Calcified Tissue International 27(2): 95-9.

•§ Chen J, Chen X, Yang K (2000). [Effects of selenium and zinc on the DNA damage caused by fluoride in pallium neural cells of rats]. Wei Sheng Yan Jiu. 29(4): 216-7. July.

•§ Chen J, Chen X, Yang K, Xia T, Xie H (2002). [Studies on DNA damage and apoptosis in rat brain induced by fluoride]. Zhonghua Yu Fang Yi Xue Za Zhi. 36(4): 222-4. July.

§ Chen J, Shan KR, Long YG, Wang YN, Nordberg A, Guan ZZ (2003). Selective decreases of nicotinic acetylcholine receptors in PC12 cells exposed to fluoride. Toxicology183(1-3): 235-42.

Feb 1.

§ Cheng TJ, Chen TM, Chen CH, Lai YK (1998). Induction of stress response and differential expression of 70 kDa stress proteins by sodium fluoride in HeLa and rat brain tumor 9L cells. Journal of Cellular Biochemistry 69(2): 221-231.

•§ Chinoy NJ, Sequeira E (1989). Fluoride induced biochemical changes in reproductive organs of male mice. Fluoride 22(1): 78-85.

•§ Chinoy NJ, Sequeira E (1989). Effects of fluoride on the histoarchitecture of reproductive organs of the male mouse. Reprod Toxicol 3(4): 261-7.

• Chinoy NJ, Pradeep PK, Sequeira E (1991). Effects of fluoride ingestion on the physiology of reproductive organs of male rats. Journal of Environmental Biology 13(1): 55-61.

• Chinoy NJ (1991). Effects of fluoride on physiology of some animals and human beings. Indian Journal of Environmental Toxicology 1(1): 17-32.

• Chinoy NJ (1991). Effects of fluoride on some organs of rats and their reversal. Proceedings of Zoological Society; Calcuta 44(1): 11-15. □□□

•§ Chinoy NJ , Sequeira E, Narayana MV (1991). Effects of vitamin C and calcium on the reversibility of fluoride-induced alterations in spermatozoa of rabbits. Fluoride 24(1): 29-39.

§ Chinoy NJ, Rao MV, Narayana MV, Neelakanta E (1991). Microdose vasal injection of sodium fluoide in the rat. Reproductive Toxicology 5(6): 505-512.

•§ Chinoy NJ, Sequeira E (1992). Reversible fluoride induced fertility impairment in male mice. Fluoride 25(2): 71-76.

• Chinoy NJ (1992). Fluoride toxicity in female mice and its reversal. In: Saxena AK, Ramamurthy R, Srirama Reddy G, Saxena VL. (Eds) Recent Advances in Life Sciences. Manu Publications, Kanpur India 1992. pp 39-50.

§ Chinoy NJ, Pradeep PK, Sequeira E (1992). Effect of fluoride ingestion on the physiology of reproductive organs of male rats. Journal of Environmental Biology 13(1): 55-61.
□
•§ Chinoy NJ, Narayana MV (1994). In vitro fluoride toxicity in human spermatozoa. Reprod Toxicol. 8(2): 155-9. March-April.

•§ Chinoy NJ, Reddy VVPC, Michael M (1994). Beneficial effects of ascorbic acid and calcium on reproductive functions of sodium fluoride-treated prepubertal male rats. Fluoride 27(2): 67-75.

•§ Chinoy NF, Narayana MV, Dalal V, Rawat M, Patel D (1995). Amelioration of fluoride toxicity in some accessory reproductive glands and spermatozoa of rat. Fluoride 28(2): 75-86.

•§ Chinoy NJ, Shukla S, Walimbe AS, Bhattacharya S (1997). Fluoride toxicity on rat testis and cauda epididymal tissue components and its reversal. Fluoride, 30(1): 41-50.

§ Chinoy NJ, Patel BC, Patel DK et al. (1997). Fluoride toxicity in the testis and cauda epididymis of guinea pig and reversal by ascorbate. Med Sci Res 25(2): 97-100.

•§ Chinoy NJ, Sharma A (1998). Amelioration of fluoride toxicity by Vitamins E and D in reproductive functions of male mice. Fluoride 31(4): 203-216.

•§ Chinoy NJ, Mehta D (1999). Effects of protein supplementation and deficiency on fluoride-

induced toxicity in reproductive organs of male mice. Fluoride 32(4): 204-214.

•§ Chinoy NJ, Sharma A (2000). Reversal of fluoride-induced alteration in cauda epididymal spermatozoa and fertility impairment in male mice. Environmental Sciences: an International Journal of Environmental Physiology and Toxicology 7(1): 29-38.

§ Chinoy NJ, Tewari K, Jhala DD (2004). FLUORIDE AND/OR ARSENIC TOXICITY IN MICE TESTIS WITH GIANT CELLS AND SUBSEQUENT RECOVERY BY SOME ANTIDOTES. Fluoride 37(3); 172-184.

• Choubisa SL et al. (2001). Endemic fluorosis in Rajasthan. Indian Journal of Environmental Health 43: 177-89.

+ Christie DP (1980). The spectrum of radiographic bone changes in children with fluorosis. Pediatric Radiology. July: 85-90.

§ Chubb C (1985). Reproductive toxicology of fluoride. 3rd International Congress of Andrology, Boston, Massachusetts. J Androl 6: 59.

• Chulavatnatol M, Yindepit S (1976). Changes in surface ATPase of rat spermatozoa in transit from the caput to the cauda epididymidis. J Reprod Fertil. 48(1): 91-7. September. □

•§ Claro E, Wallace MA, Fain JN (1990). Dual effect of fluoride on phosphoinositide metabolism in rat brain cortex. Stimulation of phospholipase C and inhibition of polyphosphoinositide synthesis. Biochem J. 15;268(3): 733-7. June.

+ Cohen-Solal ME et al. (1996). Osteomalacia is associated with high bone fluoride content in dialysis patients. Bone 19: 135S.

+ Cohen-Solal ME et al. (2002). Fluoride and strontium accumulation in bone does not correlate with osteoid tissue in dialysis patients. Nephrology Dialysis Transplantation 17: 449–454.

• Cohn PD (1992). A brief report on the association of drinking water fluoridation and the incidence of osteosarcoma among young males. Produced under an interagency agreement between the New Jersey Department of Environmental Protection and Energy and the New Jersey Department of Health. November.

§ Collins TFX, Sprando RL, Black TN, Shackelford ME, Black TN, Ames MJ, Welsh JJ, Balmer MF, Olejnik N, Ruggles DI (1995). Developmental toxicity of sodium fluoride in rats. Food Chem Toxicol. 33(11): 951-60. November.

§ Collins TFX, Sprando RL, Black TN, Shackelford ME, Bryant MA, Olejnik N, Ames MJ, Rorie JI, Ruggles DI.(June 2001). Multigenerational evaluation of sodium fluoride in rats. Food Chem Toxicol. 39(6): 601-13. June.

§ Collins TFX, Sprando RL, Black TN, Shackelford ME, Olejnik N, Ames MJ, Rorie JI, Ruggles DI (August 2001). Developmental toxicity of sodium fluoride measured during multiple generations. Food Chem Toxicol. 39(8): 867-76. August.

+ Connett E (2001). Sulfuryl Fluoride. Comments submitted to US EPA from Ellen Connett on the Proposed Pesticide Temporary Tolerances that appeared in the September 5, 2001, Federal Register. September 29.

+ Connett E, Connett P (2002). Written Objections and Request for Hearing in the matter of: Sulfuryl fluoride; Temporary Pesticide Tolerances. Final Rule. Docket control number OPP-301166A. April 8.

+ Connett E (2004). Fluoride's effect on the brain. Submission to the National Research Council committee, Toxicologic risk of fluoride in drinking water; BEST-K-02-05-A. April 19.

+ Connett E (2004a). Fluoride's adverse effects on the Male Reproductive system. Submission to the National Research Council committee, Toxicologic risk of fluoride in drinking water; BEST-K-02-05-A. May 3.

§ Connett E (2005). Part 2. "Inerts" used in Pesticides. New Source of Fluoride Exposure. Submission to National Research Council Committee Toxicological Risk of Fluoride in Drinking Water; BEST-K-02-05-A. July 21.

+ Connett E (2005a). Comments submitted to EPA on Dow AgroSciences petition to establish Fluoride and Sulfuryl fluoride tolerances for a large number (over 600) of raw and processed foods (Federal Register, March 4, 2005). April 19.

+ Connett P, Connett E (2002). Comments submitted to EPA on DowAgroSciences petition to establish Fluoride and Sulfuryl fluoride tolerances for a large number (40) of raw and processed foods (Federal Register, February 15, 2002). March 18.

§ Connett P, Connett M, Connett E, Neurath C, Allen P, Feldman J (2004). Written Objections and Request for Hearing in the matter of: Sulfuryl Fluoride; Pesticide Tolerance. Final Rule. Docket control number OPP-2003-0373. March.

§ Connett P, Neurath C, Connett M (2005a). Revisiting the fluoride-osteosarcoma connection in the context of Elise Bassin's findings: Part 1. Submission to the NRC review panel on the Toxicologic Risk of Fluoride in Drinking Water. March 2.

§ Connett P, Neurath C, Connett M (2005b). Revisiting the fluoride-osteosarcoma connection in the context of Elise Bassin's findings: Part II. Submission to the NRC review panel on the Toxicologic Risk of Fluoride in Drinking Water. March 21; revised April 8.

•§ Cook HA (1971). Fluoride studies in a patient with arthritis. The Lancet 1: 817.

• Cooper C et al. (1991). Water fluoridation and hip fracture. Letter. Journal of the American Medical Association 266: 513-514. (A reanalysis of data presented in 1990 paper).

+ Cortes DF et al. (1996). Drinking water fluoride levels, dental fluorosis, and caries experience in Brazil. Journal of Public Health Dentistry 56: 226-8

+ County of San Diego (California) (2005). Office of the Medical Examiner. Toxicology Report. Name: Williams, Linh Da. [Attached to Appendix B]. March 29.

+ County of San Diego (California) (2005). Office of the Medical Examiner. Investigative Report. Name: Williams, Linh Da. Attached to Appendix B]. July 12.

+ County of San Diego (California) (2005). Office of the Medical Examiner. Amended Autopsy Report. Linh Da Willams. [Attached to Appendix B]. August 23.

+ Cunha-Cruz J, Nadanovsky P (2005). Dental fluorosis increases caries risk. Journal of Evidence Based Dental Practice 5: 170-171.

•§ Czechowicz K, Osada A, Slesak B (1974). Histochemical studies on the effect of sodium fluoride on metabolism in Purkinje's cells. Folia Histochem Cytochem (Krakow). 12(1): 37-44.

§ Czerwinski E, Lankosz W (1977). Fluoride-induced changes in 60 retired aluminum workers.

Fluoride 10(3): 125-136.

§ Czerwinski E et al. (1988). Bone and joint pathology in fluoride-exposed workers. Archives of Environmental Health 43: 340-343.

•§ Dambacher MA et al. (1986). Long-term fluoride therapy of postmenopausal osteoporosis. Bone 7: 199-205.

• Danielson C et al. (1992). Hip fractures and fluoridation in Utah's elderly population. Journal of the American Medical Association 268(6): 746-748.

§ Dean HT (1936). Chronic endemic dental fluorosis (mottled enamel). J. Amer. Med. Assoc.107: 1269-1273.

§ Dean HT, Jay P, Arnold FA, Elvove E (1941) Domestic water and dental caries. I. A dental caries study, including L.acidophilus estimations, of a population severely affected by mottled enamel and which for the past 12 years has used a fluoride-free water. Pub. Health Rep. 56: 365-381.

§ Dean HT, Arnold FA, Elvove E (1942) Domestic water and dental caries.V. Additional studies of relation of fluoride domestic waters to dental caries experience in 4,425 white children, aged 12 to 14 years, of 13 cities in 4 states. Pub. Health Rep. 57: 1155-1179.

§ Dean HT, cited by Exner FB (1960) In his analytical commentary on the 1960 Testimony of Dr. H. T. Dean in the Suit to Enjoin Fluoridation of Chicago's Water (Schuringa versus Chicago).

§ Demole, V (1970). Toxic effects on the thyroid. In: Fluorides and Human Health. World Health Organization Monograph Series No. 59. Geneva. pp. 255-261.

• DenBesten PK, Crenshaw MA (1984). The effects of chronic high fluoride levels on forming enamel in the rat. Archives of Oral Biology 29: 675-9.

• Denbesten PK et al. (1985). Changes in the fluoride-induced modulation of maturation stage ameloblasts of rats. Journal of Dental Research 64: 1365-70.

§ Department of Health & Human Services. (U.S. DHHS) (1991). Review of Fluoride: Benefits and Risks, Report of the Ad Hoc Committee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs.

•§ Derryberry OM et al. (1963). Fluoride exposure and worker health. Archives of Environmental Health 6: 503-511.

+ Dolan T et al. (1978). Determination of fluoride in deboned meat. Journal of the Association of Official Analytical Chemists 61: 982-985.

§ Dong Y et al. (1991). The clinical features of 160 cases of acute sodium silico fluoride poisoning. CHIN J PREV MED 25(5): 269-271.

§ Dow AgroSciences (2004). ProFume Specimen label. [EPA accepted 1/26/04; CA accepted 5/18/05; Not yet accepted in NY]. February 10, 2004

§ Dow AgroSciences (2005). ProFume Specimen label. [EPA accepted 7-15-05; Not yet accepted in CA, FL, NY]. August 18, 2005.

§ Dow AgroSciences (2005a). ProFume Specimen label. UK LABEL.

+ Dow AgroSciences (2005b). Container label and applicator manual for ProFume® gas fumigant. August.

•§ Du L (1992). [The effect of fluorine on the developing human brain]. Zhonghua Bing Li Xue Za Zhi 21(4): 218-20. August.

• Dunipace AJ et al. (1995). Effect of aging on animal response to chronic fluoride exposure. Journal of Dental Research 74: 358-68.

• Dunipace AJ et al. (1998). Chronic fluoride exposure does not cause detrimental, extraskeletal effects in nutritionally deficient rats. Journal of Nutrition 128: 1392-400.

§ Durango Software (2005) Dietary Exposure Evaluation Model, DEEM-FCID version 2.14. Information online at:

• Eble DM et al. (1992). Fluoride concentrations in human and rat bone. Journal of Public Health Dentistry 52: 288-291.

§ Eichler HG, Lenz K, Fuhrmann M, Hruby K (1982). Accidental ingestion of NaF tablets by children--report of a poison control center and one case. International Journal of Clinical Pharmacology, Therapy, and Toxicology 20(7): 334-8. July.

§ Eichmiller FC, Eidelman N, Carey CM (2005). Controlling the fluoride dosage in a patient with compromised salivary function. Journal of the American Dental Association 136: 67-70.

§ Eilperin J (2005). Professor at Harvard is being investigated. Fluoride-cancer link may have been hidden. Washington Post. July 13.

+ EkstrandJ (1981). No evidence of transfer of fluoride from plasma to breast milk. British Medical Journal 283: 761-762. September 19.

+ Ekstrand J et al. (1994). Fluoride pharmacokinetics in infancy. Pediatric Research 35:157–163.

§ Ekstrand J (1996). Fluoride Metabolism. Chapter 4. In: Fejerskov O, Ekstrand J, Burt B, Eds. Fluoride in Dentistry, 2nd Edition. Munksgaard, Denmark. Pp 55-65.

•§ Elbetieha A, Darmani H, Al-Hiyasat AS (2000). Fertility effects of sodium fluoride in male mice. Fluoride 33(3): 128-134.

• Enomoto K, Asakawa T (1983). Separation and properties of a regulatory GTPase activity associated with the adenylate cyclase system in rat brain synaptic plasma membranes. Biochem Int. 6(1): 81-91. January. □

• Everett ET et al. (2002). Dental fluorosis: variability among different inbred mouse strains. Journal of Dental Research 81: 794-8.

§ Environmental Working Group (2005). Petition to National Toxicology Program nominating fluoride in tap water for inclusion in the Report on Carcinogens. June 6.

•§ Fa-Fu L et al. (1991). The relationship of a low-iodine and high-fluoride environment to subclinical cretinism in Xinjiang. Iodine Deficiency Disorder Newsletter. Vol. 7. No. 3.

§ FAN (Fluoride Action Network Pesticide Project) (2004). Cryolite Use in California for years 2002 and 1991-2000; and estimated use in US for 1992.

§ FAN (Fluoride Action Network Pesticide Project) (2005). Fluoride pesticide residue tolerances

approved by US EPA as of July 15, 2005.

• Farley JR, Wergedal JE, Baylink DJ (1983). Fluoride directly stimulates proliferation and alkaline phosphatase activity of bone-forming cells. Science 222: 330-332. October 31.

§ FDA (1995). Estimating Exposure To Direct Food Additives And Chemical Contaminants in the Diet. Center for Foor Safety & Applied Nutrition. Office of Premarket Approval. Prepared by Michael J. DiNovi and Paul M. Kuznesof. September.

§ FDA (1997). Part 355 – Anticaries drug products for over-the-counter human use.

§ Fein NJ, Cerklewski FL (2001). Fluoride content of foods made with mechanically separated chicken. Journal of Agricultural Food Chemistry
49(9): 4284-6. September.

+ Field RA, et al. (1976). Characteristics of mechanically deboned meat, hand separated meat and bone residue from bones destined for rendering. Journal of Animal Science 43: 755-762.

+ Fisher RL. Medcalf TW, Henderson MC (1989). Endemic fluorosis with spinal cord compression. A case report and review. Archives of Internal Medicine 149: 697-700.

+ Fomon SJ, Ekstrand J, Ziegler EE (2000). Fluoride intake and prevalence of dental fluorosis; trends in fluoride intake with special attention to infants. Journal of Public Health Dentistry 60(3): 131-139. Summer.

§ Food and Nutrition Board (FNB) (2004). Dietary Reference Intakes for Water, Potassium, Sodium Cloride, and Sulfate. Panel on Dietary Reference Intakes for Electrolytes and Water. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Institute of Medicine of the National Academies. The National Academies Press. Washington DC. Note: We have also referred to this document as IOM, 2004.

•§ Franke J et al. (1975). Industrial fluorosis. Fluoride 8(2): 61-83.

•§ Fratzl P et al. (1996). Effects of sodium fluoride and alendronate on the bone mineral in minipigs: a small-angle x-ray scattering and backscattered electron imaging study. Journal of Bone and Mineral Research 11: 248-253.

•§ Freni SC (1994). Exposure to high fluoride concentrations in drinking water is associated with decreased birth rates. Journal of Toxicology and Environmental Health 42(1): 109-21. May.

•§ Frolkis VV, Tanin SA, Gorban YN (1997). Age-related changes in axonal transport. Experimental Gerontology 32(4-5): 441-50. July-October.

• Fujiwara-Tsukamoto Y, Isomura Y, Nambu A, Takada M (2003). Excitatory gaba input directly drives seizure-like rhythmic synchronization in mature hippocampal CA1 pyramidal cells. Neuroscience 119(1): 265-75.

§ Galletti P, Joyet G (1958). Effect of Fluorine on Thyroidal Iodine Metabolism in Hyperthyroidism. Journal of Clinical Endocrinology 18: 1102-1110.

•§ Gardiner IM, de Belleroche J (1990). Modulation of gamma-aminobutyric acid release in cerebral cortex by fluoride, phorbol ester, and phosphodiesterase inhibitors: differential sensitivity of acetylcholine release to fluoride and K+ channel blockers. Journal of Neurochemistry 54(4): 1130-5. April.

+ Ge Y, et al. (2005). Comet assay of DNA damage in brain cells of adult rats exposed to high

fluoride and low iodine. Fluoride 38:175-282.

§ Geeraerts F, Gijs G, Finne E, Crokaert R (1986). Kenetics of fluoride penetration in liver and brain. Fluoride 19(3): 108-112.

• Gerster JC et al. (1983). Bilateral fractures of femoral neck in patients with moderate renal failure receiving fluoride for spinal osteoporosis. British Medical Journal (Clin Res Ed) 287(6394): 723-5.

§ Gessner BD, Beller M, Middaugh JP, Whitford GM (1994). Acute fluoride poisoning from a public water system. New England Journal of Medicine 330: 95-9.

•§ Ghosh D, Das(Sarkar) S, Maiti R, Jana D, Das (2002). Testicular toxicity in sodium fluoride treated rats: association with oxidative stress. Reprod Toxicol. 16(4): 385. July.

• Glock GE et al. (1941). The retention and elimination of fluoride in bones. Biochemical Journal 35: 1235-1239.

•§ Godfrey PP, Watson SP (1988). Fluoride inhibits agonist-induced formation of inositol phosphates in rat cortex. Biochem Biophys Res Commun. 155(2): 664-9. September 15.

•§ Goh EH, Neff AW (2003). Effects of fluoride on Xenopus embryo development; Food and Chemical Toxicology 41: 1501-1508.

+ Goldman SM, Sievers ML,Templin DW (1971). Radiculomyopathy in a southwestern Indian due to skeletal fluorosis. Arizona Medicine. 28(9): 675-677. September.

• Gordon SL, Corbin SB (1992). Summary of Workshop on Drinking Water Fluoride Influence on Hip Fracture on Bone Health. Osteoporosis International 2: 109-117.

+ Green K (2005). Fault is disputed in death, gassing. Woman was inside a tented building. The San Diego Union-Tribune (California). March 10.

+ Groth E III (1973). Two issues of science and public policy: air pollution control in the San Francisco Bay area and fluoridation of community water supplies. A dissertation submitted to the Department of Biological Sciences and the Committee on Graduate Studies of Stanford University. In partial fulfillment of the requirements for the degree of Doctor of Philosophy. Pages iii, 296-297, 299-303. May.

•§ Guan ZZ (1986). [Morphology of the brain of the offspring of rats with chronic fluorosis]. Zhonghua Bing Li Xue Za Zhi 15(4): 297-9. December.

+ Guan ZZ, et al. (1988). Synergistic action of iodine-deficiency and fluorine-intoxication on rat thyroid. Chinese Medical Journal 101(9):679-84.

•§ Guan Z, Wang Y, Xiao K (1997). [Influence of experimental fluorosis on phospholipid content and fatty acid composition in rat brain]. Zhonghua Yi Xue Za Zhi 77(8): 592-6. August.

•§ Guan ZZ, Wang YN, Xiao KQ, Dai DY, Chen YH, Liu JL, Sindelar P, Dallner G (1998). Influence of chronic fluorosis on membrane lipids in rat brain. Neurotoxicology and Teratology 20(5): 537-42. September-October.

• Gunawan J, Debuch H (1985). Alkenylhydrolase: a microsomal enzyme activity in rat brain. Journal of Neurochemistry 44(2): 370-5. February.

+ Gupta SK, Khan TI, Gupta AB, Gupta KC, Jain P, Gupta A (2001). Compensatory

hyperparathyroidism following high fluoride ingestion – a clinico-biochemical correlation. Indian Pediatrics. 38: 139-146. February 17.

•§ Gutteridge DH et al. (2002). A randomized trial of sodium fluoride (60 mg) +/- estrogen in postmenopausal osteoporotic vertebral fractures: increased vertebral fractures and peripheral bone loss with sodium fluoride; concurrent estrogen prevents peripheral loss, but not vertebral fractures. Osteoporosis International 13(2): 158-70.

• Haesungcharern A, Chulavatnatol M (1978). Inhibitors of adenylate cyclase from ejaculated human spermatozoa. J Reprod Fertil. 53(1): 59-61. May.

§ Haguenauer D et al. (2000). Fluoride for the treatment of postmenopausal osteoporotic fractures: a meta-analysis. Osteoporosis International 11: 727-38.

• Haimanot RT (1990). Neurological complications of endemic skeletal fluorosis, with special emphasis on radiculo-myelopathy. Paraplegia 28:244-51.

• Hall LL, Smith FA, De Lopez OH, Gardner DE (1972). Direct potentiometric determination of total ionic fluoride in biological fluids. Clinical Chemistry 18(12): 1455-8.

• Hanhijarvi H (1975). Inorganic plasma fluoride concentrations and its renal excretion in certain physiological and pathological conditions in man. Fluoride 8(4): 198-207.

+ Hanley TR Jr., Calhoun LL, Kociba RJ, Greene JA (1989). The effects of inhalation exposure to sulfuryl fluoride on fetal development in rats and rabbits. Fundamental and Applied Toxicology, 13: 79-86.

•§ Hedlund LR, Gallagher JC (1989). Increased incidence of hip fracture in osteoporotic women treated with sodium fluoride. Journal of Bone and Mineral Research 4: 223-5.

• Hefti A, Marthaler TM (1981). Bone fluoride concentrations after 16 years of drinking water fluoridation. Caries Research 15(1): 85-9.

• Hegmann KT et al. (2000). See Horne BD et al.

•§ Heller KE, Eklund SA, Burt BA (1997). Dental caries and dental fluorosis at varying water fluoride concentrations. Journal of Public Health Dentistry 57(3): 136-143.

Hileman B (1998). Chemical and Engineering News.

+ Hodge HC, Cox GJ (1950). The toxicity of fluorides in relation to their use in dentistry. Journal of the American Dental Association 40:440-451.

• Hodge HC (1979). The Safety of Fluoride Tablets or Drops. In: Johansen E, Taves DR, Olsen TO, Eds. Continuing Evaluation of the Use of Fluorides. AAAS Selected Symposium. Westview Press, Boulder, Colorado. pp. 253-274.

§ Hoffman DJ, Pattee OH, Wiemeyer S (1985). Effects of fluoride on screech owl reproduction: teratological evaluation, growth, and blood chemistry in hatchlings. Toxicology Letters 26(1): 19-24. July.

§ Hongslo CF, Hongslo JK, Holland RI (1980). Fluoride sensitivity of cells from different organs. Acta Pharmacologica et Toxicologica 46: 73-77.

• Horne BD, Gren LH, Hegmann KT, Knight S, Orme HT,Lyon JL (2000). The effects of fluoridation on degenerative joint disease (DJD) and hip Fractures. Abstract # 71 of the 33rd

annual meeting of the Society for Epidemiological Research. American Journal of Epidemiology S18. Note: we had cited this under Hegmann KT et al.

+ Huraib S et al. (1993). Pattern of renal osteodystrophy in haemodialysis patients in Saudi Arabia. Nephrology Dialysis Transplantation 8: 603-8.

• Husdan H et al. (1976). Serum ionic fluoride: normal range and relationship to age and sex. Clinical Chemistry 22: 1884-8.

•§ Ihnatovych I, Novotny J, Haugyicoya R, Bourova L, Mares P, Svoboda P (2002). Ontogenetic development of the G protein-mediated adenylyl cyclase signalling in rat brain. Brain Research. Developmental Brain Research 133(1): 69-75. Jan 31.

§ Inkielewicz I, Krechniak J (2003). FLUORIDE CONTENT IN SOFT TISSUES AND URINE OF RATS EXPOSED TO SODIUM FLUORIDE IN DRINKING WATER. FLUORIDE 36(4): 263-266.

• Inkovaara J et al. (1975). Prophylactic fluoride treatment and aged bones. British Medical Journal 3(5975): 73-4.

•§ Institute of Medicine [IOM] (1997). Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board. National Academy Press.

•§ Isaacson RL, Varner JA, Jensen KF (1997). Toxin-induced blood vessel inclusions caused by the chronic administration of aluminum and sodium fluoride and their implications for dementia. Annals of the New York Academy of Sciences 825: 152-166.

§ Ito S, Negishi M. Mochizuki-Oda N, Yokohama H, Hayaishi O (1991). Sodium fluoride mimics the effect of prostaglandin E2 on catecholamine release from bovine adrenal chromaffin cells. Journal of Neurochemistry 56(1): 44-51. Jan.

• Ittel TH et al. (1992). Effect of fluoride on aluminum-induced bone disease in rats with renal failure. Kidney International 41: 1340-1348.

• Jackson D, Weidman SM (1958). Fluorine in human bone related to age and the water supply of different regions. Journal of Pathological Bacteriology 76: 451-459.

+ Jackson RD, Kelly SA, Noblitt TW, Zhang W, Wilson ME, Dunipace AJ, Li Y, Katz BP, Brizendine EJ, Stookey GK (1997). Lack of effect of long-term fluoride ingestion on blood chemistry and frequency of sister chromatid exhange in human lymphocytes. Environmental and Molecular Mutagenesis 29: 265-271.

• Jacobsen SJ et al. (1990). Regional variation in the incidence of hip fracture: US white women aged 65 years and olders. Journal of the American Medical Association 264(4): 500-2.

• Jacobsen SJ et al. (1992). The association between water fluoridation and hip fracture among white women and men aged 65 years and older; a national ecologic study. Annals of Epidemiology 2: 617-626.

• Jacqmin-Gadda H et al. (1995). Fluorine concentration in drinking water and fractures in the elderly. Journal of the American Medical Association 273: 775-776.

• Jacqmin-Gadda H et al. (1998). Risk factors for fractures in the elderly. Epidemiology 9(4): 417-423.

•§ Janiszewska G, Lachowicz L, Wojtkowiak R (1984). Effect of certain agents on subcellular

cAMP level in different areas of rat brain. Acta Physiologica Polonica 35(3): 199-206. May-June.

§ Jiang CX, Fan QT, Cheng XM, Cui LX (2005). [Relationship between spermatogenic cell apoptosis and serum estradiol level in rats exposed to fluoride]. Wei Sheng Yan Jiu 34(1): 32-4. Jan.

+ Johnson LC (1965). Histogenesis and mechanisms in the development of osteofluorosis. In: H.C.Hodge and F.A.Smith, eds : Fluorine chemistry, Vol. 4. New York, N.Y., Academic press (1965) 424-441.

• Johnson W et al. (1979). Fluoridation and bone disease in renal patients. In: Johansen E, Taves DR, Olsen TO, Eds. Continuing Evaluation of the Use of Fluorides. AAAS Selected Symposium. Westview Press, Boulder, Colorado. pp. 275-293.

• Jolly SS (1970). Hydric fluorosis in Punjab (India). In: Vischer TL. Fluoride in Medicine. Hans Huber: Switzerland. pp. 106-121.

§ Jolly SS et al. (1980). Kidney changes and kidney stones in endemic fluorosis. Fluoride 13(1): 10-16.

+ Jones JJ (2005). Re: Objections and request for a hearing concerning sulfuryl fluoride tolerances. Letter from James J. Jones, Director, Office of Pesticide Programs (Washington DC) to Fluoride Action Network and Beyond Pesticides. June 2.

• Juncos LI, Donadio JV Jr. (1972). Renal failure and fluorosis. Journal of the American Medical Association 222: 783-5.

§ Kaminsky LS et al. (1990). Fluoride: benefits and risks of exposure. Critical Reviews of Oral Biology and Medicine 1(4): 261-81.

§ Kanwar KC, Vig PS, Kalla NR (1983). In vitro inhibition of testosterone synthesis in the presence of fluoride ions. IRCS Med. Sci. 11: 813-814.

• Katz S, Tenenhouse A (1973). The relation of adenyl cyclase to the activity of other ATP utilizing enzymes and phosphodiesterase in preparations of rat brain; mechanism of stimulation of cyclic AMP accumulation by NaF. British Journal of Pharmacology 48(3): 505-15. July.

§ Kay AR, Miles R, Wong RK (1986). Intracellular fluoride alters the kinetic properties of calcium currents facilitating the investigation of synaptic events in hippocampal neurons. J Neurosci. 6(10): 2915-20. Oct.

• Kaye M et al. (1960). Bone disease in chronic renal failure with particular reference to osteosclerosis. Medicine 39: 157-190.

• Keller C (1991). Fluorides in drinking water. Unpublished results. Discussed in: Gordon SL, Corbin SB. (1992). Summary of Workshop on Drinking Water Fluoride Influence on Hip Fracture on Bone Health. Osteoporosis International 2: 109-117.

• Kierdorf U, Richards A, Sedlacek F, Kierdorf H (1997). Fluoride content and mineralization of red deer (Cervus elaphus) antlers and pedicles from fluoride polluted and uncontaminated regions. Archives of Environmental Contamination and Toxicology 32: 222-227.

• Kierdorf U, Kierdorf H, & Boyde A (2000). Structure and mineralisation density of antler and pedicle bone in red deer (Cervus elaphus .) exposed to different levels of environmental fluoride: a quantitative backscattered electron imaging study. Journal of Anatomy 196: 71-83.

+ Kimm VJ (1984). The adverse health effects of fluorosis. Letter from Victor J. Kimm, Director, US EPA Office of Drinking Water, to William D. Ruckelshaus, EPA Administrator. July 26.

• Koh ET, Clarke SL (1997). Effects of fluoride and aluminum exposure to dams prior to and during gestation on mineral compositions of bone and selected soft tissues of female mice dams and pups. FASEB J. 11(3):A406. Feb.

•§ Kour K, Singh J (1980). Histological Finding of Mice Testes Following Fluoride Ingestion. Fluoride 13(4): 160-162.

§ Krasowska A, Wlostowski T (1992). The effect of high fluoride intake on tissue trace elements and histology of testicular tubules in the rat. Comp Biochem Physiol C. 103(1): 31-4. September.

•§ Krasowska A, Wlostowski T (1996). Photoperiodic elevation of testicular zinc protects seminiferous tubules against fluoride toxicity in the bank vole (Clethrionomys glareolus). Comp Biochem Physiol C Pharmacol Toxicol Endocrinol. 113(1): 81-4. January.

• Krishnamachari KA, Krishnaswamy K (1973). Genu valgum and osteoporosis in an area of endemic fluorosis. The Lancet 2: 877-879.

• Kroger H et al. (1994). The effect of fluoridated drinking water on axial bone mineral density—a population-based study. Bone Mineral 27(1): 33-41.

+ Krupanidhi S, Cherry KN (2005). Teratogenicity due to fluoride. FASEB Journal 19(4): A58. March 4.

• Kula K (1978). The influence of human menopausal gonadotropin, natrium fluoride and cyproterone acetate on the spermatogenesis in immature rats. Andrologia 10(3): 223-33. May-June. □

•§ Kumar SP, Harper RA (1963). Fluorosis in Aden. British Journal of Radiology 36: 497-502.

•§ Kumar A, Susheela AK (1994). Ultrastructural studies of spermiogenesis in rabbit exposed to chronic fluoride toxicity. International Journal of Fertility and Menopausal Studies. 39(3): 164-71. May-June.

•§ Kumar A, Susheela AK (1995). Effects of chronic fluoride toxicity on the morphology of ductus epididymis and the maturation of spermatozoa of rabbit. Int J Exp Pathol. 76(1): 1-11. February.

• Kuo HC, Stamm JW (1974). Fluoride levels in human rib bone: a preliminary study. Canadian Journal of Public Health 65(5): 359-61.

• Kurttio PN et al. (1999). Exposure to natural fluoride in well water and hip fracture: A cohort analysis in Finland. American Journal of Epidemiology 150(8): 817-824.

•§ Lafage MH et al. (1995). Comparison of alendronate and sodium fluoride effects on cancellous and cortical bone in minipigs. A one-year study. Journal of Clinical Investigation 95(5): 2127-33.

§ Lantz O et al. (1987). Fluoride-induced chronic renal failure. American Journal of Kidney Disorders 10(2): 136-9.

§ Lavoie D (2005). Harvard professor investigated in fluoride research flap. The Associated Press. July 13.

•§ Levy SM, Guha-Chowdhury N (1999). Total fluoride intake and implications for dietary fluoride supplementation. Journal of Public Health Dentistry 59: 211-23.

• Levy SM et al. (2003). Patterns of fluoride intake from 36 to 72 months of age. Journal of Public Health Dentistry 63(4): 211-20.

• Li CS et al. (1986). Relationships between ionic fluoride, total fluoride, calcium, phosphorus, and magnesium in serum of fluorosis patients. Fluoride 19(4): 184-187.

• Li C, Ke X (1990). Ionic, nonionic, and total fluoride in human serum. Fluoride 23(4): 164-170.

§ Li L (2003). The biochemistry and physiology of metallic fluoride: action, mechanism, and implications. Crit Rev Oral Biol Med 14: 100-14.

• Li PP, Sibony D, Warsh JJ (1990). Guanosine 5'-O-thiotriphosphate and sodium fluoride activate polyphosphoinositide hydrolysis in rat cortical membranes by distinct mechanisms. Journal of Neurochemistry 54(4): 1426-32. April. □

•§ Li Y et al. (1994). [Effect of excessive fluoride intake on mental work capacity of children and a preliminary study of its mechanism] Hua Hsi I Ko Ta Hsueh Hsueh Pao 25(2): 188-91.

•§ Li Y et al. (2001). Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. Journal of Bone and Mineral Research 16(5): 932-9.

• Li XS (1995). Effect of Fluoride Exposure on Intelligence in Children. Fluoride 28(4): 189-192.

•§ Li X, Song L, Jope RS (1996). Cholinergic stimulation of AP-1 and NF kappa B transcription factors is differentially sensitive to oxidative stress in SH-SY5Y neuroblastoma: relationship to phosphoinositide hydrolysis. J Neurosci .1;16(19): 5914-22. October.

•§ Lin Fa-Fu et al. (1991). Note: We incorrectly used this citation – Fa-Fu L.

• Liteplo RG et al. (1994). Inorganic fluoride: Evaluation of risks to health from environmental exposure in Canada. Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews 12: 327-344.

•§ Litosch I (1987). Guanine nucleotide and NaF stimulation of phospholipase C activity in rat cerebral-cortical membranes. Studies on substrate specificity. The Biochemical Journal 15; 244(1): 35-40. May.

§ Liu JL, Xia T, Yu YY, Sun XZ, Zhu Q, He W, Zhang M, Wang A (2005). [The dose-effect relationship of water fluoride levels and renal damage in children] Wei Sheng Yan Jiu 34(3): 287-8.

§ Liu WX (1989). [Experimental study of behavior and cerebral morphology of rat pups generated by fluorotic female rat]. Zhonghua Bing Li Xue Za Zhi 18(4): 290-2. December.

•§ Long YG, Wang YN, Chen J, Jiang SF, Nordberg A, Guan ZZ (2002). Chronic fluoride toxicity decreases the number of nicotinic acetylcholine receptors in rat brain. Neurotoxicology and Teratology 24(6): 751-7. Nov-Dec.

•§ Lu Y, Sun ZR, Wu LN, Wang X, Lu W (2000). EFFECT OF HIGH-FLUORIDE WATER ON INTELLIGENCE IN CHILDREN. Fluoride 33(2): 74-78.

•§ Lu X-H, Li G-S, Sun B (2000). Study of the mechanism of neurone apoptosis in rats from the chronic fluorosis. Chinese Journal of Endemiology 2000;19(2):96-8; as cited and abstracted in Fluoride 34(1): 82.

•§ Luke J (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildord, UK.

•§ Luke J (2001). Fluoride Deposition in the Aged Human Pineal Gland. Caries Research 35: 125-128.

•§ Machida H (1989). [The rabbit thermo-regulatory system. Effects of high dose of sodium fluoride]. Shikwa Gakuho. 89(3): 607-26. March.

+ Manji F, Kapila S. (1986). Fluorides and fluorosis in Kenya. Part III: Fluorides, fluorosis and dental caries. Odonto-stomatologie tropicale 9:135-9.

§ Manocha SL et al. (1975). Cytochemical response of kidney, liver and nervous system to fluoride ions in drinking water. Histochemical Journal 7: 343-355.

+ Mann J et al. (1990). Fluorosis and dental caries in 6-8-year-old children in a 5 ppm fluoride area. Community Dentistry and Oral Epidemiology 18: 77-9.

+ Mann J et al. (1987). Fluorosis and caries prevalence in a community drinking above-optimal fluoridated water. Community Dentistry and Oral Epidemiology 15: 293-5.

• Mansfield P (1999). The distribution of urinary fluoride concentration in the UK. Fluoride 32(1): 27-32.

§ Marcus WL (1990). Fluoride conference to review the NTP draft fluoride report. US EPA Office of Water. Memorandum. May 1.

§ Marcus WL (1995). Interview with Dr. Gary Null. March 10. EXCERPT.

• Marier J, Rose D (1977). – see Rose D, Marier J.

+ Marumo F, Iwanami S (2001). High fluoride concentrations in the serum and bone of patients with chronic renal failure. Fluoride 34(3): 213.

• Massler M, Schour I (1952). Relation of endemic dental fluorosis to malnutrition. Journal of the American Dental Association 44: 156-165.

• May DS, Wilson MG (1992). Hip fractures in relation to water fluoridation: an ecologic analysis. Unpublished results. Discussed in: Gordon SL, Corbin SB. (1992). Summary of Workshop on Drinking Water Fluoride Influence on Hip Fracture on Bone Health. Osteoporosis International 2: 109-117.

§ Mazze RI et al. (1977). Inorganic fluoride nephrotoxicity: prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 46(4): 265-71.

• McDonagh M et al. (2000). A systematic review of public water fluoridation. Report 18, NHS [National Health Service] Centre for Reviews and Dissemination, University of York, York, UK.

§ Medical Research Council (2002). Medical Research Council Working Group Report: Water. Fluoridation and Health, London, Medical Research Council.

• Mehdi AWR, Al-Soudi KA, Al-Jiboori NAJ, Al-Hiti MK (1983). Effect of high fluoride intake on chicken performance, ovulation, spermatogenesis and bone fluoride content. Fluoride 16(1): 37-43

+ Menoyo I et al. (2005). Effect of fluoride on the secretion of insulin in the rat.

Arzneimittelforschung 55:455-60.

• Michael M et al. (1996). Investigations of soft tissue functions in fluorotic individuals of North Gujarat. Fluoride 29(2): 63-71.

• Mihashi M, Tsutsui T (1996). Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. Mutation Research/Genetic Toxicology, 368(1): 7-13. May.

+ Misra UK et al. (1988). Endemic fluorosis presenting as cervical cord compression. Archives of Environmental Health 43:18-21.

§ Mohamed AH, Chandler ME (1982). Cytological effects of sodium fluoride on mice. Fluoride 15(3): 110-118.

•§ Mooradian AD, Scarpace PJ (1992). Beta-adrenergic receptor activity of cerebral microvessels in experimental diabetes mellitus. Brain Research 26: 583(1-2): 155-60.

• Morgan L et al. (1998). Investigation of the possible associations between fluorosis, fluoride exposure, and childhood behavior problems. Pediatric Dentistry - 20:4, 244- 252.

• Mosekilde L et al. (1987). Compressive strength, ash weight, and volume of vertebral trabecular bone in experimental fluorosis in pigs. Calcified Tissue Research 40: 318-322.

•§ Mullenix PJ, Denbesten PK, Schunior A, Kernan WJ (1995). Neurotoxicity of sodium fluoride in rats. Neurotoxicology and Teratology 17(2): 169-77. Mar-Apr.

• Nanba T, Ando M, Nagata Y, Kitajima S, Nakazawa K (1981). Distribution and different activation of adenylate cyclase by NaF and of guanylate cyclase by NaN3 in neuronal and glial cells separated from rat cerebral cortex. Brain Research 218(1-2): 267-77. Aug 10. □

•§ Narayana MV, Chinoy NJ (1994). Reversible effects of sodium fluoride ingestion on spermatozoa of the rat. International Journal of Fertility 39(6): 337-346.

•§ Narayana MV, Chinoy NJ (1994). Effect of fluoride on rat testicular steroidogenesis. Fluoride 27(1): 7-12.

+ National Academy of Sciences. (1989). Recommended Dietary Allowances: 10th Edition. Commission on Life Sciences, National Research Council, National Academy Press.

+ National Institute for Literacy (2005). Frequently asked questions. Online as of December 2005.

• National Institute for Public Health and Environmental Protection [NIPHEP]. (1989). Slooff W, Eerens HC,Janus JA, Ros JPM. Integrated criteria document fluorides. Report No 758474010. The Netherlands.

+ National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (2004). Few Americans are aware they have chronic kidney disease. NIH News. National Institutes of Health. US Department of Health and Human Services. December 17.

•§ National Research Council [NRC] (1993). Health effects of ingested fluoride. Report of the Subcommittee on Health Effects of Ingested Fluoride. National Academy Press, Washington, DC. ONLINE LINK http://www.nap.edu/books/030904975X/html/

• National Toxicology Program [NTP] (1990). Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3f1 Mice. Technical report Series No. 393. NIH Publ. No 91-

2848. National Institute of Environmental Health Sciences, Research Triangle Park, N.C.

+ Neurath C et al. (2005). Objections and request for hearing. Docket No. OPP-2005-0174. Sulfuryl fluoride; pesticide tolerance. Final Rule. Submission to US Environmental Protection Agency from Fluoride Action Network, the Environmental Working Group, and Beyond Pesticides. September 13.

+ Neurath C et al. (2005a). Objections and request for hearing. Table 6. Studies reporting effects on the male reproductive system from fluoride.

• Nijjar M, Belgrave RL (1997). Regulation of Ca2+ homeostasis by glucose metabolism in rat brain. Molecular and Cellular Biochemistry 176(1-2): 317-26. November. □

• Ng AHM et al. (2004). Association between fluoride, magnesium, aluminum and bone quality in renal osteodystrophy. Bone 34: 216-224..

§ O'Duffy JD et al. (1986). Mechanism of acute lower extremity pain syndrome in fluoride-treated osteoporotic patients. American Journal of Medicine 80: 561-566.

•§ Orcel P et al. (1990). Stress fractures of the lower limbs in osteoporotic patients treated with fluoride. Journal of Bone and Mineral Research 5(Suppl 1): S191-4.

•§ Ortiz-Perez D, Rodriguez-Martinez M, Martinez F, Borja-Aburto VH, Castelo J, Grimaldo JI, de la Cruz E, Carrizales L, Diaz-Barriga F (2003). Fluoride-induced disruption of reproductive hormones in men. Environmental Research 93(1): 20-30. September.

• Pak CY (1989). Fluoride and osteoporosis. Proceedings of the Society for Experimental Biology and Medicine 191: 278-86.

• Pak CY et al. (1994). Slow-release sodium fluoride in the management of postmenopausal osteoporosis. A randomized controlled trial. Annals of Internal Medicine 120(8): 625 32.

• Pandit CG et al. (1940). Endemic fluorosis in South India. Indian Journal of Medical Research 28: 533-558.

• Parkins FM et al. (1974). Relationships of human plasma fluoride and bone fluoride to age. Calcified Tissue Research 16: 335-8.

•§ Pati and Bhunya (1987). Genotoxic effect of an environmental pollutant, sodium fluoride, in mammalian in vivo test system. Caryologia, 40:1-2; 79-87.

§ Paul V, Ekambaram P, Jayakumar AR (1998). Effects of sodium fluoride on locomotor behavior and a few biochemical parameters in rats. Environmental Toxicology and Pharmacology 6:187-191.

• Perkins JP, Moore MM (1971). Adenyl cyclase of rat cerebral cortex. Activation of sodium fluoride and detergents. The Journal of Biological Chemistry 246(1): 62-8. Jan 10.

§ Pesticide Action Network (PAN) (2005). California Pesticide Use. Cryolite - Pesticide use statistics for 2003. ONLINE LINK:
http://www.pesticideinfo.org/Detail_ChemUse.jsp?Rec_Id=PC35073

+ Pesticide News 68 (UK) (2005). Sulfuryl fluoride kills bystander. Page 23. June.

• Phipps KR, Burt BA (1990). Water-borne fluoride and cortical bone mass: A comparison of two communities. Journal of Dental Research 69: 1256-1260.

• Phipps KR et al. (2000). Community water fluoridation, bone mineral density and fractures: prospective study of effects in older women. British Medical Journal 321: 8604.

• Pinet A, Pinet F (1968). Endemic fluorosis in the Sahara. Fluoride 1(2): 86-93.

§ Pinto R, Vieira C, Mota-Filipe H, Silva-Lima B (1998). NaF may disturb male fertility in rodents. Toxicology Letters 95: 214. Supplement 1. July.

§ Plesneva SA, Nalivaeva NN, Zhuravin IA (1998). Adenylate cyclase system of the rat striatum: regulatory properties and the effects of gangliosides. Neuroscience and Behavioral Physiology 28(4): 392-6. July-August.

• Polzik EV et al. (1993). Factors of individual predisposition to occupational fluorosis. Fluoride 26(4): 257-262.

• Polzik EV et al. (1994). A method for estimating individual predisposition to occupational fluorosis. Fluoride 27(4): 194-200.

§ Popov LI, Filatova RI, Shershever AS (1974). Aspects of nervous system affections in occupational fluorosis. GIG TR PROF ZABOL (5). 25-27.

§ Pradhan KM, Arora NK, Jena A, Susheela AK, Bhan MK (1995). Safety of ciprofloxacin therapy in children: magnetic resonance images, body fluid levels of fluoride and linear growth. Acta Paediatrica 84(5): 555-60. May.

• Public Health Service [PHS] (1991). Review of fluoride: benefits and risks. Report of the Ad Hoc Subcommittee on Fluoride. Washington, DC.

•§ Publicover SJ (1991). Brief exposure to the G-protein activator NaF/AlCl3 induces prolonged enhancement of synaptic transmission in area CAl of rat hippocampal slices. Exp Brain Res. 84(3): 680-4.

§ Pushpalatha T, Srinivas M, Sreenivasula Reddy P (2005). Exposure to high fluoride concentration in drinking water will affect spermatogenesis and steroidogenesis in male albino rats. Biometals.18(3): 207-12. June.

§ Ramseyer WF et al. (1957). Effect of sodium fluoride administration on body changes in old rats. Journal of Gerontology 12: 14-19.

§ Reggabi M et al. (1984). Renal function in residents of an endemic fluorosis area in southern Algeria. Fluoride 17(1): 35-41.

• Richards A et al. (1994). Normal age-related changes in fluoride content of vertebral trabecular bone - Relation to bone quality. Bone 15: 21-26.

• Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Fay MP, Feuer EJ, Edwards BK (eds). (2003) SEER Cancer Statistics Review, 1975-2000, National Cancer Institute. Bethesda, MD

+ Rigalli A, Ballina JC, Roveri E, Puche RC (1990). Inhibitory effect of fluoride on the secretion of insulin. Calcified Tissue International 46:333-8.

+ Rigalli A, Ballina JC, Puche RC (1992). Bone mass increase and glucose tolerance in rats chronically treated with sodium fluoride. Bone Mineral 16:101-8.

+ Rigalli A, Alloatti R, Menoyo I, Puche RC (1995). Comparative study of the effect of sodium fluoride and sodium monofluorophosphate on glucose homeostasis in the rat. Arzneimittelforschung 45:289-92.

•§ Riggs BL et al. (1990). Effect of Fluoride treatment on the Fracture Rates in Postmenopausal Women with Osteoporosis. New England Journal of Medicine 322: 802-809.

+ Rimoli C et al. (1991). Relationship between serum concentrations of flecainide and fluoride in humans. Boll Chim Farm 130:279-82.

• Ringe JD, Meunier PJ (1995). What is the future for fluoride in the treatment of osteoporosis? Osteoporosis International 5: 71-4.

§ Riordan PJ (1993). Perceptions of dental fluorosis. Journal of Dental Research 72: 1268-74.

• Ritzen EM, Hagenas L, Ploen L, French FS, Hansson V (1977). In vitro synthesis of rat testicular androgen-binding protein (ABP). Molecular and Cellular Endocrinology 8(4): 335-46. October.

• Robinson C, Kirkham J (1990). The effect of fluoride on the developing mineralized tissues. Journal of Dental Research 69(Spec Issue): 685-91.

• Roholm K (1937). Fluoride intoxication: a clinical-hygienic study with a review of the literature and some experimental investigations. London: H.K. Lewis Ltd. Pages 144, 201-209, 278-282.

§ Roschger P et al. (1995). Bone mineral structure after six years fluoride treatment investigated by backscattered electron imaging (BSEI) and small angle x-ray scattering (SAXS): a case report. Bone 16: 407.

• Rose D, Marier J, (1977). Environmental Fluoride. National Research Council of Canada. Associate Committe on Scientific Criteria for Environmental Quality. NRCC No. 16081.

§ Ross BM, McLaughlin M, Roberts M, Milligan G, McCulloch J, Knowler JT (1993). Alterations in the activity of adenylate cyclase and high affinity GTPase in Alzheimer's disease. Brain Research 622(1-2): 35-42. Sep 17.

+ Ruiz-Payan A, Duarte-Gardea M, Ortiz M, Hurtado R (2005). Chronic effects of fluoride on growth, blood chemistry, and thyroid hormones in adolescents residing in northern Mexico. Paper presented at the XXVIth Conference of the International Society for Fluoride Research. September 26-29. Fluoride 38(3): 46.

• Runge H, Franke J (1989). Radiological modification of the skeletal system among aluminum smelter workers: A 15-year retrospective study. Fluoride 22(4): 157-164.

•§ Sarri E, Claro E (1999). Fluoride-induced depletion of polyphosphoinositides in rat brain cortical slices: a rationale for the inhibitory effects on phospholipase C. Int J Dev Neurosci. 17(4): 357-67. July.

• Sauerbrunn BJ, Ryan CM (1965). Chronic fluoride intoxication with fluorotic radiculomyelopathy. Annals of Internal Medicine 63: 1074-1078.

•§ Savas S et al. (2001). Endemic fluorosis in Turkish patients: relationship with knee osteoarthritis. Rheumatology International 21: 30-5.

§ Sawyer Ostrom G (1996). Cryolite on grapes/Fluoride in wines - A guide for growers and vintners to determine optimum cryolite applications on grapevines. CATI Viticulture and Enology

Research Center. CATI Publication #960601.

• Scarpa M, Vianello F, Rigo A, Viglino P, Bracco F, Battistin L (1993). Uptake and life time of fluoride ion in rats by 19F-NMR. Magnetic resonance imaging 11(5): 697-703. □

+ Schlegel HH (1974). Industrial skeletal fluoroses: preliminary report on 61 cases from aluminum smeleter. Sozial und Praventivmed. 19:269-74. (Abstracted in: Fluoride 1975; 8(3):177)

•§ Schlesinger ER et al. (1956). Newburgh-Kingston caries-fluorine study XIII. Pediatric findings after ten years. Journal of the American Dental Association 52: 296.

•§ Schnitzler CM et al. (1990). Bone fragility of the peripheral skeleton during fluoride therapy for osteoporosis. Clinical Orthopaedics (261): 268-75.

• Schofield PJ, Comerford MJ, de Jongh KS (1983). Comparative inhibition profiles of human brain and mouse liver L-hexonate dehydrogenase. Comp Biochem Physiol B. 76(4): 869-73.

§ Schuld A (2004). Fluoride-Iodine Antagonism: Some History. Parents for Fluoride Poisoned Children website.

§ Shafer TJ, Mundy WR, Tilson HA (1993). Aluminum decreases muscarinic, adrenergic, and metabotropic receptor-stimulated phosphoinositide hydrolysis in hippocampal and cortical slices from rat brain. Brain Research 629(1):133-40. November 26.

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

•§ Shao Q, Wang Y, Guan Z (2000). [Influence of free radical inducer on the level of oxidative stress in brain of rats with fluorosis]. Zhonghua Yu Fang Yi Xue Za Zhi 34(6): 330-2. November.

+ Shapiro JR (1983a). Untitled. Letter and draft on the nondental toxicity of fluoride in drinking water. Letter from Jay R. Shapiro, M.D., Deputy Director, The Clinical Center, National Institutes of Health, Bethesda, Maryland 20205. Draft pages 1-15.

+ Shapiro JR (1983b). Report to the Surgeon General. By the Ad Hoc Committee on the Non-Dental Health Effects of Fluoride in Drinking Water. September 26.

•§ Shashi (1990). Histopathological changes in rabbit testes during experimental fluorosis. Folia Morphol (Praha) 38(1): 63-5.

•§ Shashi A (1992). Studies on alterations in brain lipid metabolism following experimental fluorosis. Fluoride 25(2): 77-84.

•§ Shashi A (1992). Biochemical effects of fluoride on lipid metabolism in the reproductive organs of male rabbits. Fluoride 25(3): 149-154.

§ Shashi, Kaur D (1992). Testicular proteins and DNA in experimental fluorosis. Indian J Pathol Microbiol. 35(4): 351-6. October.

•§ Shashi A, Singh JP, Thapar SP (1994). Effect of long-term administration of fluoride on levels of protein, free amino acids and RNA in rabbit brain. Fluoride 27(3): 155-159. □

§ Shashi A (2003). Histopathological investigation of fluoride-induced neurotoxicity in rabbits. Fluoride 36(2): 95-105.

§ Shen X, Zhang Z, XU X (2004). [Influence of combined iodine and fluoride on phospholipid and fatty acid composition in brain cells of rats]. Wei Sheng Yan Jiu 33(2): 158-61. March.

• Shi, Jingpu, Dai, Guojun, Zhang Zhiyu, et al. (1995). Relationship Between Bone Fluoride Content, Pathological Change in Bone of Aborted Fetuses and Maternal Fluoride Level . Zhonghua Yu Fang Yi Xue Za Zhi (Chinese Journal of Preventive Medicine). 29(2): 103-105. March.
[Article in Chinese. Translation of article enclosed.]

•§ Shivarajashankara YM, Shivashankara AR, Gopalakrishna Bhat P, Hanumanth Rao S (2001). Effect of fluoride intoxication on lipid peroxidation and antitoxidant systems in rats. Fluoride 34(2): 108-113.

•§ Shivarajashankara YM, Shivashankara AR, Bhat PG, Rao SH (2002). Brain lipid peroxidation and antioxidant systems of young rats in chronic fluoride intoxication. Fluoride 35(3): 153-160.

•§ Shivarajashankara YM, Shivashankara AR, Gopalakrishna Bhat P, Muddanna Rao S, Hanumanth Rao S (2002). Histological changes in the brain of young fluoride-intoxicated rats. Fluoride 35(1): 12-21.

§ Shortt HE et al. (1937). Endemic fluorosis in the Madras presidency. Indian Journal of Medical Research 25: 553-568.

•§ Siddiqui AH (1955). Fluorosis in Nalgonda district, Hyderabad-Deccan. British Medical Journal ii. 1408-1413. December 10.

• Siddiqui AH (1970). Neurological complications of skeletal fluorosis with special reference to lesions in the cervical region. Fluoride 3(2): 91-96.

• Siegel SM, Grove BD, Carr PA (2002). SSeCKS immunolabeling in rat primary sensory neurons. Brain Research 926(1-2): 126-36. February 1. □

• Singer L, Ophaug RH (1979). Concentrations of ionic, total, and bound fluoride in plasma. Clinical Chemistry 25: 523-5.

• Singh A et al. (1961). Skeletal fluorosis and its neurological complications. Lancet 1: 197-200.

•§ Singh A et al. (1963). Endemic fluorosis: Epidemiological, clinical and biochemical study of chronic fluoride intoxication in Punjab. Medicine 42: 229-246.

•§ Singh A, Jolly SS (1970). Chronic toxic effects on the skeletal system. In: Fluorides and Human Health. World Health Organization. pp. 238-249.

• Singh KB, Dominic CJ (1975). Sodium fluoride-induced changes in the hypothalamic neurosecretory system of the spotted owlet, Athene brama Temminck. Endocrinol Exp. 9(2): 149-55. June. □

•§ Singla VP et al. (1976). Symposium on the non-skeletal phase of chronic fluorosis: The Kidneys. Fluoride 9(1): 33-35.

• Sogaard CH et al. (1994). Marked decrease in trabecular bone quality after five years of sodium fluoride therapy--assessed by biomechanical testing of iliac crest bone biopsies in osteoporotic patients. Bone 15(4): 393-99.

•§ Sogaard CH, Mosekilde L, Schwartz W, Leidig G, Minne HW, Ziegler R (1995). Effects of fluoride on rat vertebral body biomechanical competence and bone mass. Bone 16(1): 163-9.

§ Song K et al. (1991). Ultrastructural observations of testes and prostate gland in rat with chronic fluorosis. J CHINA MED UNIV 19(5): 339-342.

•§ Soni MG, Kachole MS, Pawar SS (1984). Alterations in drug metabolising enzymes and lipid peroxidation in different rat tissues by fluoride. Toxicology Letters 21(2): 167-72. May.

•§ Sowers MR et al. (1986). The relationship of bone mass and fracture history to fluoride and calcium intake: a study of three communities. American Journal of Clinical Nutrition 44(6): 889-98.

•§ Sowers M et al. (1991). A prospective study of bone mineral content and fracture in communities with differential fluoride exposure. American Journal of Epidemiology 133: 649-660.

+ Sowers M et al. (2005). Elevated serum fluoride concentrations in women are not related to fractures and bone mineral density.
Journal of Nutrition 135:2247-52.

§ Sprando RL, Black TN, Ames MJ, Rorie JI, Collins TFX (1996). Effect of intratesticular injection of sodium fluoride on spermatogenesis. Food Chem Toxicol. 34(4):377-84. April.

•§ Sprando RL, Collins TFX, Black TN, Rorie J, Ames MJ, O'Donnell M (1997). Testing the potential of sodium fluoride to affect spermatogenesis in the rat. Food Chem Toxicol. 35(9): 881-90. September.

•§ Sprando RL, Collins TFX, Black TN, Olejnik N, Rorie J (1998). Testing the potential of sodium fluoride to affect spermatogenesis: a morphometric study. Food Chem Toxicol. 36(12):1117-24. December.

§ Stannard JG, Shim YS, Kritsineli M, Labropoulou P, Tsamtsouris A (1991). Fluoride levels and fluoride contamination of fruit juices. The Journal of Clinical Pediatric Dentistry 16(1): 38-40. Fall.

• Stein ID, Granik G (1980). Human vertebral bone: Relation of strength, porosity, and mineralization to fluoride content. Calcified Tissue International 32: 189-194.

• Sternweis PC (1986). The purified alpha subunits of Go and Gi from bovine brain require beta gamma for association with phospholipid vesicles. The Journal of Biological Chemistry 261(2): 631-7. –January 15.

+ Structural Pest Control Board (Texas) (2002). Meeting minutes. Joe C. Thompson Conference Center, Austin, Texas. February 12. Pages 1, 14-16, 23.

• Strunecka A and Patocka J (1999). Pharmacological and toxicological effects of aluminofluoride complexes. Fluoride, 32(4): 230-242.

§ Strunecka A, Strunecky O, Patocka J (2002). Fluoride plus aluminum: useful tools in laboratory investigations, but messengers of false information. Physiol Res. 51(6): 557-64.

+ Sun DJ et al. (2005). Dose-response relationship between dental fluorosis and fluoride in brick tea. Abstract. Presented at the 26th International Society for Fluoride Research in Wiesbaden, Germany (September 2005). Fluoride 38(3) 253.

•§ Sun Z-R, Liu F-Z, Wu L-N, et al. (2000). Effects of high fluoride drinking water on the cerebral functions of mice. Chinese Journal of Endemiology;19(4): 262-3; as cited and abstracted in Fluoride 2001; 34(1): 80.

+ Surgeon General's Ad Hoc Committee on 'Non-Dental Health Effects of Fluoride." (1983).

Transcript of Proceedings, National Institutes of Health, Bethesda, Maryland, April 19.

• Susheela AK et al. (1981). Chemical Profile of Human Serum in Fluoride Toxicity and Fluorosis: 1. Total Protein-Bound Carbohydrates, Seromucoid and Fluoride Levels. Fluoride 14(4): 150-154.

•§ Susheela AK, Kumar A (1991). A study of the effect of high concentrations of fluoride on the reproductive organs of male rabbits, using light and scanning electron microscopy. J Reprod Fertil. 92(2): 353-60. July.

•§ Susheela AK, Jethanandani P (1996). Circulating testosterone levels in skeletal fluorosis patients. J Toxicol Clin Toxicol. 34(2): 183-9.

§ Susheela AK, Kumar A (1997). Ultrastructural studies on the leydig cells of rabbits exposed to chronic fluoride toxicity. Environ Sci 5(2): 79-94.

• Takahashi K, Akiniwa K, Narita K (2001). Regression analysis of cancer incidence rates and water fluoride in the U.S.A. based on IACR/IARC (WHO) data (1978-1992). International Agency for Research on Cancer. J Epidemiol. 11(4): 170-9. July. □

+ Takahashi Y (1995). Effects of fluoride on bone metabolism in patients with hemodialysis. Bulletin of the Osaka Medical College 41: 27-35.

+ Tanimura Y (1994). Studies on serum fluoride and bone metabolism in patients with long term hemodialysis. Bulletin of the Osaka Medical College 40: 65-72.

• Taves DR et al. (1968). Hemodialysis with fluoridated dialysate. Transactions of the American Society for Artificial Internal Organs 14: 412-4.

• Taves DR (1970). New approach to the treatment of bone disease with fluoride. Federation Proceedings 29: 1185-1187.

• Taves DR, Guy WS (1979). Distribution of fluoride among body compartments. In: Johansen E, Taves DR, Olsen TO, Eds. Continuing Evaluation of the Use of Fluorides. AAAS Selected Symposium. Westview Press, Boulder, Colorado. pp. 159-185.

•§ Teotia SPS, Teotia M (1972). Cacification of the vas deferens in a patient with endemic fluorosis. Case report. Fluoride 5(2): 86-88.

+ Teotia M, Teotia SPS (1973). Further observations on endemic fluoride-induced osteopathies in children. Fluoride 6(3): 143-151.

§ Teotia SPS et al. (1976). Symposium on the Non-Skeletal Phase of Chronic Fluorosis: The Joints. Fluoride 9(1): 19-24.

• Teotia SPS, Teotia SP, Singh KP (1998). Endemic chronic fluoride toxicity and dietary calcium deficiency interaction syndromes of metabolic bone disease and deformities in India: year 2000. Indian Journal of Pediatrics 65: 371-381.

§ Tezelman S, Shaver JK, Grossman RF, Liang, W, Siperstein AE, Duh QY, Clark OH (1994). Desensitization of adenylate cyclase in Chinese hamster ovary cells transfected with human thyroid-stimulating hormone receptor. Endocrinol 134(3): 1561-9.

•§ Tiger G, Bjorklund PE, Brannstrom G, Fowler CJ (1990). Multiple actions of fluoride ions upon the phosphoinositide cycle in the rat brain. Brain Research 24;537(1-2): 93-101. December.

•§ Tiger G, Bjorklund PE, Cowburn RF, Garlind A, O'Neill C, Wiehager B, Fowler CJ (1990).

Effect of monovalent ions upon G proteins coupling muscarinic receptors to phosphoinositide hydrolysis in the rat cerebral cortex. European Journal of Pharmacology 188(1): 51-62. January 23.

•§ Tokar' VI, Savchenko ON (1977). [Effect of inorganic fluorine compounds on the functional state of the pituitary-testis system]. Probl Endokrinol (Mosk). 23(4): 104-7. July-August.

§ Tomomatsu T (1981). Hygienic study on fluoride: 4. Physiological effects of fluoride on rat. J TOKYO MED COLL 39(3): 441-460.

• Torra M et al. (1998). Serum and urine fluoride concentration: relationships to age, sex and renal function in a non-fluoridated population. Science of the Total Environment 220: 81-5.

•§ Trabelsi M, Guermazi F, Zeghal N (2001). Effect of fluoride on thyroid function and cerebellar development in mice. Fluoride 34(3): 165-173.

+ Trivedi N, Mithal A, Gupta SK, Godbole MM (1993). Reversible impairment of glucose tolerance in patients with endemic fluorosis. Diabetologia 36: 826-828.

•§ Turner CH et al. (1992). The effects of fluoridated water on bone strength. Journal of Orthopaedic Research 10(4): 581-7.

+ Turner CH, Dunipace AJ (1993). On fluoride and bone strength. Letter. Calcified Tissue International 53: 289-290.

• Turner CH, Dunipace AJ (1995). On fluoride and bone strength (letter). Calcified Tissue International 53: 289-290.

•§ Turner CH et al. (1995). Fluoride reduces bone strength in older rats. Journal of Dental Research 74(8): 1475-81.

•§ Turner CH et al. (1996a). High fluoride intakes cause osteomalacia and diminished bone strength in rats with renal deficiency. Bone 19(6): 595-601.

• Turner CH (1996b). Fluoride and the FDA: a curious case. (letter) Journal of Bone and Mineral Research 11(9): 1369-71.

• Turner CH et al. (1997). Fluoride treatment increased serum IGF-1, bone turnover, and bone mass, but not bone strength, in rabbits. Calcified Tissue International 61(1): 77-83.

• Turner CH et al. (2001). Combined effects of diets with reduced calcium and phosphate and increased fluoride intake on vertebral bone strength and histology in rats. Calcified Tissue International 69: 51-7.

§ USA Today (2004) General Mills cereals go totally whole grain.

• US EPA. (Online). Drinking Water and Health Advisories Estimated Per Capita Water Ingestion in the United States http://www.epa.gov/waterscience/drinking/percapita/

§ US EPA (1985). National Primary Drinking Water Regulations; Fluoride. Final Rule. Federal Register November 14; 50(220). [The MCL established on April 2, 1986 [51 FR 11396), finalizes interim regulations set in November 14, 1985 (50 FR 47142), and proposed in the Federal Register of May 14, 1985 (50 FR 20164).]

+ US EPA (undated, 1992 or 1993). Reregistration eligibility decision. Sulfuryl fluoride. List A. Case 0176. Environmental Protection Agency. Office of Pesticide Programs. Special Review

and Reregistrtion Division.

+ US EPA (1996). Reregistration Eligibility Decision, Cryolite. August.

+ US EPA (1997). Pesticide registration (PR) notice 97-1. Notice to manufacturers, formulators, producers, and registrants of pesticide products. January 31.

• US EPA OPP (1998). Health Effects Test Guidelines. OPPTS 870.4100 Chronic Toxicity.

• US EPA OPP (2000). Available information on assessing exposure from pesticides in food: a users guide.

+ US EPA (2001). Sulfuryl Fluoride; Proposed Pesticide Temporary Tolerances. Docket OPP-301166. Federal Register. September 5.

§ US EPA (2001a). Notice of Filing a Pesticide Petition to Establish a Tolerance for a Certain Pesticide Chemical in or on Food. Federal Register. [PF-1030; FRL-6788-2]. June 15.

+ US EPA (2002). Sulfuryl Fluoride; Temporary Pesticide Tolerances. Final Rule. Docket OPP-301166A. Federal Register. February 7.

§ US EPA (2002a). Notice of filing a pesticide petition to establish a tolerance for a certain pesticide chemical in or on food. Federal Register. Docket PF-1068. February 15.

+ US EPA (2002b). Issuance of Experimental Use Permits. Experimental Use Permit 62719-EUP-45. Federal Register. March 27.

+ US EPA (2002c). Notice of Filing a Pesticide Petition to Establish a Tolerance for a Certain Pesticide Chemical [cryolite] in or on Food. Docket OPP-2002-0007. Federal Register. April 24.

• US EPA (2002d). Determination of the appropriate FQPA safety factor(s) in tolerance assessment. Office of Pesticide Programs. February 28. Note: We cited as US EPA OPP (2002).

§ US EPA (2003) Occurrence Estimation Methodology and Occurrence Findings Report for the Six-Year Review of Existing National Primary Drinking Water Regulations. Office of Water EPA-815-R-03-006. Washington, DC.

+ US EPA (2003a). Occurrence Estimation Methodology and Occurrence Findings Report for the Six-Year Review of Existing National Primary Drinking Water Regulations. EPA-815-R-03- 006. Office of Water.

• § US EPA (2004). Sulfuryl Fluoride; Pesticide Tolerance. Final Rule. Federal Register. 40 CFR Part 180.145 (Fluorine Compounds). 40 CFR Part 180.575 (Sulfuryl fluoride). Docket OPP-2003-0373. January 23.

§ US EPA (2004a). Human Health Risk Assessment for sulfuryl fluoride and fluoride anion addressing the Section 3 registration of sulfuryl fluoride post-harvest fumigation of stored cereal grains, dried fruits and tree nuts and pest control in grain processing facilities. PP#1F6312. Federal Register Docket No. OPP-2003-0373-0002. January 20.

+ US EPA (2004b). , Flumetsulam. Chronic Dietary Exposure Assessment for the Tolerance Reassessment Eligibility Decision (TRED) Document. Memorandum from Samuel Ary, Chemist, Reregistration Branch II, Health Effects Division (7509C). August 30.

+ US EPA (2004c). Estimated per capita water ingestion and body weight in the United States – an update. EPA-822-R-00-001. Office of Water October.

§ US EPA (2005). Sulfuryl Fluoride; Pesticide Tolerance. Final Rule. Federal Register. Docket OPP-2005-0174. July 15.

§ US EPA (2005a). Sulfuryl Fluoride; Notice of Filing a Pesticide Petition to Establish Tolerances for a Certain Pesticide Chemical in or on Food. Federal Register. Docket OPP-2005-0067. March 4.

§ US EPA (2005b). Response to public comments concerning the use of sulfuryl fluoride in food handling facilities. Federal Register. Docket OPP-2005-0067-0020. July 14.

§ US EPA Unions Coalition (2005). Letter to Stephen L. Johnson, Administrator US EPA. Re: Bone Cancer-Fluoride Link. August 5.

• US EPA. (Online). Drinking Water and Health Advisories Estimated Per Capita Water Ingestion in the United States http://www.epa.gov/waterscience/drinking/percapita/

US EPA OPP (2002). See US EPA (2002d).

§ USDA (2000). Sulfuryl Fluoride: The Postharvest Fumigant of the Future? United States Department of Agriculture (USDA), Agricultural Research Service. October.

§ USDA (2003) Commodity Specification: All Purpose Egg Mix. Online at: http://www.ams.usda.gov/poultry/cp/egg/eggf/PY277/277spec.pdf

§ USDA (2003a) Pesticide Data Program: Annual Summary Calendar Year 2002. USDA Washington DC.

§ USDA (2004) Egg Purchases by Vendor 2003. Online at: http://www.ams.usda.gov/poultry/cp/egg/eggf/Egg-PurchaseSummary-2003.pdf

+ USDA (2004a). USDA national fluoride database of selected beverages and foods. Prepared by Nutrient Data Laboratory, Beltsville Human Nutrition Research Centr, Agricultural Research Service, US Department of Agriculture. October.

§ USDA (2005) Fact sheet: Focus on egg products. Online at: http://www.fsis.usda.gov/Fact_Sheets/Focus_On_Egg_Products/index.asp

§ USDA (2005a) Nutrients in food online calculator. Online at: http://199.133.10.140/codesearchwebapp/(banorwbj1tnoza55v03z5045)/codesearch.aspx

§ USDA (2005b) Amber Waves. “Will 2005 Be the Year of the Whole Grain?”

+ Usuda K, Kono K, Yoshida Y (1997). The effect of hemodialysis upon serum levels of fluoride. Nephron 75:175-8.

• Uslu B (1983). Effect of fluoride on collagen synthesis in the rat. Research and Experimental Medicine 182(1): 7-12.

•§ van der Voet GB, Schijns O, de Wolff FA (1999). Fluoride enhances the effect of aluminium chloride on interconnections between aggregates of hippocampal neurons. Arch Physiol Biochem. 107(1): 15-21. February.

•§ Vani LM, and Pratap Reddy K (2000). Effects of fluoride accumulation on some enzymes of

brain and gastrocnemius muscle of mice. Fluoride 33(1): 17-26.

•§ Varner JA, Jensen KF, Horvath W, Isaacson RL (1998). Chronic administration of aluminum-fluoride or sodium-fluoride to rats in drinking water: alterations in neuronal and cerebrovascular integrity. Brain Research 16; 784(1-2):284-98. February.

+ Velazquez-Guardarrama N, Madrigal-Bujaidar E, Molina D (2005). Genotoxic evaluation of sodium fluoride and sodium perborate in mouse bone marrow cells. Bullentin of Environmental Contamination and Toxicology 74: 566-572.

+ Vischer TL et al. (1970). Industrial fluorosis. In: TL Vischer, ed. (1970). Fluoride in Medicine. Hans Huber, Bern. pp. 96-105.

+ Wang J, Ge Y, Ning H, Wang S (2004a). Effects of high fluoride and low iodine on oxidative stress and antioxidant defense of the brain in offspring rats. Fluoride 37(4): 264-270.

+ Wang J, Ge Y, Ning H, Wang S. (2004b). Effects of high fluoride and low iodine on biochemical indexes of the brain and learning-memory of offspring rats. Fluoride 37(3): 201-208.

•§ Wang Y, Guan Z, Xiao K (1997). [Changes of coenzyme Q content in brain tissues of rats with fluorosis]. Zhonghua Yu Fang Yi Xue Za Zhi 31(6): 330-3. November.

• Warady BA et al. (1989). Plasma fluoride concentration in infants receiving long-term peritoneal dialysis. Journal of Pediatrics 115: 436-9.

• Waterhouse C et al. (1980). Serum inorganic fluoride: changes related to previous fluoride intake, renal function and bone resorption. Clinical Science 58: 145-52.

• Whitford GM, Angmar-Mansson B (1982). Note: We incorrectly used this citation – see Angmar-Mansson B, Whitford GM.

• Whitford GM, Angmar-Mansson B (1984). Note: We incorrectly used this citation – see Angmar-Mansson B, Whitford GM.

§ Whitford GM (1987). Fluoride in dental products: safety considerations. Journal of Dental Research 66: 1056-60.

•§ Whitford GM (1990). The physiological and toxicological characteristics of fluoride. Journal of Dental Research 69(Spec No): 539-49.

§ Whitford G (1996). The Metabolism and Toxicity of Fluoride. 2nd Revised Edition. Karger: Basel. p 30.

§ Whitford G (1996). Fluoride Toxicology and Health Effects. In: Fejerskov O, Ekstrand J, Burt B, Eds. Fluoride in Dentistry, 2nd Edition. Munksgaard, Denmark. p 171.

+ Whitford GM (1999). Fluoride metabolism and excretion in children. Journal of Public Health Dentistry 59(4): 224-228. Fall.

Whitford & Borke (1999). See Borke JL, Whitford GM (1999)

§ Whyte MP, Essmyer K, gannon FH, Reinus WR (2005). Skeletal fluorosis and instant tea. Am J Med. 118(1): 78-82. January.

§ Wondwossen F et al. (2004). The relationship between dental caries and dental fluorosis in areas with moderate- and high-fluoride drinking water in Ethiopia. Community Dentistry and Oral

Epidemiology 32: 337-44.

•§ World Health Organization [WHO] (2002). Environmental Health Criteria 227: FLUORIDES. World Health Organization, Geneva.

•§ Xiang Q, Liang Y, Chen L, Wang C, Chen B, Chen X, Zhou M (2003a). Effect of fluoride in drinking water on children's intelligence. Fluoride 36(2): 84-94.

§ Xiang Q, Liang Y, Zhou M, Zang H (2003b). Blood lead of children in Wamiao-Xinhuai intelligence study. Fluoride 36(3): 198-199.

• Xu RQ et al. (1997). Relations between environment and endemic fluorosis in Hohot region, Inner Mongolia. Fluoride 30(1): 26-28.

• Yildiz M et al. (2003). Bone mineral density of the spine and femur in early postmenopausal Turkish women with endemic skeletal fluorosis. Calcified Tissue International 72: 689-93.

+ Yu MH, Driver CJ (1978). The effects of fluoride on the growth and L-ascorbic acid levels of tissues from the domestic chicken (Gallus Domesticus). Fluoride 11(2): 60-66.

§ Yuan SD, Song KQ, Xie QW, Lu FY (1991). An experimental study of inhibition on lactation in fluorosis rats. ACTA PHYSIOL SIN. 43(5): 512-517.

• Zahvoronkov AA, LS Strochkova LS (1981). Fluorosis: geographical pathology and some experimental findings. Fluoride 14(4): 182-191.

• Zakrzewska H, Udala J, Blaszczyk B (2002). In vitro influence of sodium fluoride on ram semen quality and enzyme activities. Fluoride 35(3): 153-160.

• Zeiger E, Shelby MD, Witt KL (1993). Genetic toxicity of fluoride. Environmental and Molecular Mutagenesis 21(4): 309-318.

• Zerwekh JE, Antich P, Pak CY (1996). Fluoride and the FDA: a curious case. (Letter to Editor). Journal of Bone and Mineral Research 11: 1370-1371.

•§ Zhai JX, Guo ZY, Hu CL, Wang QN, Zhu QX (2003). [Studies on fluoride concentration and cholinesterase activity in rat hippocampus]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 21(2): 102-4. April.

§ Zhang C, Ling B, Liu J, Wang G (1999). [Effect of fluoride-arsenic exposure on the neurobehavioral development of rats offspring]. Wei Sheng Yan Jiu 28(6): 337-8. November.

•§ Zhang Z, Xu X, Shen X, Xu X (1999). [Effect of fluoride exposure on synaptic structure of brain areas related to learning-memory in mice]. Wei Sheng Yan Jiu 28(4): 210-2. July.

•§ Zhang Z, Shen X, Xu X (2001). [Effects of selenium on the damage of learning-memory ability of mice induced by fluoride]. Wei Sheng Yan Jiu 30(3): 144-6. May.

• Zhao LB et al. (1996). Effect of high-fluoride water supply on children's intelligence. Fluoride 29(4): 190-192.

• Zhao, Zhu Z, Yu Z, Aoki K, Misumi J, and X Zhang (1998). Long-term effects of various iodine and fluorine doses on thyroid and fluorosis in mice. Endocrine Reg 32: 63-70.

•§ Zhao XL, Gao WH, Zhao ZL (1994). [Effects of sodium fluoride on the activity of Ca2+Mg(2+)-ATPase in synaptic membrane in rat brain]. Zhonghua Yu Fang Yi Xue Za Zhi 28(5): 264-6.

September.

•§ Zhao XL, Wu JH (1998). Actions of sodium fluoride on acetylcholinesterase activities in rats. Biomed Environ Sci. 11(1):1-6. –March.

•§ Zhao ZL, Wu NP, Gao WH (1995). The influence of fluoride on the content of testosterone and cholesterol in rat. Fluoride 28(3): 128-130.

•§ Zhu XZ, Ying CJ, Liu SH, Yang KD, Wang QZ (2000). [The primary study of antagonism of selenium on fluoride-induced reproductive toxicity of male rat]. Chung-Kuo Kung Kung Wei Sheng (China Public Health). 16(8): 697-8. August.

• Zipkin L et al. (1958). Fluoride deposition in human bones after prolonged ingestion of fluoride in drinking water. US Public Health Reports 73: 732-740.