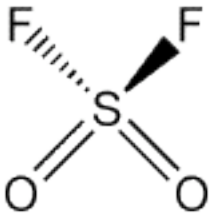
September 13, 2005

Objections and Request for Hearing

Docket No. OPP-2005-0174

Sulfuryl fluoride; Pesticide Tolerance. Final Rule.



Submitted by:

Chris Neurath, Paul Connett, Ellen Connett, Michael Connett
Fluoride Action Network
82 Judson Street, Canton NY 13617
Phone: 315-379-9200. Email: pesticides@fluoridealert.org

Richard Wiles, Sr. Vice President
Environmental Working Group
1436 U Street NW, Suite 100
Washington, DC 20009
Phone: 202-667-6982. Email: richard@ewg.org

Jay Feldman, Executive Director
Beyond Pesticides/National Coalition Against the Misuse of Pesticides
701 E Street, SE, Washington, DC 20003
Phone: 202-543-5450. Email: jfeldman@beyondpesticides.org

To:

Office of the Hearing Clerk (1900L),
Environmental Protection Agency,
1200 Pennsylvania Ave., NW, Washington, DC 20460-0001.

Public Information and Records Integrity Branch,
Information Resources and Services Division (7502C),
Office of Pesticide Programs, Environmental Protection Agency,
1200 Pennsylvania Ave., NW, Washington, DC 20460-0001.

This submission is available online at
http://www.fluorideaction.org/pesticides/epa-sf/submission.html

SUMMARY:

We wish to appeal the US EPA's granting of a Final Rule to Dow for residue tolerances of inorganic fluoride and sulfuryl fluoride on processed food comodities. The basis for our appeal is contained below

RELIEF:

In terms of the relief sought, the submitters ask US EPA to rescind the Final Rule granted for Sulfuryl fluoride residue tolerances.

FEE WAIVER:

A request for a fee waiver has been sent to the
Environmental Protection Agency,
Office of Pesticide Programs, Registration Division (7505C),
1200 Pennsylvania Avenue, NW., Washington, DC 20460.

Fluoride Action Network (FAN) requests a fee waiver under 40 C.F.R. Part 180.33 (m) as it is dedicated to working in the public interest. FAN is a project of the American Environmental Health Studies Project, a registered non-profit corporation 501(c)(3).

> 40 C.F.R. Part 180.33 (m). The Administrator may waive or refund part or all of any fee imposed by this section if the Administrator determines in his or her sole discretion that such a waiver or refund will promote the public interest or that payment of the fee would work an unreasonable hardship on the person on whom the fee is imposed. A request for waiver or refund of a fee shall be submitted in writing to the Environmental Protection Agency, Office of Pesticide Programs, Registration Division (7505C), 1200 Pennsylvania Avenue, NW., Washington, DC 20460. A fee of $2,025 shall accompany every request for a waiver or refund, except that the fee under this sentence shall not be imposed on any person who has no financial interest in any action requested by such person under paragraphs (a) through (k) of this section. The fee for requesting a waiver or refund shall be refunded if the request is granted.

This submission includes the following:

Sections:

TABLES (included separately as Attachments)

Appendix A.

Appendix B

Comments on Sprando and Collins et. al. studies: Effects in Control groups compared to NaF treated groups. (Submitted as Attachment)

Appendix C

March 30, 2005. Submission to the National Research Council Committee: Toxicologic Risk of Fluoride in Drinking Water; BEST-K-02-05-A. From Fluoride Action Network.

1. Introduction. EPA's new tolerances for fluoride residues from ProFume use are dangerously high.

1.1 Introduction. The Federal Food and Drug Certification Act (FFDCA) Section 408(b)(2)(A)(ii) requires that with respect to the setting of pesticide chemical residues on food that there should be "A reasonable certainty that no harm will result". In this respect it requires Section 408(b)(2)(C) that the EPA "to give special consideration to exposure of infants and children."

<http://www.epa.gov/fedrgstr/EPA-PEST/2005/July/Day-15/p13982.htm>

1.2 In Fluoride Action Network's (FAN) appeal of the EPA's fluoride tolerance for residues on food fumigated with sulfuryl fluoride, we will demonstrate that the EPA cannot possibly claim or demonstrate that "**there is a reasonable certainty that no harm will result** " or that they have given "to give special consideration to exposure of infants and children." Far from it. In fact, FAN will demonstrate that these tolerances "with a reasonable certainty" are likely to cause acute symptoms for a sizeable portion of the American public, especially infants and children, as well as contribute, in conjunction with many other sources of fluoride, to which the general public is routinely exposed, to exceeding the reference dose of 8 mg per day of millions of Americans. On this basis FAN appeals the July 15, 2005, Final Rule.

1.3 The fluoride residue tolerances approved for sulfuryl fluoride are the highest ever allowed in the history of U.S. EPA (US EPA 2004, 2005). We note in particular the outrageously high fluoride tolerance of 900 ppm for dried eggs.

Despite the potential dangers of such levels the EPA's analysis has been superficial and inadequate. Their claims that 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" are both clearly false. On this basis FAN appeals the July 15, 2005, Final Rule

1.4 The EPA manages to conceal the threat these new tolerances pose to the heath of the American people by a combination of gross mathematical errors, many non-conservative assumptions, and plain wishful thinking. The latter includes the notion that the reference dose of 8 milligrams per day can be defended on scientific grounds

1.5 If a scientifically defendable reference dose was calculated, as opposed to the outdated 8 mg per day (see sections 6-10), many more Americans would exceed the reference dose. In fact if science were to prevail in this matter, the vast majority of Americans would exceed a scientifically based reference dose with ProFume fluoride residues alone. On this basis FAN appeals the July 15, 2005, Final Rule

2 Three ORAL developmental neurotoxicity (DNT) studies should have been conducted prior to EPA's approval of tolerances: (1) For fluoride; (2) For sulfuryl fluoride, and (3) For combined exposure to both fluoride and sulfuryl fluoride.

2.1 **AN ORAL DNT STUDY IS NEEDED FOR FLUORIDE**.

The potential for human exposure –especially infants - to fluoride from this use of sulfuryl fluoride as a fumigant on food is very large. EPA set the highest fluoride tolerances in its history with the first-time use of sulfuryl fluoride as a food fumigant in January 2004 (US EPA 2004). Then, in the July 15, 2005, Final Rule (US EPA 2005), EPA approved an even higher fluoride tolerance: 900 ppm in/on dried eggs. The July 15, 2005, tolerances also included 70 ppm for virtually all processed foods, 125 ppm for wheat flour, 15 ppm coffee, 7 ppm cheese, 5 ppm milk. These are the most commonly consumed food commodities in the American diet.

2.1.2 As EPA states, "sulfuryl fluoride is converted to the fluoride anion in the body (US EPA 2004a)." How can EPA claim that they are proceeding with "A reasonable certainty that no harm will result" without carefully examining the large body of work that clearly indicates the potential for fluoride to adversely affect the brain, behavior, and IQ (see Sections 2.1.4- 2.1.12 below and Attachments: Tables 3, 4, 5). Brain effects have been identified in animal studies even at very low levels of exposure (Pushpalatha et al. 2005; Varner et al. 1998; Issacson et al. 1997). The effects of the new high fluoride tolerances on the fetus and young children due to the unprecedented increase of fluoride residues in/on food require a very careful assessment of risk. Because of the

well-known adverse effects on brain from animal studies, EPA was negligent in not demanding a DNT study for fluoride. No DNT study has been performed for fluoride.

2.1.3 Of the publications that EPA cites for "a comprehensive review of the toxicology of fluoride" - two were published 12 years ago, and they did not deal with fluoride's neurotoxic effects. The Medical Research Council report of 2002 (we are not aware of a 1992 report) did not deal with neurotoxic effects. The WHO 2002 report cited by EPA did not engage fluoride's neurotoxic potential in a meaningful way. Several of the studies listed below (and in Attachments: Table 3,4,5) were published after the WHO 2002 report.

2.1.4 **Fluoride crosses the blood brain barrier** (Zhai et al. 2003; Inkielewicz & Krechniak 2003; Zhai et al. 2003; Vani and Reddy 2000; Guan 1998; Mullenix et al. 1995; Geeraerts et al. 1986; Tomomatsu 1981).

2.1.5 **Fluoride accumulates in the brain.** In a 12-week study, rats fed 5 and 25 mg F-/L, in drinking water, the brain fluoride content increased "in a dose-dependent and a time-dependent manner." The fluoride content in the brains of the 25 ppm treated animals was nine times higher than controls. (Inkielewicz & Krechniak 2003)."

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

"Human studies have shown that the placenta is not in any sense a barrier to the passage of fluoride to the fetus... (WHO 2002)."

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.

2.1.7 **Fluoride facilitates aluminum's crossing the blood-brain barrier** (Varner et al. 1998). At concentrations of 1 ppm fluoride fed to rats in their drinking water elevates the aluminum level in brain (Varner et al. 1998, Isaacson et al. 1997) and the formation of beta amyloid deposits which are the classic brain abnormality of Alzheimers' disease (Varner et al. 1998). A 1999 study concluded that "aluminium interferes with the metabolism of the neuronal cytoskeleton and that this interference is potentiated by fluoride (van der Voet et al.).

2.1.8 **Fluoride damages animal brain**. Animal studies with fluoride clearly show that serious brain effects occur even at very low levels of exposure (Guan 1998; Varner 1998; Zhao 1998; Long 2002). There is a large body of work that

indicates the potential of fluoride to adversely affect the brain, behavior, and IQ deficits. (See Tables 3,4,5).

2.1.9 **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.

2.1.10 **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).

2.1.11 **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 channel 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." See Table 5.

2.1.12 **Conclusion.** The above studies, as well as those cited in our attachments (Tables 3,4,5) provide a weight-of-evidence need for a DNT study for fluoride. The public has a right-to-know the potential for effects on the fetus and children. We do not agree with EPA's assertion 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" in the absence of such studies and analysis. EPA was negligent in approving tolerances before an oral DNT study for fluoride was completed and the results known. On this basis, FAN appeals the July 15, 2005, tolerances.

2.2 THE NEED FOR AN ORAL DNT STUDYFOR SULFURYL FLUORIDE.

2.2.1 We agree with EPA on the need for an inhalation study for sulfuryl fluoride. However, the DNT study should have been completed prior to a Final Rule,

especially as four years have passed since Dow AgroSciences (DOW) first petitioned for tolerances on June 15, 2001 (US EPA 2001). The US Department of Agriculture reported in October 2000 that DOW "has begun EPA registration procedures to allow its use in postharvest situations (USDA 2000)." However, tolerances for sulfuryl fluoride were approved for processed foods on July 15, 2005 without a DNT inhalation study.

2.2.2 This approval was made despite this lack of a DNT inhalation study, and despite the fact that many animal studies reveal serious effects (see Tables 1,2). We do not agree with EPA's assertion 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 ensured that key studies like the DNT inhalation study have been conducted BEFORE they approve tolerances?

2.2.3 In addition to a DNT inhalation study, EPA should have insisted on an ORAL DNT study for sulfuryl fluoride. The highest tolerances for sulfuryl fluoride were approved for processed foods on July 15, 2005 (2 ppm for Cheese, Milk Powder, and All Processed Food; 3 ppm for nuts; and 1 ppm for dried eggs). People, including infants will not only breathe in a little of the sulfuryl fluoride resides but will be ingesting them as well. Again, how can EPA claim that they are proceeding with "A reasonable certainty that no harm will result" and they are giving "special consideration to exposure of infants and children" if they have not ensured that key studies like the DNT inhalation and oral studies have been conducted? These DNT studies should have been conducted before tolerance approvals were granted. On this basis, FAN appeals the July 15, 2005, Final Rule.

2.3 **THE NEED FOR AN ORAL DNT STUDY FOR SULFURYL FLUORIDE + FLUORIDE.**

When people consume food fumigated with sulfuryl fluoride, they have the potential to be exposed to both fluoride and sulfuryl fluoride at the same time. There is nothing in the literature to apprise the public of potential effects from this scenario. The literature only tells us that serious brain effects are observed in animals exposed to fluoride and to sulfuryl fluoride separately. The public needs to know if there is a potential for additive or synergistic effects from simultaneous exposure to fluoride and sulfuryl fluoride when they eat food fumigated with sulfuryl fluoride. We do not agree with EPA's assertion that they are proceeding with "A reasonable certainty that no harm will result" and they are giving "special consideration to exposure of infants and children" if they have not ensured that key studies like such a combined DNT oral study has been conducted. Tolerances should not have been approved until the results of such studies were available. On this basis, FAN appeals the July 15, 2005, Final Rule.

3. Some significant subpopulations will receive acutely toxic doses from fluoride residues from sulfuryl fluoride treatment of foodstuffs.

3.1 The US EPA has failed to consider any acute toxic health effects 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. How can EPA 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? On the basis of the EPA's failure to examine non-lethal acute effects FAN appeals the July 15, 2005, Final Rule.

3.2 To underline the seriousness of EPA's failure to examine non-lethal acute effects, FAN will examine how frequently the fluoride tolerance residues will lead to such acute poisoning episodes, 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).

3.3 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. On the basis of this error , and others, FAN appeals the July 15, 2005, Final Rule.

3.4 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.

3.5 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
- 90th percentile large serving: 4 eggs

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

3.6 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.

3.7 We note that the EPA has calculated a much lower dose of only 3.1 mg/egg equivalent (EPA 2005). Since they do not reference their conversion factors it is not possible to determine where their mistake is made.

3.8 Our estimates of the frequency of acute poisoning incidents are based on the EPA contention that approximately 1% of all dried eggs will be fumigated. However, it should be noted the pesticide tolerance (40 CFR Part 180.145; US EPA 2005) has no provision for enforcing this limitation of use. On this basis FAN appeals the July 15, 2005, Final Rule.

3.10 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)

3.11 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.

3.12 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.

3.13 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]). 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.

3.14 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.

3.15 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.

3.16 **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 with where we can anticipate acute (but non-lethal) effects. On this basis, FAN appeals the July 15, 2005, Final Rule.

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.

This 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 it's 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. This will include 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. On the basis of EPA's failure to perform this acute exposure analysis, FAN appeals the July 15, 2005, Final Rule.

[3.9 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 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.]

4. **Chronic dose from sulfuryl fluoride residues will push more people over the US EPA's reference dose for fluoride.**

4.1 The US EPA's health risk assessment for fluoride residues underestimates chronic doses of fluoride from consumption of ProFume fumigated foods (US EPA 2005). We have calculated the chronic exposure to the average American,

as well as to significant subpopulations. The same DEEM software and food database as used by EPA was employed. An alternative method was also used for comparison purposes. Both methods found as much as ten times higher exposures than in EPA's HRA (US EPA 2005). For some significant subpopulations, amounting to millions of Americans, this led to an exceeding of the chronic reference dose (RfD) solely as a consequence of ProFume.

4.2 The US EPA's health risk assessment for F residues may underestimate chronic doses of fluoride. 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 only. The current EPA exposure may be based solely on these processed 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.

4.3 Another possible explanation for EPA's underestimates of exposure is because they may not have used the most current pesticide label requirements on which to base their 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. No longer are there limits on maximum rates of fumigation or requirements that bulk food storage be severely reduced by a "drawdown" before fumigation. Requirements for blending after fumigation to dilute concentrations of fluoride are also eliminated.

4.4 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, as well as gone much further and eliminated most of the other usage restrictions such as drawdowns.

4.5 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. The EPA has yet to make the full Health Risk Assessment used in the July 15 Final Rule (US EPA 2005) publicly available, so we have been unable to check its assumptions or methods. How can EPA claim that they are 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? On this basis FAN appeals the July 15, 2005, Final Rule.

4.6 It is interesting to note that ProFume's registration label in the United Kingdom specifically prohibits fumigation of any quantity of flour because of the risks of residue accumulation. It further requires that the first run out of the equipment following fumigation must be discarded and that the succeeding 50 minutes of run must be blended 10:1 with unfumigated flour (Dow 2005a). On the basis of the EPA's failure to exercise similar caution FAN appeals the July 15, 2005, Final Rule.

4.7 The EPA also failed to take into account those significant subpopulations which will receive the highest exposures. This may be the result of EPA's failure to properly define the highest exposure groups. The EPA seems to have only considered age and sex groups, not diet groups. Such failures again undermine the EPA's claim that they are proceeding with "A reasonable certainty that no harm will result" from these tolerances. On this basis FAN appeals the July 15, 2005, Final Rule.

4.8 Our analyses of chronic exposure risks

We have conducted an analysis using the same software and food consumption database as the EPA (Durango Software 2005). Our assumptions concerning expected residue levels and percent of food treated are based on the EPA's summary HRA published in the Federal Register (US EPA 2005). The full details of our analysis will be provided in a forthcoming appendix. The results corresponded closely with our simplified methodology which will be described below.

4.9 Common sense combined with an examination of USDA food consumption data readily suggests that wheat (and other grains) will dominate the fluoride exposure for most people. The average American consumes about 170 grams/day of grains, mostly from wheat flour. Wheat flour has an existing tolerance of 125 ppm whereas all other RAC food categories have lower tolerances (US EPA 2005a, FAN 2005). This information should have immediately led the EPA to focus attention on exposures to people eating wheat products.

4.10 Since wheat so dominates the average consumer's exposure we performed a simplified non-conservative screening analysis focusing on wheat and grains.

4.11 Table A shows an expected tolerance for each food category based on a weighted average of the food items within each food category. Also shown is an estimate of the percentage of that food category which is fumigated. The EPA has estimated that for RACs, the percent crop treated (PCT) will be 40% for most items (US EPA 2005b, p. 40902).

4.12 For the key category, grains, the EPA has not publicly released the average residue levels of fluoride from trials. We have not assumed that the average would be the maximum tolerance of 125 ppm. Instead, we have been less conservative and chosen 60 ppm.

Table A. Calculation of fluoride ingestion due to fumigation residues
By food category in average American diet, year 2000

food category	g/day	F residues (mg/kg) average for food category	percent treated	mg/day
dairy	249	0	0	0.00
vegetables	204	1	40	0.08
meat, fish, eggs, nuts	172	2	40	0.14
grains	169	60	40	4.05
fruits	147	1	40	0.06
sweeteners	125	0	0	0.00
fats	85	0	0	0.00
total	1150			4.32

All data from USDA have been corrected for waste and other losses and are from: http://www.ers.usda.gov/data/foodconsumption/FoodGuideIndex.htm

F residues are approximate weighted averages for each food category based on approximate average residue levels found in fumigation trials.

For grains, no "drawdown factor" is employed because the proposed pesticide label has eliminated this condition of use. Also, no "processing factor" is employed for conversion from grain to flour so that this estimate will be protective of those consumers who choose whole grain products as recommended by USDA for their health benefits. See text for more details.

Percent treated is from US EPA 2005

Food categories are for Raw Agricultural Commodities (RACs)

4.13 The Table A food categories are all RACs rather than processed foods. This is to avoid the problems of determining how much wheat is in a serving of pizza for example. The EPA clearly distinguishes between the percent crop

treated (PCT) for RACs from the percent of product treated in the case of processed foods. They estimate processed foods will only have a PCT of 1%.

4.14 An important assumption we made in the calculations of Table A is that a conservative estimate will eliminate the EPA's "processing factor" and "drawdown factor" which were used in their 2004 Health Risk Assessment (US EPA 2004a). At that time the pesticide label for ProFume included the condition that before fumigation, storage bins of food commodities be drawn down to below 3 feet to reduce the quantity of food exposed to fumigation (Dow 2004). After fumigation, the fumigated food was to be blended 1:10 with unfumigated stock so as to dilute the fluoride residue level by a factor of 10x (Dow 2004). However, the revised pesticide label (Dow 2005) has eliminated this use condition. It should be noted that even if this condition had been retained, there is no enforcement mechanism or even monitoring system available to the US EPA to ensure compliance. Furthermore, it would appear that food processors have a strong financial interest in avoiding pre-fumigation drawdowns. As mentioned above, the main trade group for the grain milling industry specifically requested elimination of such conditions. Undoubtedly, the millers are concerned about the financial costs of emptying and then immediately refilling their facilities every 100 days.

4.15 For these reasons, the 10x drawdown factor used by the EPA in their earlier HRA has been eliminated in our analysis.

4.16 In the 2004 HRA the EPA also incorporated a "processing factor" for grains being milled. For wheat, application of the "processing factor" resulted in a 3x reduction in fluoride residue level of the flour. The EPA does not explain how they arrived at this factor but one can presume that this factor accounts for the wheat germ being removed from the flour when white flour is being produced from whole grain. The EPA has stated that oil and protein in food items preferentially absorb fluoride during fumigation. The wheat germ contains most of the oil and protein in wheat grain (USDA 2005a), so its removal likely explains the 3x reduction in fluoride. For non-wheat grains the EPA in 2004 used a "processing factor" of 0.78, presumably because less of the oil and protein is removed when milling corn, oats, barley, and the other grains.

4.17 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.

Returning to the analysis of fluoride exposures from a typical American diet: based on an estimated 60 ppm F residue level in grains and a 40% PCT, Table A shows that the average American diet will contain a chronic dose of over 4 mg/day F. Of this, over 90% is attributable to fumigated wheat and grains. When divided by the average American weight of 70 kg, this is a dosage of 0.06 mg/kg/day. Compare this result with the EPA's determination of 0.0093 mg/kg/day which is 6x lower (US EPA 2005, p. 40905). The EPA has made a significant underestimation. Since they provide few details or references to their data sources and methods it is impossible to determine why they have made a determination so different than the one we present here.

4.18 Perhaps they left out some food commodities as the July 15, 2005 Ruling did not cover all the proposed tolerances by Dow (US EPA 2005).

4.19 A gross mathematical error by EPA is revealed 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%. Perhaps this error accounts for their underestimation. 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.

Their underestimation may also be due to their choice of improper assumptions or insufficiently conservative assumptions as described previously.

4.20 Our determination that fumigation with sulfuryl fluoride could in fact lead to exposures of 4 mg/day amongst many Americans leads to the unavoidable conclusion that the proposed residue tolerances are much too high, even if one accepts an RfD of 8 mg/day.

4.21 This finding is made much worse if significant subpopulations are considered. For food exposure, the critical subpopulation 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.

4.22 Therefore, 30 million Americans are likely to eat larger than average portions of bread, pasta, and other grain products. From the fumigation residues alone, most could exceed the RfD of 8 mg/day or 0.114 mg/kg-bw/day.

4.23 Again, this finding is so extraordinary that it is worthwhile performing a reality check by comparing these high exposure levels to a more familiar route of exposure: through drinking water.

4.24 Very simply, 2 liters of water at 4 ppm a day is considered by the EPA the limit of what is safe (i.e. 8 mg/day). Compare this to the 170 grams a day of wheat and grain products typically consumed, 40% of which may have been fumigated with sulfuryl fluoride. When the concentration in that fumigated wheat averages 60 ppm, it yields a dose of 4 milligrams of fluoride which is the same dose as consuming one liter of water at 4 ppm i.e. half the reference dose. If we now throw in the other fumigated foods consumed and other sources of fluoride, clearly many more Americans will be pushed over the reference dose.

4.25 It is hard to understand how Dow AgroSciences and the US EPA could consider allowing residues of 900 ppm fluoride in a fairly common food commodity (dried eggs) and 125 ppm in the single largest component of many people's diets (wheat flour). But this blatant disregard for consumer's health may reflect the fundamentally flawed methodology underlying almost all aspects of the Dow and EPA health risk assessments. It certainly does not engender confidence that the tolerances for sulfuryl fluoride have been carefully designed to be fully protective of all Americans. In fact, just the opposite appears to be the case: the tolerances requested by Dow were based solely on levels found after trial fumigations. No consideration was given to the health consequences of Americans ingesting these residues and the Health Risk Assessment was essentially an afterthought which attempted to justify the safety of the levels through manipulation of facts and science.

4.26 The US EPA needs to seek an independent body to perform a Health Risk Assessment for ProFume fluoride residues, so that the public can be reassured that a small section of the pesticide division has not been captured by the interests of Dow AgroSciences. Such an HRA must consider all relevant scientific studies, especially the most current. It cannot rely on decades old reviews which have been shown to have been influenced by narrow political considerations rather than science and the public interest (Carton & Hirzy 1998; Marcus 1990, 1995; US EPA Unions 2005; Bryson 2004). It most certainly cannot put any trust in the Dow and US EPA HRAs.

4.27 **Conclusion.** The failure of the EPA to do justice to the full potential of harm from the chronic exposure to these fluoride tolerances, especially when

combined with other routine exposures that Americans have to fluoride, undermines their claim that they are proceeding with "A reasonable certainty that no harm will result" and their claim that they are giving "special consideration to exposure of infants and children. On this basis, FAN appeals the July 15, 2005, Final Rule.

5.US EPA's health risk assessment for ProFume is unsatisfactory because it is predicated on the safety of the MCLG of 4 ppm which cannot be defended scientifically.

5.1 The unacceptable risks posed by ProFume use and the new tolerance limits reviewed in sections 3 and 4 above are all predicated on maintaining the fiction that the reference dose of 8 mg per day is a safe. This reference dose is not scientifically defendable as our previous largely unanswered analysis has made clear (Appendix A). Here we summarize these arguments and based on these arguments, all the conclusions reached in Sections 3 and 4 are further re-enforced. On this basis FAN appeals the July 15, 2005, Final Rule.

5.2 The reference dose of 8 mg per day is based upon the same analysis which the US EPA used in 1986 to determine its MCLG.

5.3 . The MCLG (as well as the MCL) is currently set at 4 ppm.

5.4 In 2003 the US EPA Office of Drinking Water asked the National Academy of Sciences (NAS) to review the scientific literature pertaining to the toxicology of fluoride and offer advice on the EPA's current MCLG. This review has been largely necessitated by the extensive publication of literature on toxic end points which occur at or near this level and which have been published since the last review by the NRC in 1993. The National Research Council is expected to produce its report in late 2005 or early 2006.

5.5 However, without waiting for this NRC review to be completed, the US EPA Pesticide division has used the current MCL of 4 ppm as the basis of a health risk assessment it has performed for ProFume. How can the EPA maintain 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" with respect to increased fluoride exposure from these tolerances, if they are not willing to wait for the NRC review to be completed? On this basis, FAN appeals the July 15, 2005, Final Rule.

5.6 The scientific basis for the MCLG and MCL of 4 ppm is extremely inadequate from the perspective of the norms usually applied in calculating safe drinking water standards and other regulatory processes in setting safe standards based upon animal and epidemiological data. Any independent

analysis of this derivation would clearly undermine the EPA claims 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” from increased fluoride exposure from the proposed tolerances. On this basis, FAN appeals the July 15, 2005, Final Rule.

5.7 When a more appropriate and scientifically defendable reference dose is developed (see section 9) it becomes clear that a high proportion of the American population is currently being overdosed on fluoride (a fact which becomes apparent when one looks at the current dental fluorosis rates in children, see discussion in section 10.4) and no further additions to this current exposure burden should be countenanced by the US EPA. Until the US EPA takes into account this pre-existing overdose situation they cannot claim that they are proceeding with “A reasonable certainty that no harm will result” or that they are giving "special consideration to exposure of infants and children" in this matter of further exposure. On this basis, FAN appeals the July 15, 2005, Final Rule.

5.8 We further argue that even if one accepts the MCLG of 4 ppm, the reference dose derived from it (8 mg/day) is being exceeded already by millions of people in the US. This being the case no additional source of fluoride must be allowed to enter the US food supply because this will further increase the number of people who will exceed the reference dose and exacerbate the risks posed to those who are already above this dose. On this basis, FAN appeals the July 15, 2005, Final Rule.

65. **The US EPA derivation of the 4 ppm MCLG for fluoride is scientifically flawed.**

6.1 Before discussing the problems with EPA’s MCLG, we start first with EPA’s description of how the MCLG was derived:

> "For fluoride, both the MCL and the MCLG have been set at 4.0 ppm in order to protect against crippling skeletal fluorosis. The MCLG was established in 1986 [FR 51 (63)] and is based on a LOAEL of 20 mg/day, a safety factor of 2.5, and an adult drinking water intake of 2 L/day." (US EPA 2004a)

6.1 Before discussing the problems with EPA’s MCLG, we start first with EPA’s description of how the MCLG was derived:

> "For fluoride, both the MCL and the MCLG have been set at 4.0 ppm in order to protect against crippling skeletal fluorosis. The MCLG was

established in 1986 [FR 51 (63)] and is based on a LOAEL of 20 mg/day, a safety factor of 2.5, and an adult drinking water intake of 2 L/day." (US EPA 2004a)

6.2 Let us break this explanation down into its component parts:

a) The end point chosen was crippling skeletal fluorosis.
b) The LOAEL offered for this was 20 milligrams per day.
c) The safety factor offered to protect the most vulnerable is 2.5.
d) The amount of water drunk is 2 liters.

6.3 The calculation is as follows: 20 milligrams per day divided by 2.5 (safety factor) = 8 milligrams per day. If one assumes that someone drinks 2 liters of water a day the safe level is 4 milligrams per liter, because if someone drank 2 liters of water at this level they would receive 8 milligrams of fluoride. Thus the derived MCLG is 4 ppm.

6.4 To put that "safe" level into perspective, 4 ppm is 400-800 times higher than the level found in mothers' milk (0.005 - 0.011 ppm, Institute of Medicine, 1997).

7. **What is wrong with the EPA's 1986 determination of the MCLG of 4 ppm?**

7.1 This derivation is hopelessly wrong on all four steps. Even at the time, the inadequacies of this derivation was pointed out by some EPA scientists like Dr. Robert Carton and Dr. William Hirzy , who claimed that it was manipulated for political reasons (Carton & Hirzy 1998). Today, with the benefit of more research findings the inadequacies are even more glaring. Let us examine each step of the calculation.

7.2 **The end point of skeletal fluorosis.**

7.2.1 Today there are many other end points of fluoride's toxicity which have been reported in literally hundreds of peer reviewed and published articles. The NRC will be reviewing these.

7.2.2 Even in 1986, bone damage was not the only toxic end point discussed in the literature. Considerable discussion, for instance, had taken place about thyroid dysfunction. In 1958 Galletti and Joyet found that the thyroid function of patients with hyperthyroidism could be lowered by daily doses of fluoride between 2.5 and 4.52 and 10 milligrams per day. Such doses are as low as one quarter of the EPA's reference dose of 8 mg of fluoride per day for bone damage. In Russia in 1985, Bachinskii et al. found that normal thyroid function was lowered at 2.3 ppm. If we assumed that these citizens drank two liters of water per day, their daily dose would have been 4.6 milligrams.

7.2.3 Even if the EPA could justify limiting the discussion of fluoride's toxic end points to bone damage, there were other findings available to the EPA in 1986 which indicated a lower observable adverse effect level than crippling skeletal fluorosis. For example, the EPA should have considered one of the findings of the Newburgh-Kingston fluoridation trial (1945-55). The authors Schlesinger et al. (1956) found a statistically significant increase in cortical bone defects in the children in the fluoridated community compared to the non-fluoridated community (13.5% versus 6.5 %). US EPA scientists should have been made aware of this finding because NAS reviewers drew special attention to it in 1977 in the context of questions about a potential relationship between fluoridation and osteosarcoma in young males. The strength of the cortical bone is critically important in the protection of the appendicular skeleton from bone fracture. Such defects were associated with a dose of about 1-2 milligrams per day.

7.2.4 Since 1986, meanwhile, a voluminous literature has been published indicating that fluoride can weaken bone before it causes crippling fluorosis. This literature includes clinical trials (Dambacher 1986; Hedlund 1989; Bayley 1990; Orcel 1990; Riggs 1990; Schnitzler 1990; Gutteridge 2002); animal studies (Turner 1992; Lafage 1995; Sogaard 1995; Turner 1995; Fratzl 1996; Turner 1996); and epidemiological investigations (Sowers 1986; Sowers 1991; Alarcon Herrera 2001; Li 2001).

7.2.5 Of particular interest are the clinical trials of Hedlund (1989); Bayley (1989), Orcel (1990), and Gutteridge (2002), for the doses used in these trials were only 21 to 25 mg per day. Considering the short term duration of these trials (less than 4 years), they should be regarded as highly relevant to the EPA's MCL. Considering that the evidence strongly indicates that bone fracture occurs before crippling fluorosis, it is imperative that EPA justify why crippling fluorosis remains the appropriate endpoint for bone health, instead of bone fracture.

7.3 **The LOAEL of 20 mg per day.**

7.3.1 Even if the EPA chooses to ignore bone fracture, and all the other non-skeletal end points (see section 8), and continues to use the end point of skeletal fluorosis, it is both unscientific and contrary to common sense to choose the crippling phase of skeletal fluorosis as the LOWEST OBSERVABLE ADVERSE EFFECT LEVEL. Skeletal fluorosis is estimated to have three clinical phases and a pre-clinical phase (DHHS, 1991). According to the Department of Heath and Human Services (DHHS 1991), painful arthritic symptoms can begin in the first clinical phase of fluorosis, before the onset of crippling. The existence of arthritic symptoms in the pre-crippling stage of the disease has been widely reported in the literature (Singh & Jolly 1970; Cook 1971; Franke 1975; Teotia 1976; Czerwinski 1977; Carnow 1981; Czerwinski 1988; Roschger 1995; Savas 2001; Eichmiller 2005). While not everyone with pre-crippling clinical fluorosis will experience arthritic pain (Franke 1975), the evidence is clear that some people

will. Thus, if skeletal fluorosis is the endpoint of concern, EPA's LOAEL should be set to protect against the pre-crippling clinical effects.

7.3.2 Even if EPA chose to continue ignoring the pre-crippling effects of fluorosis, it would still need to update the LOAEL for crippling fluorosis. The NRC(1993) panel lowered the LOAEL for crippling skeletal fluorosis to 10 milligrams per day (On page 59 of their report the authors write: "Crippling skeletal fluorosis might occur in people who have ingested 10-20 mg of fluoride per day for 10-20 years"), but strangely they did so without recommending a corresponding MCLG of 2 ppm.

7.3.5 Moreover, the EPA based their MCLG on a chronic dose lasting only 10 years, not a lifetime of 70 to 100 years. People drink water and consume food their entire lives, not just for 10 years. Fluoride steadily accumulates in the bone and other calcifying tissues over a lifetime. Studies have shown a clear age dependence on bone fluoride levels in humans as old as their 80s. For crippling skeletal fluorosis the EPA NRC(1993) should have included an additional factor of 7 to 10 to account for lifetime accumulation of fluoride.

7.4 **The safety margin of 2.5**.

7.4.1 The EPA failed to use the customary safety factor of 10 to adjust a LOAEL (20 mg per day) to a NOAEL. (see also the discussion in 8.3.5) Considering the fact that the 20 mg/day figure is based on only 10 years of exposure, and that it does not protect against the pre-crippling clinical phase of fluorosis which has been documented to cause arthritic pains in some people, the reduced safety factor of 2.5 is not justified.

7.4.2- The EPA failed to use another safety factor 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 (Room 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.

7.4.3 The EPA makes it very clear why the standard protective safety factors were sacrificed in their calculation, when they say it was to allow "sufficient concentration of fluoride in water to realize its beneficial effects in protecting against dental caries." In other words, the EPA is protecting the water fluoridation program. This kind of consideration may have had a place in the discussions when they moved from an MCLG to an MCL, but it should not have been a factor in determining the MCLG. For an MCLG the task is to determine a safe level, based on scientific studies of toxic end points, and that analysis should not have been distorted by any consideration of a supposed beneficial level.

7.4.6 The current NRC panel has made it clear that they are not considering any supposed beneficial levels of fluoride (panel discussion at a public hearing August 12, 2003).

7.5 **The assumption that the amount of water drunk is 2 liters.**

There are two problems when we move from the supposedly safe level of 8 milligrams per day to an MCLG of 4 ppm:

7.5.1 First, the average person may drink 2 liters of water per day. But millions of people drink far more than this. Indeed, some agencies are actually, the Food and Nutrition Board (FNB) of the National Academies now recommends that males over the age of 18 drink 3 liters of water per day (FNB 2004). According to FNB, over 5% of males between consume at least 5 liters of water a day, while 1% of males between the age of 19 and 50 consume at least 9 liters of water a day. Over 5% of adult females consume over 4 liters a day, while 1% of females consume over 5.5 liters a day (FNB 2004; Appendix E).

7.5.2 Second, no allowance was made for other sources of fluoride people are digesting from food, beverages, pesticide residues and dental products. As recently documented by White (2005), some individuals in the US can ingest over 25 mg/day from tea alone.

8**. Adjusting the MCLG for the EPA's incorrect derivation.**

8.1 Even if we limit ourselves to an end point of skeletal fluorosis the MCLG needs to be reduced. As detailed in Appendix C, evidence and protocol would necessitate lowering the MCLG by a factor of 40:

> **2x** (to update LOAEL with revised estimate [10 mg/day] for crippling fluorosis);
> **2x** (to update LOAEL to protect against arthritic effects occurring prior to crippling fluorosis);
> **4x** (to utilize standard safety factor of 10 instead of 2.5); and
> **2.5x** (to protect individuals with high water consumption).

8.2 Total downward adjustment = x40 (even this neglects an adjustment for others sources of fluoride).

8.3 If we make this adjustment the MCLG of 4 ppm would be lowered to 0.1 ppm (4 ppm divided by 40 = 0.1 ppm).

8.4 Note in this discussion we have not introduced an extra safety factor for children exposed to pesticides as required in the Food Quality Protection Act (FQPA)

8.5. The formal reason the EPA gives for not applying the FQPA factor for children was their claim that skeletal fluorosis is a chronic problem and not of an extra concern for children. However, the work of Alarcon-Herrera et al. (2001) indicates that bone damage may well be a problem for children at levels of fluoride exposure which cause dental fluorosis.

8.6 Moreover, with other toxic end points now published (e.g. lowering of IQ, see next section) children are specifically at risk and thus the FQPA factor should also be applied for these end points. In this case the US EPA claims that: "The Agency has determined that a 10X FQPA safety factor in the form of a data base uncertainty factor (UFDB) is [not] needed to account for the lack of the DNT study since the available data provide no basis to support reduction or removal of the default 10X factor."

8.7 **Conclusion:** Only by ignoring all end points except crippling skeletal fluorosis could the EPA get away with the following statement from their final rule: "EPA believes no additional safety factor for the protection of children is necessary " – FR Jan 23, 2004. This is unacceptable and unscientific. Thus their claim that that they are proceeding with "A reasonable certainty that no harm will result" and that they are following the mandates of the FFDCA, which requires (see Section 408(b)(2)(C)) that the EPA "give special consideration to exposure of infants and children" are both clearly false. On this basis FAN appeals the July 15, 2005, Final Rule.

We shall see from the next section that a dismissal of all other end points is cavalier and amounts to a failure to exert due diligence in their regulatory duty to protect children from potential harm.

9. **Taking into account the research published since the NRC (1993) review.**

The current NRC panel will have to consider the scientific studies on fluoride's toxic end points that have been published since 1993. In our view for the EPA to believe that all the end points discussed below will resolve themselves conveniently in favor of leaving crippling skeletal fluorosis as the lone end point of regulatory concern, and thus to proceed with permitting the registration of ProFume and approving greatly increased food tolerance limits for fluoride on over 200 foodstuffs, WITHOUT waiting for the NRC's considered view of the matter, is reckless in the extreme. It MUST constitute a failure to exercise due diligence in the matter.

Some of the key studies that the NRC will be reviewing will include:

9.**1 Brain damage in animals**.. There have been over 30 studies indicating that fluoride can damage animal brain (see listing in Table 3, 4). In some cases brain damage is caused at very low doses. For example, Varner et al. (1998) fed rats

with 1 ppm fluoride in water (i.e. the same level used in water fluoridation programs) for 1 year and showed kidney damage, brain damage and uptake of aluminum into the brain (see 10.1.4). In addition, the studies by Dr. Guan and colleagues (Guan 1998; Long 2002; Chen 2003) 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.

9.1.1 **Fluoride crosses the blood brain barrier** (Zhai et al. 2003; Inkielewicz & Krechniak 2003; Vain and Reddy 2000; Guan et al 1998; Mullenix et al. 1995; Gerents et al. 1986; Tomomatsu 1981).

In a 12-week study, rats fed 5 and 25 mg F-/L, in drinking water, the brain fluoride content increased "in a dose-dependent and a time-dependent manner." The fluoride content in the brains of the 25 ppm treated animals was nine times higher than controls. According to the authors, "Fluoride in soft tissues is associated with structural changes and disorders in their function. (Inkielewicz & Krechniak 2003)." See also Chino et. al 1995; Shahs 1992 & 2001; Shivarajashankara et al. 2001.

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

> "Human studies have shown that the placenta is not in any sense a barrier to the passage of fluoride to the fetus. There is a direct relationship between the serum fluoride concentration of the mother and that of the fetus; the cord serum concentration is 75% that of the maternal fluoride concentration. From the fetal blood, fluoride is readily taken up by the calcifying fetal bones and teeth (WHO 2002: Environmental Health Criteria 227; citing Sheen & Takes, 1974)."

9.1.3 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.

9.1.4 **Fluoride helps aluminum cross the blood-brain barrier** (Varner et al. 1998). Fluoride elevates the aluminum level in brain (Varner et al. 1998, Isaacson et al. 1997) and the formation of beta amyloid deposits which are the classic brain abnormality of Alzheimers' disease.

9.1.5 **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." See Table 5.

9.1.6 **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

9.2. **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).

9.3 **Endocrine disruption.**

Dow AgroSciences makes the extraordinary claim that there is no evidence that fluoride causes any damage to the endocrine system (U.S. EPA 2002, 2005a). This assertion flies in the face of the voluminous literature which indicates 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.

9.3.**1 Effects on the Male Reproduction system**

9.3.1.1 There is a substantive body of published papers that detail fluoride's adverse effects on the male reproductive system (see Table 6). The predominant effect reported in animal studies is fluoride's potential to affect male fertility.

9.3.1.2 **Fluoride accumulates in the rodent testis** in a dose-dependent and time-dependent manner (Kiang CX et al. 2005; Inkielewicz & Krechniak 2003; Krasowska & Wlostowski 1996; Tomomatsu 1991).

9.3.1.3 Inkielewicz & Krechniak (2003) report a twelve-fold increase in the fluoride content of rat testis after a 12 week regimen of 24 mg F-/L in drinking water.

9.3.1.4 Some published papers reporting effects: (see also Attachment: Table 6)

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.

9.3.1.5 The Sprando & Collins et. al. studies

The Sprando and Collins et. al. team published 6 papers on fluoride's effects in Food and Chemical Toxicology (1995, 1996, 1997, 1998, June 2001, August)

and are frequently cited by those who would dismiss ALL concerns of fluoride's effect on the male reproductive system.

These rat studies should have been the "gold standard" for investigating fluoride's effects. They were initiated to determine fluoride's effects on male reproduction (1996, 1997, 1998); female developmental toxicity (1995); and multigenerational effects (June 2001 and August 2001).

For such an important federally funded project, it is surprising that not one of these 6 published papers presented fluoride levels in blood, bone, urine, tissue, or organs for NaF-treated groups or for the Controls.

In March 2004, Ellen Connett of Fluoride Action Network spoke with Robert Collins, one of the authors, about these studies. Dr. Collins stated that samples of blood, bone, tissue, and organs from all experiments were given to a FDA researcher for analysis of fluoride levels. However, the results of this analysis have not been published, and, according to Dr. Collins, it is unlikely that it will be published.

> This is unfortunate, because without publication of the fluoride levels in blood, bone, tissue, and organs in their animals, the findings of Sprando and Collins are seriously compromised, especially in view of the anomalous findings in their controls.

Included as part of this submission is an Appendix that reviews the adverse effects observed in the Control group vs treated groups in the Sprando and Collins et. al studies. (See attachment: APPENDIX B)

9.3.2 **G-proteins.**

9.3.2.1 G-proteins are involved in transmitting signals across membranes from water soluble messengers arriving out 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.

9.3.2.2 There are some 3000 biochemical experiments which document that fluoride in the presence of a trace amount of aluminum ion can 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. In other words it may not just be an endocrine disrupter it may be SUPER endocrine disrupter. Of particular concern would be at the interface of soft and hard tissues. (See attachment: Table 5)

9.3.3 **The Pineal Gland**

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

9.3.3.2 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 fluoride 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).

9.3.3.3 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)."

9.3.3.4 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. Moreover, governments do not appear inclined to follow up on - or repeat - these important findings. The MRC(2002) actually rated such a research need as lower than follow up studies on dental fluorosis! Such a cavalier attitude to such a potentially important finding is hard to fathom.

9.3.3.5 Until Jennifer Luke's work many people were unaware that the pineal gland produced the same crystals of calcium hydroxyapatite as the bones and teeth. According to Luke's 1997 PhD thesis:

> "It is remarkable that the pineal gland has never been analysed separately for F because it has several features which suggest that it could accumulate F. It has the highest calcium concentration of any normal soft tissue in the body because it calcifies physiologically in the from of hydroxyapatite (HA). It has a high metabolic activity coupled with a very profuse blood supply: two factors favouring the deposition of F in mineralizing tissues. The fact that the pineal is outside the blood-brain barrier suggests that pineal HA could sequester F from the bloodstream if it has the same strong affinity for F as HA in the other mineralizing tissues (Luke 1997, page 1).
>
> "After a half a century of the prophylactic use of fluorides in dentistry, we now know that fluoride readily accumulates in the human pineal gland. In

> fact, the aged pineal contains more fluoride than any other normal soft tissue... However, the pineal gland is unique in that it can be classified as a soft or as a mineralizing tissue. In terms of mineralized tissue, the mean fluoride concentration in the pineal calcification was equivalent to that in severely fluorosed bone and more than four times higher than in corresponding bone ash, i.e., 8,900 ± 7,700 vs. 2,040 ± 1,100 mg/kg, respectively. The calcification in two of the 11 pineals analysed in this study contained extremely high levels of fluoride: 21,800 and 20,500 mg/kg (Luke 1997, page 167)."

9.3.3.6 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.

9.3.4 **Thyroid function**

9.3.4.1 For a long period in Europe (approximately 1930 –60) doctors used sodium fluoride to lower the activity of patients who suffered from hyperthyroidism. The doses used were remarkably low - 2-10 mg fluoride /day (Galleti and Joyet, 1958).

9.3.4.2 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.”

9.3.4.3 However, Bachinskii et al. (1985).showed that <u>normal</u> 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 NRC in 1993. In 2004, in response to our bringing up this paper as part of our comments on ProFume, scientists at the EPA claimed that they couldn’t respond to this paper because it was in Russian! We have provided a translation of this paper just in case the EPA still has not found a translator for this 3 page paper. (see link to English translation in references under Bachinskii.)

9.3.4.4 The search for a mechanism of how fluoride might lower thyroid activity has a very long and elusive history . Some, noting the fact that fluoride and iodide are both halides, have suggested that fluoride competes with iodide for uptake into the thyroid gland. This does not appear to be the case. Nor does fluoride appear to compete with iodide in its insertion into the thyroid hormone molecules (the thyroid hormones T3 and T4 contain 3 and 4 iodine atoms respectively). A more promising hypothesis is that fluoride mimics the thyroid stimulating hormone (TSH) by switching on its associated G-protein. However, this is puzzling because, taken at face value, this would suggest that fluoride would stimulate thyroid activity, not lower it. A possible explanation has come from Tezelman et al. who have suggested that overproduction of cyclic AMP (the second messenger) leads to a feedback mechanism resulting in a desensitization of the TSH receptor, thus ultimately leading to reduced activity of the gland.

9.3.4.5 Considering the rampant and increasing problem of hypothyroidism in the United States, and the millions of people drinking fluoridated water, this issue needs urgent attention. In 1999, the second most prescribed drug of the year was Synthroid, which is a hormone replacement drug used to treat hypothyroidism. Problems associated with an underactive thyroid gland include depression, fatigue, weight gain, muscle and joint pains, increased cholesterol levels, and heart disease.

9.4 **Dental fluorosis.**

9.4.1 Dental fluorosis rates in children are increasing in the US. Even in unfluoridated communities (i.e. with less than 0.7 ppm natural fluoride) rates are as high as 20% and in fluoridated communities approximately 30% of children have dental fluorosis on at least two teeth (Heller et al, 1997).

9.4.2 A recent CDC report (CDC, 2005) indicates that the average dental fluorosis rates in American children (including both fluoridated and unfluoridated communities) has risen by 9.2% between 1987 and 2002, from 22.8% to 32 %. (CDC 2005) The figures include 3.4% of children in the moderate and severe categories.

9.4.3 Such overall rates of moderate and severe dental fluorosis would have been unthinkable to the early promoters of fluoridation as highlight by the following statements from H. Trendley Dean, the first director of the National Institute of Dental Research. Dean's studies on dental fluorosis and dental caries provided the platform for the country's water fluoridation program.

9.4.4 Dean classified dental fluorosis into the following categories: questionable; very mild; mild; moderate and severe. The comments listed below clearly indicate that he felt that any level of fluorosis above the very mild would be unacceptable.

a) In 1936, in an address to the Seventh Annual Meeting of the American Medical Association, Dean stated:

"from the continuous use of water containing about 1 part per million, it is probable that the very mildest forms of mottled enamel may develop in about 10% of the group." (my emphasis) (Dean, 1936)

b) After describing the percentages and severity of mottled enamel, which would be expected at higher fluoride concentrations, Dean wrote:

"In other words, we are dealing with a low grade chronic fluoride poisoning of children …" (Dean, 1936)

c) In 1942, in his famous "21 City" paper, Dean wrote:

"Strikingly low dental caries prevalence was found associated with the continuous use of domestic waters whose fluoride (F) content was as low as about 1 part per million, a concentration which under the conditions prevailing in the localities studied produced only sporadic instances of the mildest forms of dental fluorosis of no practical esthetic significance." (my emphasis) (Dean, 1942, p.1178)

d) In 1952, Dean had this to say in testimony before the Delaney Committee of the US Congress:

"We don't want any 'mild' when we are talking about fluoridation. We don't want to go that high and we don't have to go that high…I don't want to recommend any fluoridation where you get any 'mild'" (Dean 1952).

e) In 1941, Dean wrote:

"It is obvious that whatever effect the waters with relatively high fluoride content (over 2.0 ppm of F) have on dental caries is largely of academic interest; the resultant permanent disfigurement of many of their users far outweighs any advantage that might accrue from the partial control of dental caries" (my emphasis) (Dean, 1946, p.762)

9.4.5 The standard response of those who still enthusiastically promote water fluoridation, which includes the ADA and the CDC, is that dental fluorosis is just a cosmetic problem and not a health effect.

9.4.6 This position ignores the psychological impacts that children undoubtedly experience who have moderate or severe dental fluorosis.

9.4.7 It also fails to consider that this SYSTEMIC effect indicates some alteration of the biochemistry of the growing tooth (Aoba & Fejerskov 2002). There is no law that says that the same interference in the tooth's biochemistry will not occur in other tissues. Thus it has always been a hope of fluoridation promoters, rather than a proven fact, that the presence of dental fluorosis signaled no other damage to the body.

9.4.8 In 2001, Alarcon-Herrera et al. showed that, in a high endemic area for fluoride in Mexico (1.5 – 5.5 ppm fluoride in water), bone fractures in children increased linearly with the severity of dental fluorosis. There may be other differences in these Mexican children and most American children, however the approach of using dental fluorosis – a known marker of fluoride exposure before the eruption of the permanent teeth – as a biometric in epidemiological studies on fluoride's possible impact on children's development and health makes good sense. Inexplicably, this has seldom been done in fluoridating countries. We are flying blind on fluoride's impact on the child's developing tissues. This is not the case in India and China where they take fluoride's toxicity seriously.

9.5 **Hip fractures in the elderly.** While the results of epidemiological studies on hip fractures in the elderly have been mixed, the most recent study from China by Li et al. (2001) shows a convincing dose related increase. Compared to hip fracture rates in a village at 1 ppm, the rates doubled in villages between 1.5 ppm and 3.5 ppm and tripled at 4.3 – 8 ppm. The daily dose at 1.5 ppm was estimated to be 6.85 milligrams per day. For no apparent scientific reason pro-fluoridation governments either downplay or ignore this study.

9.6 **Kidney.**

9.6.1 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 1 ppm areas.

9.6.2 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).

9.6.3 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. (See also Attachment: Table 2, sulfuryl fluoride effects on kidney)

9.7 **Osteosarcoma in young males.**

9.7.1 As the press has now made very clear (Begley 2005, Eilperin 2005, Lavoie 2005) Dr. Elise Bassin (PhD thesis, 2001), using a more sophisticated analysis of a matched case-control study than performed hitherto, has reported a significant increase in osteosarcoma in boys exposed to fluoride in their 6th, 7th and 8th years (i.e. during their mid childhood growth spurt). This study is not only important in its own right but may explain why some previous studies did not find a study between fluoride and osteosarcoma.

9.7.2 Using a weight of evidence analysis Bassin's result shifts the balance of animal and human findings to a probable link between fluoride exposure and osteosarcoma in males . See FAN's two-part submission to the NRC (Connett et al. 2005 a, b). This view is shared by the Environmental Working Group (2005); and eleven unions representing over 7000 professionals at the US EPA (US EPA Unions). If the NRC review panel concurs with this assessment, then fluoride must be considered a probable human carcinogen and the MCLG should be set at zero.

9.8 **Conclusion.** The failure of the EPA to examine seriously any of the end points discussed in section 10, instead of placing their reliance on out-of-date reviews and an MCLG (which was based on 70 year old data for only one end point in adults), makes a mockery of their claim that they are proceeding with "A reasonable certainty that no harm will result". It also underlines their failure to follow the other critical mandate of the FFDCA, which requires (see Section 408(b)(2)(C)) that the EPA "give special consideration to exposure of infants and children" since many of these end points are of special concern for infants and children. In our view, it is reckless to proceed with permitting more fluoride exposure to Americans – especially infants and children -without the EPA conducting a very careful analysis of the literature pertaining to fluoride's impacts on the health of infants and children. It compounds this recklessness that the EPA is not even prepared to wait for the NRC to review this literature for them, even though the EPA itself requested this review. On all these points FAN appeals the July 15, 2005, Final Rule.

10. **A new science-based MCLG**

10.1 As discussed above if the NRC accepts that fluoride is a probable human carcinogen based on Bassin's and previous work, the NRC will have to

recommend an MLCG of zero. This again lends weight and common sense to the argument that the EPA should wait for the NRC to complete its review for giving any green light for the use of ProFume as a fumigant on food or the sanctioning of the highest fluoride tolerance limits it has ever issued.

10.2 It should also be noted that 11 EPA unions representing over 7000 professionals working at the EPA have written to Stephen Johnson requesting that EPA set a "maximum contaminant level goal for fluoride at zero, in accordance with Agency policy for all likely or known human carcinogens (US EPA Unions)." Again the caution of so many professionals – many of them very familiar with risk assessment procedures - is in sharp contrast with the handful of people pushing this matter through in the EPA's Pesticide's division.

10.3 Even if the NRC panel does not recommend an MCLG of zero, there are several things which are very apparent. Unless every one of the end points discussed in section 10 above are thrown out.

a) The MCLG of 4 ppm cannot be defended, even if one restricts oneself to skeletal fluorosis and other bone damage

b) If science prevails, the MCLG will have to be lowered.

c) An MCLG cannot be justified above 0.1 ppm, and possibly not above the level found in mothers milk (0.01 ppm).

d) This would force the cancellation of the practice of water fluoridation at 1 ppm, which would greatly reduce exposure both directly and indirectly in processed foods and beverages currently prepared with fluoridated water.

e) Even with such a cancellation there is enough fluoride from other sources to exceed a reference dose related to an MCLG of 0.1 ppm. Any scientifically defendable reference dose is being exceeded by many, if not most, Americans.

10.4 Clearly, no further increased fluoride exposure in the human food chains can be tolerated. On this basis FAN appeals the July 15, 2005, Final Rule.

11 **Even if the MCLG remains at 4 ppm many Americans still exceed the reference dose (8 mg/day) derived from it.**

11.1 .If, despite the science presented above, the MCLG remains at 4 ppm, it can still be easily shown that many Americans are exceeding the reference dose of 8 mg/day from which it was derived, and the reference dosage (for a 70 kg adult) of 0.115 mg/kg/day. We present several scenarios below:

a) 8 mg/day will be exceeded by someone living in an area with levels of fluoride at 4 ppm in their water, if they drink the FNB's recommended 3 liters per day: 3 liters/day x 4 mg/liter = 12 mg/day.

b) 8 milligrams per day will be exceeded by people living in an area with levels of 2.7 ppm and higher if they drink the FNB's recommended 3 liters of water per day:3 liters x 2.7 mg/liter = 8.1 mg/day.

c) 8 milligrams per day will be exceeded by people living in an area with levels of fluoride in their water of 2 ppm, if they drink more than 4 liters per day: 4.1 liters/day x 2 mg/liter = 8.2 mg/day. (This would apply to about 5% of adult females and 10% of adult males according to FNB's 2004 data).

d) 8 milligrams per day will be exceeded by people living in an area with levels of 1 ppm in their water if they consume 8 liters of water per day. (This would apply to over 1% of adult males according to FNB's 2004 data).:

e) 8 milligrams per day will be exceeded by heavy tea drinkers (Whyte 2005), particularly when combined with fluoride from other sources, including optimally fluoridated water.

11.2 In addition, an interesting additional source of provide is presented by a drinker of Californian wines. For many years vineries have used cryolite as a protection against fungal growth. This leaves fluoride residues in the wine.

11.3 Researchers from California State University in Fresno conducted a 5 year study (1990-1994) on vineyards throughout the San Joaquin Valley <http://cati.csufresno.edu/verc/rese/96/960601/>. They found that "[m]ultiple applications of Cryolite during the growing season significantly increase fluoride in wines." Notably they found fluoride levels between 3 – 10 ppm in several varieties of wine. And, most significantly, they found levels of 12 ppm in some varieties of Zinfandel and French Columbard. At 12 ppm, one liter of wine would result in a dose of 12 mg of fluoride.

11.4 In 1997, "analyses of nineteen California wines revealed fluoride concentrations ranging from 0.23 to 2.80 ppm (mean 1.02 ppm, with seven samples above the international limit of 1 ppm)." (Burgstahler, 1997).

11.5 Because of European requirements on imported wine, the levels of fluoride in Californian wine has been falling but it is important to note that this may not apply to wines not designed for export to Europe. Cryolite use on California wine grapes was reported to be 110,326 pounds in 2002 and 37,035 pounds in 2003 (FAN 2004, PAN 2005).

11.6 Thus a glass or two or more of Californian wine per day would add still further to the daily intake of fluoride and thus add more people to each scenario above.

11.7 **Conclusion:** EPA's failure to consider or examine any one of these scenarios makes a mockery of their claim that that they are proceeding with "A reasonable certainty that no harm will result" from the tolerances. On this basis FAN appeals the July 15, 2005, Final Rule

12. Comments on the EPA's attempt to use a new reference dose of 10 mg/day.

12.1 In their responses to FAN's critique of the HRA performed by the pesticide division and their reliance on an outdated MCLG of 4 ppm and the reference dose of 8 mg/day, the EPA has offered an alternative reference dose. To do this they use a 1997 report by the Food and Nutritional Board (FNB) of the Institute of Medicine (I0M).

12.2 Unfortunately, the small section of this FNB-IOM report devoted to fluoride is very poor scientifically on the issue of fluoride's toxicity and their derivation of an upper tolerance level (UL) for fluoride is highly dubious. There are not many independent fluoride researchers who would agree that its safe to have a dose of fluoride of 10 mg/day every day from 8 years to death.

12.3 The IOM's utilization of an Uncertainty Factor of 1 for skeletal fluorosis was profoundly inappropriate. For a report professing such a great deal of certainty on skeletal fluorosis, it is ironic to note that one of its key authors (Gary Whitford) stated one year earlier, in 1996, that 10 mg/day of fluoride could cause crippling skeletal fluorosis. Whitford had reached this conclusion as well during his work for the NRC in 1993. In the NRC's 1993 report, it was Whitford who authored the chapter on skeletal fluorosis which stated that doses as low as 10 mg/day could cause crippling fluorosis. Somehow, however, between 1996 and 1997, Gary Whitford (without any new dose information on skeletal fluorosis published in the literature) changed his estimate from 10 mg/day causing crippling skeletal fluorosis to one where it causes only the pre-clinical or stage 1 of clinical fluorosis (IOM, 1997) . For an estimate to change so greatly, without any new evidence to support the change, raises many questions about the "certainty" of IOM's "uncertainty factor" of 1.

12.4 We also note that IOM's reference to NRC's 1993 discussion of skeletal fluorosis is incorrect. IOM cites the NRC report as saying that 10 mg/day was associated with preclinical or phase 1 fluorosis. This is what IOM states:

> "…extensive reviews of the scientific literature revealed no adverse effects unless fluoride intakes were greater than 10 mg/day for 10 or more years (Kaminsky et al., 1990; NRC,1993; USPHS, 1991). At these high chronic

> intake levels, the risk of skeletal changes consistent with preclinical or stage 1 skeletal fluorosis increases" (IOM 1997).

However, what the NRC (1993) report states is that 10 mg/day could cause crippling fluorosis – not just preclinical or phase 1. Here is their exact quote:

> "Crippling skeletal fluorosis might occur in people who have ingested 10-20 mg of fluoride per day for 10-20 years." (NRC 1993).

12.5 On page 310 of their report, the FNB-IOM authors state:

> "…extensive reviews of the scientific literature revealed no adverse effects unless fluoride intakes were greater than 10 mg/day for 10 or more years (Kaminsky et al., 1990; NRC,1993; USPHS, 1991). At these high chronic intake levels, the risk of skeletal changes consistent with preclinical or stage 1 skeletal fluorosis increases."

We note that the latest review they cite here is 1993. So at the time of publication the FNB-IOM was at least four years out of date on the primary literature. By no stretch of the imagination can this be described as an "extensive review of the literature". Attempts by Dr. Paul Connett and Dr. J. William Hirzy to bring recent literature to the FNB's attention at a public hearing in September 1997 was totally ignored as were follow up letters signed by 13 scientists.

12.6 So if the FNB-IOM was four years out of date in 1997, then the EPA's use of their findings in 2005 makes them 12 years out of date!

12.7 Some of the key studies that had been published by the time the FNB-IOM went to press included Freni's study on lowered fertility in counties with fluoride in the drinking water at 3 ppm or more (Freni, 1994) and many studies indicating fluoride's impacts on reproduction in animals. While the ADA cites a "personal communication" which has criticized Freni's work, this has never been published or sent to the author for rebuttal. Nor have any other critiques. If there were legitimate reasons for dismissing Freni's findings then they should have been aired by the FNB-IOM authors not just simply ignored. The same now applies to the EPA.

12.8 Another very important study was Mullenix's study of fluoride's impact on rat brain (Mullenix et al. 1995) and subsequent studies from China on the lowering of IQ. The earlier studies had weaknesses but the FNB-IOM should have addressed them and not ignored them completely. The EPA is on even more shaky ground because they have not only ignored the early studies but also the latest one by Xiang 2003 a and b) which eliminated most of these weaknesses.

12.9 Other examples of literature ignored by both the FNB-IOM in 1997 and the EPA in their Final ruling are given in section 10 above.

12.10 So once again in groping for this weak and dated FNB-IOM review to buttress its dubious reference dose the EPA provides another example of its failure to follow the mandates of the FFDCA - Section 408(b)(2)(A)(ii) and Section 408(b)(2)(C) which requires them, with respect to the setting of pesticide chemical residues on food that there should be "A reasonable certainty that no harm will result" and that they give "special consideration to exposure of infants and children." Again on this basis FAN appeals the July 15, 2005, Final Rule.

12.11 There is also a huge inconsistency in the EPA relying on the Food and Nutrition Board of the IOM (IOM 1997) for their opinions on this matter because this same agency (FNB 2004) advocates that adults consume 3 liters of water a day, whereas the EPA's MCLG is derived assuming that Americans only drink two liters a day! In actual fact a good proportion of Americans drink far more water than this, as we have discussed above. Again this underlines the very poor science underpinning the MCLG and the reference dose derived from it. Such inconsistencies are a further basis for FAN's appeal of the July 15, 2005 Final Rule.

13. **Conclusions**

13.1 Throughout this submission FAN has indicated the numerous places for the basis of our appeal of the July 15, 2005 Final Rule.

13.2 It is hard to understand how Dow AgroSciences and the US EPA could consider allowing residues of 900 ppm fluoride in a fairly common food commodity (dried eggs) and 125 ppm in the single largest component of many people's diets (wheat). But this disregard for consumer's health may reflect the fundamentally flawed methodology underlying almost all aspects of the Dow and EPA health risk assessments. It certainly does not engender confidence that the proposed sulfuryl fluoride tolerances have been carefully designed to be fully protective of all Americans. In fact, just the opposite appears to be the case: the tolerances requested by Dow were based solely on levels found after trial fumigations. No consideration was given to the health consequences of Americans ingesting these residues and the HRA was essentially an afterthought which attempted to justify the safety of the levels through manipulation of facts and science.

13.3 EPA's HRA must consider all relevant scientific studies, especially the most current. It cannot rely on decades old reviews which have been shown to have been influenced by narrow political considerations rather than science and the public interest [Carton, Marcus, EPA unions, Bryson]. It most certainly can not put any trust in the Dow and US EPA HRAs.

13.4 Meanwhile, the NRC panel might make such an exercise moot, if they return a recommendation for an MCLG of zero or less than 1 ppm.

14. **References**

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

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

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

Anderson R, Beard JH, Sorley D (1980). Fluoride intoxication in a dialysis unit—Maryland. Morb. Mortal. Wkly. Rep. VOL 29 ISS Mar 28, P134-136.

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

Anon (1978). Nonskeletal fluorosis. Fluoride 11(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. J Biol Chem. Apr 3. FULL STUDY

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.

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

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. TEXT IN ENGLISH

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. FULL TEXT

Bassin EB. (2001). Association Between Fluoride in Drinking Water During Growth and Development and the Incidence of Ostosarcoma for Children and Adolescents. Doctoral Thesis, Harvard School of Dental Medicine. FULL TEXT: CHAPTER 3

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. http://www.fluoridealert.org/news/2323.html

Beltrán-Aguilar ED, Griffin SO, Lockwood SA (2002). Prevalence and trends in enamel fluorosis in the United States from the 1930s and 1980s. J Am Dent Assoc 133:157--66. Abstract

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

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. FULL STUDY

Borasio PG, Cervellati F, Pavan B, Pareschi MC (2004). "Low" concentrations of sodium fluoride inhibit neurotransmitter release from the guinea-pig superior cervical ganglion. Neurosci Lett. Jul 1;364(2):86-9. FULL TEXT available at Science Direct.

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

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. Abstract

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

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

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

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

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.

Chen J, Shan KR, Long YG, Wang YN, Nordberg A, Guan ZZ (2003). Selective decreases of nicotinic acetylcholine receptors in PC12 cells exposed to fluoride. Toxicology. Feb 1;183(1-3):235-42. Abstract. FULL TEXT available at Science Direct.

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. Jul;36(4):222-4. Abstract

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. Jul;29(4):216-7. Abstract

CHENG T.J., 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. Abstract

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.

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

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 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, 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 NJ, Narayana MV (1994). In vitro fluoride toxicity in human spermatozoa. Reprod Toxicol Mar-Apr;8(2):155-9. Abstract

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

Chinoy NJ, Pradeep PK, Sequeira E. (1992). Effects of fluoride ingestion on the physiology of reproductive organs of male rats. Journal of Environmental Biology 13 (1) 55-61.

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. Abstract

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

Chinoy NJ, Sequeira E (1989). Fluoride induced biochemical changes in reproductive organs of male mice. Fluoride 22(2):78-85.

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

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 Jun 15;268(3):733-7. Abstract

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. Jun;39(6):601-13. FULL TEXT available at Science Direct.

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. Aug;39(8):867-76. FULL TEXT available at Science Direct.

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. Nov;33(11):951-60. FULL TEXT available at Science Direct.

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 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. FULL TEXT

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. FULL TEXT

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. FULL TEXT

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

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

Czerwinski E, Lankosz W. (1977). Fluoride-induced changes in 60 retired aluminum workers. Fluoride 10: 125-136.

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

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. Toxic effects on the thyroid. In Fluorides and Human Health; WHO: Geneva, 1970, pp. 255-261.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.

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. Department of Health and Human Services, USA.

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

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 LABEL

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

Du L (1992). [The effect of fluorine on the developing human brain]. Zhonghua

Bing Li Xue Za Zhi Aug;21(4): 218-20. Abstract

Durango Software (2005) Dietary Exposure Evaluation Model, DEEM-FCID version 2.14. Information online at: http://www.durango-software.com/software/deem.html

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. Int J Clin Pharmacol Ther Toxicol. Jul;20(7): 334-8. Abstract

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. http://www.fluoridealert.org/news/2313.html

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

Environmental Protection Agency. (1985). National Primary Drinking Water Regulations; Fluoride. Final Rule. Federal Register November 14; 50(220): 47144.

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

Ekstrand J. (1996). Fluoride metabolism. In: Fejerskov O, Ekstrand J, Burt B, Eds. Fluoride in Dentistry, 2nd Edition. Munksgaard, Copenhagen. pp. 55-87.

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) (2005). Table 1. Fluoride pesticide residue tolerances approved by US EPA as of July 15, 2005. TABLES

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

FDA (1995) Estimating Exposure To Direct Food Additives And Chemical Contaminants in the Diet. Online at:

http://www.cfsan.fda.gov/~dms/opa-cg8.html

Fein NJ, Cerklewski FL. Fluoride content of foods made with mechanically separated chicken. J Agric Food Chem. 2001 Sep;49(9):4284-6. Abstract

Food and Drug Administration (FDA) (1997). Part 355 – Anticaries drug products for over-the-counter human use. FULL TEXT

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. ONLINE EDITION

Franke J, et al. (1975). Industrial fluorosis. Fluoride 8: 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. J Toxicol Environ Health. 1994 May;42(1):109-21.

Frolkis VV, Tanin SA, Gorban YN (1997). Age-related changes in axonal transport. Exp Gerontol Jul-Oct;32(4-5): 441-50. Abstract

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. J Neurochem Apr;54(4):1130-5.

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

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. Abstract

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

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

Goh EH, Neff AW (2003). Effects of fluoride on Xenopus embryo development. Food Chem Toxicol. Nov;41(11): 1501-8. Abstract. FULL TEXT available at Science Direct. □

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. Neurotoxicol Teratol Sep-Oct;20(5): 537-42. Abstract

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 Aug;77(8): 592-6. Abstract

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

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

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

Hedlund LR, Gallagher JC. (1989). Increased incidence of hip fracture in osteoporotic women treated with sodium fluoride. Journal of Bone and Mineral Research 2:223-5.

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. Abstract

Hoffman DJ, Pattee OH, Wiemeyer S (1985). Effects of fluoride on screech owl reproduction: teratological evaluation, growth, and blood chemistry in hatchlings. Toxicol Lett. Jul;26(1): 19-24. Abstract

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

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 Res Dev Brain Res. Jan 31;133(1): 69-75. FULL TEXT

available at Science Direct.

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. FULL STUDY

Institute of Medicine. (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. J Neurochem Jan;56(1): 44-51. Abstract

Janiszewska G, Lachowicz L, Wojtkowiak R (1984). Effect of certain agents on subcellular cAMP level in different areas of rat brain. Acta Physiol Pol May-Jun;35(3):199-206. Abstract

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 Jan;34(1): 32-4. Abstract

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

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,

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 Oct;6(10): 2915-20. FULL STUDY

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. Sep;103(1): 31-4. Abstract

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 Jan;113(1):81-4. Abstract . FULL TEXT available at Science Direct.

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 Feb;76(1): 1-11. Abstract

Kumar A, Susheela AK (1994). Ultrastructural studies of spermiogenesis in rabbit exposed to chronic fluoride toxicity. Int J Fertil Menopausal Stud May-Jun;39(3):164-71. Abstract

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

Lafage MH, et al. (1995). Comparison of alendronate and sodium fluoride effects on cancellous and cortical bone in minipigs. A one-year study. Journal of Clinical Investigations 95(5):2127-33.

Lantz O, et al. (1987). Fluoride-induced chronic renal failure. American Journal of Kidney Disorders 10(2):136-9. Abstract

Lavoie D (2005). Harvard professor investigated in fluoride research flap. The Associated Press. July 13.
http://www.fluoridealert.org/news/2323.html

Levy SM, Guha-Chowdhury N (1999). Total fluoride intake and implications for dietary fluoride supplementation. J Public Health Dent. Fall;59(4):211-23. Abstract

Li L. (2003). The biochemistry and physiology of metallic fluoride: action, mechanism, and implications. Crit Rev Oral Biol Med 14:100-14. FULL STUDY

Li Y, et al. (2001). Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. J Bone Miner Res. 16(5): 932-9. Abstract

Li Y, Li X, Wei S (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. Abstract

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 Oct 1;16(19): 5914-22. FULL STUDY

Litosch I (1987). Guanine nucleotide and NaF stimulation of phospholipase C activity in rat cerebral-cortical membranes. Studies on substrate specificity. Biochem J May 15;244(1): 35-40. Abstract

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 Dec;18(4): 290-2. Abstract

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. Neurotoxicol Teratol Nov-Dec;24(6): 751-7. Abstract. FULL TEXT available at Science Direct.

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.

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. FULL STUDY

Luke J. (2001). Fluoride Deposition in the Aged Human Pineal Gland. Caries Res. 35: 125-128. Abstract

Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildord, UK.

Machida H (1989). [The rabbit thermo-regulatory system. Effects of high dose of sodium fluoride]. Shikwa Gakuho Mar;89(3):607-26. Abstract

Manocha SL, et al. (1975). Cytochemical response of kidney, liver and nervous system to fluoride ions in drinking water. Histochemical Journal 7: 343-355. Abstract

Marcus WL (1990). Fluoride conference to review the NTP draft fluoride report. US EPA Office of Water. Memorandum. May 1. FULL TEXT http://www.fluoridealert.org/health/cancer/ntp/marcus-memo.html

Marcus WL (1995). Interview with Dr. Gary Null. March 10. EXCERPT http://www.fluoridealert.org/health/cancer/ntp/marcus-interview.html

Mazze RI, et al. (1977). Inorganic fluoride nephrotoxicity: prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 46(4): 265-71. Abstract

Medical Research Council (MRC 2002) Medical Research Council Working Group Report: Water. Fluoridation and Health, London, Medical Research Council.

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. Res Jun 26;583(1-2): 155-60. Abstract

Mullenix PJ, Denbesten PK, Schunior A, Kernan WJ (1995). Neurotoxicity of sodium fluoride in rats. Neurotoxicol Teratol Mar-Apr;17(2):169-77. Abstract. FULL TEXT available at Science Direct.

Narayana MV, Chinoy NJ (1994). Effect of fluoride on rat testicular steroidogenesis. Fluoride 27(1): 7-12.

Narayana MV, Chinoy NJ (1994). Reversible effects of sodium fluoride ingestion on spermatozoa of the rat. International Journal of Fertility 39(6): 337-346. Abstract

National Research Council (1993). Health Effects of Ingested Fluoride. National Academy Press, Washington DC. FULL REPORT

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. Environ Res Sept;93(1): 20-30. Abstract. FULL TEXT available at Science Direct.

Pati PC, Bhunya SP (1987). Genotoxic effect of an environmental pollutant, sodium flouride, 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.

Pesticide Action Network (PAN) (2005). California Pesticide Use. Cryolite - Pesticide use statistics for 2003. ONLINE LINK

Pinto R, Vieira C, Mota-Filipe H, Silva-Lima B (1998). NaF may disturb male fertility in rodents. Toxicology Letters Volume 95, Supplement 1, July, Page 214. FULL TEXT available at Science Direct.

Plesneva SA, Nalivaeva NN, Zhuravin IA (1998). Adenylate cyclase system of the rat striatum: regulatory properties and the effects of gangliosides. Neurosci Behav Physiol Jul-Aug;28(4):392-6. Abstract

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 Paediatr. 1995 May 84(5):555-60. Abstract

Publicover SJ (1991). Brief exposure to the G-protein activator NaF/AlCl3 induces prolonged enhancement of synaptic transmission in area CAI of rat hippocampal slices. Exp Brain Res 84(3):680-4. Abstract

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 Jun; 18(3): 207-12. Abstract. FULL TEXT available at Science Direct.

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: 35-41.

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.

Riordan PJ. (1993). Perceptions of dental fluorosis. Journal of Dental Research 72:1268-74.

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.

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 Res. Sep 17; 622(1-2):35-42. Abstract

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 Jul;17(4):357-67. Abstract

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. FULL TEXT

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 Orthopedics (261):268-75.

Schuld A. (1999). Fluoride-Iodine Antagonism: Some History. Parents for Fluoride Poisoned Children. http://64.177.90.157/pfpc/html/thyroid_history.html

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 Res. Nov 26; 629(1):133-40. Abstract

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 Nov;34(6):330-2. Abstract

Shashi A (2003). Histopathological investigation of fluoride-induced neurotoxicity in rabbits. Fluoride 36: 95-105. FULL STUDY

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 (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. Oct;35(4):351-6. Abstract

Shashi (1990). Histopathological changes in rabbit testes during experimental fluorosis. Folia Morphol (Praha) 38(1):63-5. Abstract

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 Mar;33(2):158-61. Abstract

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. FULL STUDY

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. FULL STUDY

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. FULL STUDY

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 (Dec 10): 1408-1413.

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.

Singla VP, et al. (1976). The kidneys. Fluoride 9: 33-35.

Sogaard CH, et al. (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. Toxicol Lett May;21(2):167-72. Abstract

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 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.

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 Dec;36(12):1117-24. FULL TEXT available at Science Direct.

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. ood Chem Toxicol Sep;35(9):881-90. FULL TEXT available at Science Direct.

Sprando RL, Black TN, Ames MJ, Rorie JI, Collins TFX (1996). Effect of intratesticular injection of sodium fluoride on spermatogenesis. Food Chem Toxicol Apr;34(4):377-84. FULL TEXT available at Science Direct.

Stannard JG, Shim YS, Kritsineli M, Labropoulou P, Tsamtsouris A (1991). Fluoride levels and fluoride contamination of fruit juices. J Clin Pediatr Dent. 1991 Fall;16(1):38-40. Abstract

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. FULL STUDY

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.

Susheela AK, Kumar A (1997). Ultrastructural studies on the leydig cells of rabbits exposed to chronic fluoride toxicity. Environ Sci 5(2):79-94.

Susheela AK, Jethanandani P (1996). Circulating testosterone levels in skeletal fluorosis patients. J Toxicol Clin Toxicol 34(2):183-9. Abstract

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 Jul;92(2):353-60. Abstract

Teotia SPS, et al. (1976). Symposium on the Non-Skeletal Phase of Chronic Fluorosis: The Joints. Fluoride 9(1): 19-24.

Teotia SPS, Teotia M (1972). Cacification of the vas deferens in a patient with endemic fluorosis. Case report. Fluoride 5(2):86-88.

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. FULL STUDY

Tiger G, Bjorklund PE, Brannstrom G, Fowler CJ.(1990). Multiple actions of fluoride ions upon the phosphoinositide cycle in the rat brain. Brain Res Dec 24;537(1-2):93-101. Abstract

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. Eur J Pharmacol Jan 23;188(1):51-62. Abstract

Tokar' VI, Savchenko ON (1977). [Effect of inorganic fluorine compounds on the functional state of the pituitary-testis system]. Probl Endokrinol (Mosk) Jul-Aug;23(4):104-7. Abstract

Tomomatsu T (1981). Hygienic study on fluoride: 4. Physiological effects of fluoride on rat. J TOKYO MED COLL 39 (3): 441-460.

Trabelsi M, Guermazi F, Zeghal N (2001). Effect of fluoride on thyroid function and cerebellar development in mice. Fluoride 34(3):165-173. FULL STUDY

Turner CH, et al. (1996). High fluoride intakes cause osteomalacia and diminished bone strength in rats with renal deficiency. Bone 19:595-601.

Turner CH, et al. (1995). Fluoride reduces bone strength in older rats. Journal of Dental Research 74:1475-81.

Turner CH, et al. (1992). The effects of fluoridated water on bone strength. Journal of Orthopedic Research 10:581-7.

USA Today (2004) General Mills cereals go totally whole grain. Online at: http://72.14.207.104/search?q=cache:SlwfYrUM7YYJ:www.usatoday.com/money/industries/food/2004-09-30-whole-grain_x.htm+kelloggs+%22whole+grain%22&hl=en&ie=UTF-8

USDA (2000). Sulfuryl Fluoride: The Postharvest Fumigant of the Future? United States Department of Agriculture (USDA), Agricultural Research Service. October.
http://www.fluorideaction.org/pesticides/sulfuryl.fluoride.usda.2000.htm

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 (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?” Online at: http://www.ers.usda.gov/AmberWaves/June05/Features/Will2005WholeGrain.htm

US EPA (2001). Notice of Filing a Pesticide Petition to Establish a Tolerance fora Certain Pesticide Chemical in or on Food. Federal Register. June 15.

US EPA (2002). Notice of filing a pesticide petition to establish a tolerance for a certain pesticide chemical in or on food. Federal Register. [PF-1068; FRL-6822-2]. February 15.

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. http://www.epa.gov/safewater/standard/review/pdfs/support_6yr_occurancemethods_final.pdf

US EPA (2004). Sulfuryl Fluoride; Pesticide Tolerance. Final Rule. Federal Register. 40 CFR Part 180. [OPP-2003-0373; FRL-7342-1]. 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. FULL TEXT

US EPA (2005). Sulfuryl Fluoride; Pesticide Tolerance. Final Rule. Federal Register. 40 CFR Part 180. [OPP-2005-0174; FRL-7723-7]. 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. [OPP-2005-0067; FRL-7701-8]. March 4. FULL TEXT

US EPA (2005b). Response to public comments concerning the use of sulfuryl fluoride in food handling facilities. Federal Register Docket No. OPP-2005-0067-0020. July 14. FULL TEXT

US EPA Unions Coalition (2005). Letter to Stephen L. Johnson, Administrator US EPA. Re: Bone Cancer-Fluoride Link. August 5. FULL TEXT

Vanaja P – see Paul, V

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 Feb;107(1):15-21. Abstract

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. FULL STUDY

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 Res Feb 16;784(1-2):284-98. Abstract. FULL TEXT available at Science Direct.

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; Nov;31(6):330-3. Abstract

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. (1990). The physiological and toxicological characteristics of fluoride. Journal of Dental Research 69(Spec Issue):539-49.

Whitford GM. (1987). Fluoride in dental products: safety considerations. Journal of Dental Research 66: 1056-60.

Whyte MP, Essmyer K, gannon FH, Reinus WR (2005). Skeletal fluorosis and instant tea. Am J Med. 2005 Jan;118(1):78-82. Abstract

World Health Organication (WHO) (2002). Fluorides. Environmental Health Criteria 227. Geneva, 2002. FULL TEXT

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: 84-94. FULL STUDY

Xiang Q, Liang Y, Zhou M, Zang H (2003b). Blood lead of children in Wamiao-Xinhuai intelligence study. Fluoride 36: 198-199. FULL TEXT

YUAN S-D, SON K-Q, XIE Q-W, LU F-Y (1991). An experimental study of inhibition on lactation in fluorosis rats. ACTA PHYSIOL SIN; 43(5): 512-517. Abstract

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 Apr; 21(2):102-4. Abstract

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 Nov;28(6):337-8. Abstract

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 May;30(3):144-6. Abstract

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 Jul;28(4):210-2. Abstract

Zhao XL, Wu JH (1998). Actions of sodium fluoride on acetylcholinesterase activities in rats. Biomed Environ Sci Mar 11(1):1-6. Abstract

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.

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 Sep;28(5):264-6. Abstract

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 Sep;28(5):264-6. Abstract

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) Aug;16(8):697-8.