Comments on

the U.S. EPA's

Registration Review for Cryolite

Prepared for the

U.S. Environmental Protection Agency

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Prepared by:

Paul Connett, Ph.D.
Ellen Connett
Michael Connett
Chris Neurath
Tara Blank, Ph.D.

Fluoride Action Network
82 Judson Street
Canton, NY
(802) 338-5577
info@fluoridealert.org

Summary

1. Introduction

Cryolite is an inorganic insecticide that has been registered in the United States since 1957 for use on agricultural crops and ornamentals. In accordance with the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the U.S. Environmental Protection Agency Office of Pesticide Programs (EPA OPP) has opened the registration review process for cryolite to determine if this pesticide can still be used "without unreasonable adverse effects on human health or the environment" (Federal Register, 2011a).

2. OPP must discontinue its promulgation of cryolite, as it does not meet the safety standard in FFDCA Section 408.

According to the EPA Office of Water (OW), children younger than age 7 are routinely exposed to fluoride levels that exceed the "safe" dose recently proposed by OW (RfD=0.08 mg/kg/day; EPA OW, 2010a). Even when exposure estimates are recalculated to exclude the fluoride contribution from sulfuryl fluoride (as proposed by EPA OPP; FR, 2011b), the aggregate exposure to fluoride for this major identifiable population subgroup (children) does not meet the safety standard in FFDCA Section 408.

EPA may only promulgate a pesticide tolerance determined to be "safe"—meaning that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information" (FDA, 2009). OPP must therefore suspend its promulgation of cryolite, based on the same rationale as recently stated for sulfuryl fluoride (FR, 2011b).

Such a position would be greatly magnified if OW or OPP were to recognize that the RfD of 0.08 mg/kg/day underestimates the toxic problems posed to infants and young children, as explained in FAN's submission to the EPA OW (19 April 2011) and FAN's submission to OPP on sulfuryl fluoride (5 July 2011), and further summarized in 3.1. below.

3. FAN's Additional Concerns

The Fluoride Action Network (FAN) would also like to take this opportunity to raise a number of additional concerns that we have with information presented and decisions made in the current documents by EPA's OPP regarding the Registration Review of cryolite.

3.1. The reference dose for fluoride upon which OPP is relying was not based on sound scientific evidence of lack of harm.

3.2. OPP should question OW's use of severe dental fluorosis as the critical effect associated with exposure to fluoride.

3.3. OPP has unreasonably reduced the FQPA Safety Factor for cryolite to 1X.

While the OW has declared severe dental fluorosis the critical effect associated with fluoride exposure, the occurrence of a number of other potentially more serious effects have been documented in the scientific literature at doses below that which cause severe dental fluorosis—including neurological, endocrine, renal, and skeletal effects, as well as the psychological effects associated with mild/moderate dental fluorosis. EPA has also unreasonably delayed determining the carcinogenicity status of fluoride. Furthermore, OW's recently proposed reference dose (RfD) was not based on scientific evidence of lack of harm, but rather on a 70-year-old study of only white children (Dean, 1942), coupled with the perceived oral benefits of ingested fluoride, which are now outdated concepts. Thus OPP should question the use of severe dental fluorosis as the most sensitive indicator of fluoride overexposure, should dispute OW's assertion that an RfD of 0.08 mg F/kg/day is a "safe" dose of fluoride for every person in the United States to consume daily and over a lifetime, and should seriously reconsider its decision to exclude any uncertainty factor from its calculations.

3.4. OPP has ignored the necessity of several required studies of cryolite based on assumptions or inadequate data.

EPA has made a number of serious errors in its determination of which data are necessary for completion of the Registration Review process for cryolite. Many of these errors were due to the use of inappropriate assumptions, rather than sound scientific evidence.

*3.4.1. OPP should require that testing for adverse effects include cryolite and **all** of its degradation products and complexes.*

Cryolite degrades to fluoride, aluminum, and sodium in the environment, but according to EPA, the only degradation product of concern is fluoride, and the only effect of concern is severe dental fluorosis. While OPP is requiring that free ion concentrations of Al^{3+}, F^{-}, and Na^{+} be used to estimate toxicity, this ignores the effects of complexes formed from these ions. Aluminofluoride complexes are formed spontaneously in water containing fluoride and trace amounts of aluminum. These complexes have been found to stimulate various G proteins, and thus may "mimic or potentiate the action of numerous extracellular signals and significantly affect many cellular responses" (Strunecka and Patocka, 1999). OPP should therefore immediately require that toxicity testing of cryolite be extended to include *all* of its degradation products, including the various aluminofluoride complexes formed under different aquatic conditions.

3.4.2. OPP should require neurotoxicity testing for cryolite and all of its degradation products, including aluminofluoride complexes.

Fluoride has been implicated as a potential neurotoxin (e.g. see Appendix A; Valdez-Jiménez et al., 2011), while aluminum is a known neurotoxin (e.g. Forbes et al., 2002; Savory et al., Unpublished; Bondy, 2010). OPP has unfortunately relied on OW's use of severe dental fluorosis as the most sensitive endpoint for fluoride exposure, stating that "more sensitive neurotoxic effects are not expected" (EPA OCSPP, 2011b, p. 5). However, OW was irresponsible in its analysis, in that it failed to consider the voluminous evidence of fluoride's potential to harm the developing brain, even at doses below that which cause severe dental fluorosis. Thus, OPP should also require that cryolite and its degradation products and complexes immediately be subjected to neurotoxicity testing.

3.4.3. OPP should consider the endocrine disrupting potential of cryolite's degradation products and complexes.

Fluoride is a known endocrine disruptor (NRC, 2006). OPP should therefore require that cryolite and its degradation products and complexes immediately undergo testing for endocrine disruption potential, instead of waiting for cryolite to be included among the pesticides being tested by EPA's Endocrine Disruptor Screening Program (EDSP).

3.4.4. OPP has failed to consider dermal routes of exposure

No dermal toxicity studies are required for cryolite, as it is assumed that "the charged nature of parent cryolite and degradate (fluoride ions) make extensive dermal absorption unlikely" (EPA OCSPP, 2011b, p. 4). However, while no dermal toxicity tests have ever been conducted for cryolite, the consequences of dermal exposure to various fluoride compounds have been documented (e.g. ATSDR, 2003; FAN, Undated). OPP should not ignore potential risks via dermal absorption, especially among agricultural workers, based on an untested assumption. OPP should therefore require dermal testing of cryolite and its degradation products and complexes.

3.4.5. OPP has failed to include amphibians in the Ecologial Risk Assessment

OPP states that "The assessment of risk for direct effects to non-target organisms makes the assumption that the toxicity of cryolite to birds is similar to terrestrial-phase amphibians and reptiles. The same assumption is made for fish and aquatic-phase amphibians." (EPA OCSPP, 2011a, p. 20). However, these assumptions ignore that amphibians have been shown to be extremely sensitive to toxins, and are considered "valuable indicators of environmental stress" (Blaustein and Wake, 1995; Blaustein et al., 2003. OPP should therefore require that risk assessments be conducted for amphibians exposed to cryolite and all of its degradation products and complexes.

3.4.6. OPP should require reproductive/developmental toxicity/teratogenicity testing for terrestrial and aquatic species.

OPP assumes that because cryolite is "practically nontoxic to avian species on an acute oral and sub-acute dietary basis" and is "no more than slightly toxic to small mammals on an acute oral basis" (EPA OCSPP, 2011a, p. 13), that chronic risk to birds and small mammals is not expected. However, it is well known that the developing embryo and fetus is much more vulnerable to toxins than is the adult form. Furthermore, for all but mammalian species, acute exposure of the female at the time of ovulation and fertilization potentially establishes a situation of chronic exposure for the duration of embryological development. Thus OPP should require reproductive/developmental toxicity/teratogenicity testing for all representative terrestrial and aquatic species exposed to cryolite and all of its degradation products and complexes.

3.4.7. OPP should require chronic toxicity testing for aquatic animals.

It is stated that OPP "typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments", and that "OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information" (EPA OCSPP, 2011b, p. 9). However, there is ample evidence to indicate that certain sub-populations are already overexposed to fluoride, as mentioned by OPP (EPA OCSPP, 2011b, p. 3). These groups include infants and children, minorities, and low-income populations. OPP should, according to its own standards regarding Environmental Justice, give special consideration to these groups when making decisions regarding the regulation of cryolite.

3.5. OPP has failed to adequately consider Environmental Justice concerns.

Several sub-populations have been shown to be disproportionately harmed by fluoride's toxicity, including low-income people, certain minority groups, and infants and children. OPP's recent aggregate risk assessment for fluoride was based on OW's analysis of fluoride, which included flawed methodology, inappropriate assumptions, and refusal to consider the voluminous scientific evidence indicating that the harmful effects of fluoride exposure extend beyond just the teeth. The decision by OPP to reduce the FQPA Safety Factor for fluoride to 1X was determined via similar parameters, based largely on OW's findings. However, as discussed in Section 3.3., OW's use of a safety factor of 1 is scientifically unjustified. Failure of OPP to acknowledge differences in racial, socioeconomic, and developmental exposure or response to fluoride—or any of the degradation products or complexes of cryolite—is ignoring EPA's own stated goal of achieving Environmental Justice for all Americans.

4. Conclusions

For the many reasons submitted above, FAN calls for a phase out of the use of cryolite as a pesticide on food. The most important reason is that the OPP has itself established that children under 7 years of age are already exceeding the newly proposed RfD for fluoride (a known residue left with cryolite applications) from a combination of existing sources. As FAN believes that this RfD of 0.08 mg/kg/day was derived by OW with inadequate and sometimes inappropriate assumptions, and that this RfD should and will be lowered, the situation with cryolite will become even more untenable. The only possible way that this situation may be relieved is for the major source of fluoride—namely, the practice of water fluoridation—to be eliminated.

1. Introduction

Cryolite is an inorganic insecticide that has been registered in the United States since 1957 for use on agricultural crops and ornamentals. In accordance with the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the U.S. Environmental Protection Agency Office of Pesticide Programs (EPA OPP) has opened the registration review process for cryolite to determine if this pesticide can still be used "without unreasonable adverse effects on human health or the environment" (Federal Register, 2011a).

Thus far in the Registration Review process for cryolite, the following documents have been released:

- PRD Appendix A: Food/Feed and Non-Food/Non-Feed Uses Considered in Registration Review Work Planning, Cryolite (27 April 2010)
- Cryolite Screening Level Usage Analysis (SLUA; 21 June 2010)
- BEAD Chemical Profile for Registration Review: Cryolite (10 November 2010)
- Problem Formulation for the Ecological Risk and Drinking Water Exposure Assessments for Cryolite (8 March 2011)
- Human Health Assessment Scoping Document in Support of Registration Review (16 March 2011)

OPP states that "Cryolite is not identified as a cause of impairment for any water bodies listed as impaired under section 303(d) of the Clean Water Act" (EPA OCSPP, 2011a, p. 22). However, it should be acknowledged that two of the degradation products of cryolite, aluminum and fluoride, are among the major causes of impairment of water bodies in the United States. Aluminum (TMDLs: 1974) is second only to iron as the most frequent cause of impairment in the Specific State Pollutants that make up the National Metals (other than mercury) Pollutant group (EPA, 2011b), while fluoride (TMDLs: 78) is the most frequent cause of impairment in the Specific State Pollutants that make up the National Toxic Inorganics Pollutant group (EPA, 2011c). According to EPA, agriculture is indicated as a probable source contributing to impairments affecting more rivers, streams, lakes, reservoirs, ponds, and wetlands that virtually any other source (EPA, 2011d, National Probable Sources Contributing to Impairments). Among the probable sources that make up the National Agricultural Probable Source Group is runoff from agricultural lands.

Cryolite contains approximately 55% fluorine and 13% aluminum (EPA OCSPP, 2011a, Table 4, p. 10). Thus, the more than 1.2 million pounds of active ingredient used on agricultural crops (EPA, 2010b, p. 2) contribute over 660,000 pounds of fluorine and more than 156,000 pounds of aluminum to the environment each year. These estimates do not include use of cryolite on ornamental plants, unreported registered usage (e.g. small acerage crops), or non-agricultural use sites (e.g. turf, post-harvest, mosquito control, etc.). In fact, according to EPA "There are no usage data for cryolite from our available sources on ornamental plants and nursery crops" (EPA OCSPP, 8 Sept 2010, p. 3), although the California Department of Pesticide Regulation estimates that 1,850 pounds of cryolite were used on nursery stocks in 2008.

OPP states that "The maximal seasonal application of cryolite is not expected to exceed average elemental soil concentrations of Al, F, and Na" (EPA OCSPP, 2011a, p. 9). While the estimated amount of aluminum released into the environment via cryolite application to those agricultural crops listed in the SLUA for cryolite (EPA, 2010b, p. 2) would constitute only 0.7% of the total aluminum reportedly released (EPA Toxic Release Inventory, TRI, 2009, aluminum, Total On- and Off Site Disposal or Other Releases), the amount of fluorine released via the same cryolite application would equate to FIVE TIMES the fluorine released in 2009 from all sources reported (EPA, TRI, 2009, fluorine, Total On- and Off Site Disposal or Other Releases).

In addition to the potential for environmental harm due to runoff from agricultural applications, cryolite is the main source of fluoride in wine and California grapes and grape products (e.g. table grapes, raisins, grape juice) (NRC, 2006, p. 38). Considering the high consumption rates of these products in the United States, as well as the overexposure to fluoride presently experienced by many Americans via drinking water (i.e. artificial water fluoridation) and dental products—the immense burden of protecting both the environment and the American people from the potential harms of cryolite and its degradation products and complexes falls squarely on the shoulders of EPA's OPP.

2. Cryolite does not meet the safety standard defined in FFDCA Section 408, and thus OPP must withdraw all tolerances for cryolite residues on foodstuffs.

According to a recent exposure analysis by EPA's Office of Water (OW), "Some young children are being exposed to fluoride up to about age 7 at levels that increase the risk for severe dental fluorosis" (EPA OW, 2010b, p. 108). Earlier this year, EPA proposed to grant objections with regard to tolerances established for sulfuryl fluoride and fluoride "because it agrees that aggregate exposure to fluoride for certain major identifiable population subgroups does not meet the safety standard in FFDCA section 408" (Federal Register, 2011b, p. 3423).

Recalculating the fluoride exposure estimates with revised parameters—including elimination of the contribution of fluoride from sulfuryl fluoride (as proposed by EPA OPP; FR, 2011b); reduced contribution from drinking water (i.e. using 0.7 mg F/L, as recommended by U.S. Department of Health and Human Services; DHHS, 2011); and increased contribution from toothpaste intake (i.e. two brushings per day, as recommended by OPP; FR, 2011b, p. 3438)—still results in fluoride overexposure of children under age 7 (Table 1). That is, it can be expected that these children will routinely be exposed to levels of fluoride that exceed that recently proposed as "safe" by OW (Rfd=0.08 mg/kg/day; EPA OW, 2010b).

Age (years)	Weight (kg)	DWI [a]	FI [b]	BI [b]	TI [c]	SI [b]	Total (mg/day)	Weight-Adjusted Total (mg/kg/day)
0-<0.5	6	0.69	0.18	--	--	--	0.87	0.145
0.5-<1	9	0.68	0.25	--	0.14	0.02	1.09	0.121
1-<4	14	0.51	0.16	0.36	0.68	0.04	1.75	0.125
4-<7	21	0.66	0.35	0.54	0.44	0.04	2.03	0.097
7-<11	32	0.70	0.41	0.60	0.36	0.04	2.11	0.067
11-<14	51	0.99	0.47	0.38	0.40	0.04	2.28	0.045
>14	70	1.40	0.38	0.59	0.20	0.02	2.59	0.037

Table 1. Total fluoride intake estimates and weight-adjusted intake estimates for adults and children.
[a] DWI=Fluoride from Drinking Water Intake; Consumers only 90th percentile water consumption rates based on data from EPA OW, 2010b, Table 3-6, p. 69; calculated with 0.7 mgF/L, as recommended by DHHS, 2011.
[b] FI=Fluoride from Food Intake; BI=Fluoride from Beverage Intake; SI=Fluoride from Soil Intake; Data from EPA OW, 2010b, p. 98.
[c] TI=Fluoride from Toothpaste Intake; based on brushing twice daily, as determined by EPA OPP (FR, 2011b, p. 3440).

According to EPA, total exposure to fluoride from cryolite is estimated to be 0.0012 mg/kg/day for non-nursing infants, and 0.0023 mg/kg/day for children 1-6 years old (EPA OW, 2010b, Appendix A, Attachment 4, p. 25). As indicated in Table 1, children

less than 7 years of age are already exceeding OW's recently proposed reference dose (RfD) for fluoride of 0.08 mg/kg/day (EPA OW, 2010a).

EPA may only promulgate a pesticide tolerance that has been determined to be "safe"—meaning that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information" (FDA, 2009). While the Relative Source Contribution (RSC) for cryolite may not seem significant (Table 2), any additional source of fluoride beyond that which already exceeds the "safe" dose for children must not be allowed by OPP.

Age (years)	Weight (kg)	Weight-Adjusted F from Cryolite (mg/kg/day)	Total F from Cryolite (mg/day)	RSC
0-<0.5	6	0.0012	0.0072	1.98
0.5-<1	9	0.0012	0.0108	0.99
1-<4	14	0.0023	0.0322	1.84
4-<7	21	0.0023	0.0483	2.38

Table 2. Relative Source Contribution (RSC) for fluoride exposure from cryolite in children under 7 years. Data from EPA OW, 2010b, Appendix A, Attachment 4, p. 25.

As stated for sulfuryl fluoride, "EPA cannot conclude that there is a reasonable certainty of no harm for certain major identifiable groups from aggregate exposure to fluoride…[and] cannot make the required finding that the sulfuryl fluoride and fluoride tolerances are "safe" (FR, 2011b, p. 3442). The same must hold true for cryolite.

3. Additional concerns of FAN

3.1. The reference dose for fluoride upon which OPP is relying was not based on sound scientific evidence of lack of harm.

The reference dose (RfD) for fluoride recently proposed by EPA's Office of Water (OW), 0.08 mg F/kg/day, was based on the perceived oral benefits of fluoride, instead of on sound scientific evidence of lack of harm. However, determination of a safe RfD should be blind to benefits. These may play a part in moving from a scientifically determined maximum contaminant level goal (MCLG) to a federally enforceable maximum contaminant level (MCL), which is frequently a compromise between the ideal (MCLG) and the practical (MCL), since the latter takes into account the costs of removal of natural pollutants.

Fluoride is considered a contaminant by EPA, but OW has improperly offered it a protected status due to presumed benefits for oral health. OW states "it should be recognized that fluoride is a nutrient" (EPA OW, 2010b, p. 39). However, the misconception that fluoride is a nutrient that followed the publication of *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride* (IOM, 1997) was corrected in a 1999 joint letter from the Presidents of the National Academy of Sciences and the Institute of Medicine:

> "… First, let us reassure you with regard to one concern. Nowhere in the report is it stated that fluoride is an essential nutrient. If any speaker or panel member at the September 23rd [IOM] workshop referred to fluoride as such, they misspoke.

The Adequate Intake (AI) for fluoride was established by the IOM in 1997, prior to recognition that "the major anticaries benefit of fluoride is topical and not systemic" (NRC, 2006, p.16). This predominant mode of action is now also accepted by the Centers for Disease Control and Prevention (CDC, 2001), as well as numerous researchers (e.g. Zero et al., 1992; Rölla and Ekstrand, 1996; Featherstone, 1999; Limeback, 1999; Clarkson and McLoughlin, 2000; Warren and Levy, 2003; Fejerskov, 2004; Hellwig and Lennon, 2004; Pizzo et al., 2007; Cheng et al., 2007). Despite this, OW has not corrected for these incongruities.

To demonstrate that a substance is an essential nutrient it is necessary to starve the animal of the substance in its diet and then show that a disease accrues. This has not been done for fluoride. Not a single biochemical process in the animal body has been shown to need fluoride as a positive factor. To the contrary, many biochemical processes and mechanisms have been shown to be harmed by fluoride (Barbier et al., 2010).

Another indicator that fluoride is not a nutrient necessary for proper human development is the extremely low levels of fluoride that are found in human breast milk. For infants,

nutritional status should be determined based on what is present, and at what levels, in breast milk. Breast milk averages only 0.007 mg F/L (NRC, 2006, p. 40). Even with high maternal fluoride exposure, nursing children receive only 0.2% of the mother's fluoride intake (Şener et al, 2007). For example, mothers living in areas where the concentration of fluoride in water is naturally high (9 mg/L), and thus daily maternal intake of fluoride is also high (up to 37.2 mg/day), maintain breast milk with very low concentrations of fluoride (0.033 mg/L) (Opinya et al, 1991). Despite sharp increases of fluoride concentrations in blood plasma following a bolus ingestion of fluoride, the concentration of fluoride in breast milk remains relatively unchanged (Ekstrand et al, 1981, 1984). Thus there is likely an evolutionary mechanism that prevents infants from receiving high doses of fluoride from their mother's milk. The sensitive brains and bodies of breast-fed infants are therefore protected from the developmental effects of this toxin.

As will be discussed in the next section, several adverse health effects have been observed at doses of fluoride lower than OW's RfD of 0.08 mg/kg/day. OPP should therefore question OW's recently proposed RfD for fluoride as the level that is safe for every person—including pregnant women, infants, persons with diabetes or kidney disease, and the elderly—to consume daily, and over a lifetime.

3.2. OPP should question OW's use of severe dental fluorosis as the critical effect associated with exposure to fluoride.

The critical effect is the "adverse effect most likely to occur at the lowest exposure level" (EPA OW, 2010a, p. 87). OW claims that the proposed RfD for fluoride, as determined for the critical effect of severe dental fluorosis, "is applicable to the entire population since it is also protective for the endpoints of severe fluorosis of primary teeth, skeletal fluorosis and increased risk of bone fracture in adults" (EPA OW, 2010a, p. 107). OW also claims that "there is no clear evidence that fluoride will cause other types of adverse health effects…at levels as low as those associated with severe dental fluorosis" (2 mg/L; EPA OW, 2010a, p. 87). However, OW has failed to offer convincing scientific evidence for either of these assertions, as numerous other adverse effects have been observed at levels below, or similar to, that which is known to cause severe dental fluorosis—including neurological, endocrine, renal, and skeletal effects. Also worthy of mention are the adverse psychological effects experienced by those with mild to moderate dental fluorosis.

3.2.1. Neurological effects

One of the most startling effects of fluoride's toxicity is on the developing brain. Neurological effects have been found to occur at levels of fluoride that offer no adequate margin of safety relative to OW's newly proposed RfD. Unfortunately, according to OPP, "since the residue of concern for cryolite is the fluoride ion, for which the most sensitive endpoint has been determined to be severe dental fluorosis based on extensive review of available data, more sensitive neurotoxic effects are not expected. Therefore, neurotoxicity studies are not required for cryolite." (EPA OCSPP, 2011b, p. 5). However, OW completely ignored the voluminous data on the neurological effects of fluoride. Simply because OW refused to consider neurotoxic effects of fluoride, OPP cannot assume that they do not exist.

When the NRC (2006) panel looked at the animal and human studies on fluoride's interaction with the brain it concluded:

> 1) On the basis of information largely derived from histological, chemical, and molecular studies, it is apparent that fluorides have the ability to interfere with the functions of the brain and the body by direct and indirect means. (p. 187)

The NRC panel looked at FIVE IQ studies, and drew special attention to the study by Xiang et al. (2003a), which they considered the best designed.

> 2) Several studies from China have reported the effects of fluoride in drinking water on cognitive capacities (X Li et al., 1995; Zhao et al., 1996; Lu et al., 2000; Xiang et al., 2003a; 2003b). Among the studies, the one by Xiang et al. (2003a)

had the strongest design. This study compared the intelligence of 512 children (ages 8-13) living in two villages with different fluoride concentrations in the water. The IQ test was administered in a double-blind manner. The high-fluoride area (Wamiao) had a mean water concentration of 2.47 ± 0.79 mg/L (range 0.57-4.50 milligrams per liter [mg/L]), and the low-fluoride area (Xinhuai) had a mean water concentration of 0.36 ± 0.15 mg/L (range 0.18-0.76 mg/L). The populations studied had comparable iodine and creatinine concentrations, family incomes, family educational levels, and other factors. The populations were not exposed to other significant sources of fluoride, such as smoke from coal fires, industrial pollution, or consumption of brick tea. Thus, the difference in fluoride exposure was attributed to the amount in the drinking water. Mean urinary fluoride[1] concentrations were found to be 3.47 ± 1.95 mg/L in Wamiao and 1.11 ± 0.39 mg/L in Xinhuai. Using the combined Raven's Test for Rural China, the average intelligence quotient (IQ) of the children in Wamiao was found to be significantly lower (92.2 ± 13.00; range, 54-126) than that in Xinhuai (100.41 ± 13.21; range, 60-128). pp. 205-6.

> The IQ scores in both males and females declined with increasing fluoride exposure. The number of children in Wamiao with scores in the higher IQ ranges was less than that in Xinhuai. There were corresponding increases in the number of children in the lower IQ range. Modal scores of the IQ distributions in the two villages were approximately the same. A follow-up study to determine whether the lower IQ scores of the children in Wamiao might be related to differences in lead exposure disclosed no significant difference in blood lead concentrations in the two groups of children (Xiang et al., 2003b). (pp. 205-6)

The NRC (2006) panel's overall conclusion based on its review of these five IQ studies was:

> 3) A few epidemiologic studies of Chinese populations have reported IQ deficits in children exposed to fluoride at 2.5 to 4 mg/L in drinking water. Although the studies lacked sufficient detail for the committee to fully assess their quality and relevance to U.S. populations, the consistency of the results appears significant enough to warrant additional research on the effects of fluoride on intelligence. (p. 8)

The NRC (2006) report reproduced the two graphs from the Xiang et al. (2003a) study showing the difference in IQ curves for the two villages for both males and females, and are shown here in Figures 3 and 4.

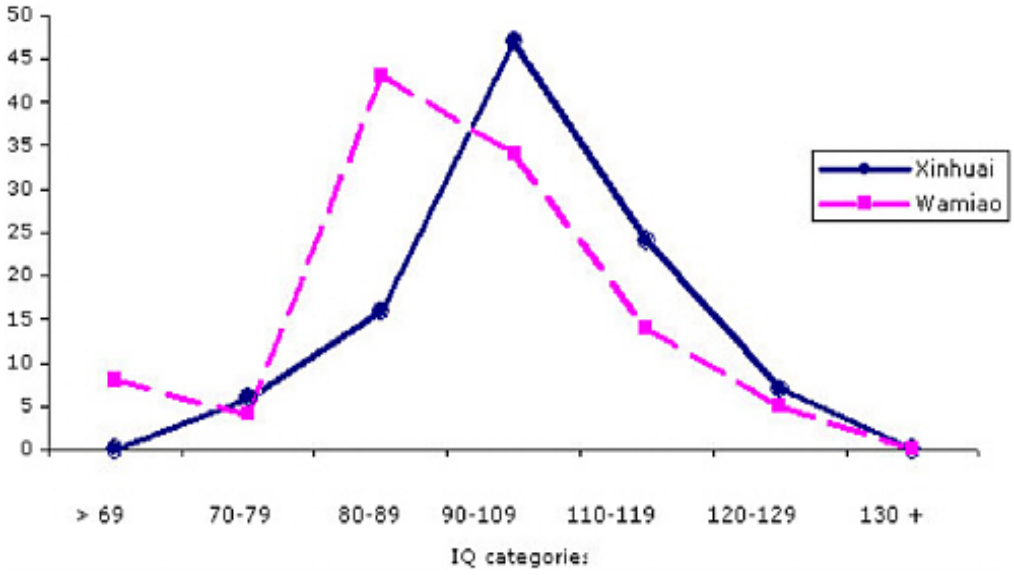

Figure 3. Distribution of IQ scores from males in Wiamiao and Xinuai. Source: data from Xiang et al. 2003a (as shown in NRC, 2006, Figure 7-2, p. 207).

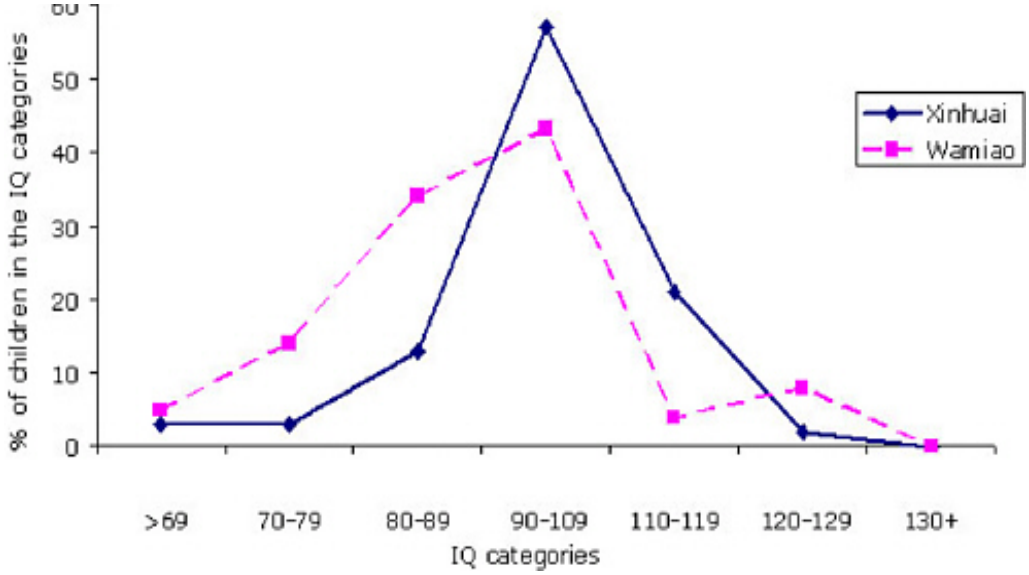

Figure 4. Distribution of IQ scores from females in Wiamiao and Xinuai. Source: data from Xiang et al. 2003a (as shown in NRC, 2006, Figure 7-1, p. 207).

Since the NRC panel wrote its report in 2006, many more animal studies have been published and another NINETEEN IQ studies (including one from Mexico, one from Iran, one from India, and the rest from China) have been either published or translated and made available in English. FAN has kept the EPA informed about these studies, so it cannot be claimed that it is not aware of their existence. A listing of all studies can be obtained in Appendix A.

An updated version of Xiang's (2003a) work, which included new information about the relationship between the level of fluoride in the children's plasma and the IQ lowering, was accepted for publication in *Environmental Health Perspectives* (the journal of the National Institute of Environmental Health Sciences, NIEHS) and made available online on December 17, 2010. This publication was later withdrawn when it was found that some of the other material had been previously published. However, for those who have used criticisms of the methodologies of some of these 24 IQ studies to justify ignoring the issue completely, it is important to note that the Xiang paper successfully passed the peer review process of this important journal.

If OW had published its health risk assessment soon after NRC review was published in 2006, perhaps they could be excused for accepting only the three end points (severe dental fluorosis, stage II skeletal fluorosis and bone fractures) that the panel recommended at the time as a basis of determining a more protective MCLG. However, as far as the onerous task of protecting the public from pollutants that might cause harm, the EPA should not have limited itself to the science covered in the NRC report, but instead taken advantage of work that has been published since, especially this important new work on the brain. Science does not stand still. The EPA is obliged to use the best and latest science in fulfilling its mandate to protect the health of the American people. By ignoring the many studies on the brain it is not doing so.

Another IQ study published in 2011 by Ding et al. investigated the effects of low levels of fluoride on IQ. Children were exposed to 0.3 to 3 mg F/L fluoride via drinking water. The authors found a very significant linear correlation ($p < 0.0001$) between fluoride levels in the children's urine and lowered IQ (Figure 5). They calculated that there will be a lowering of IQ by 0.59 points for each increase of 1 mg/L urinary fluoride.

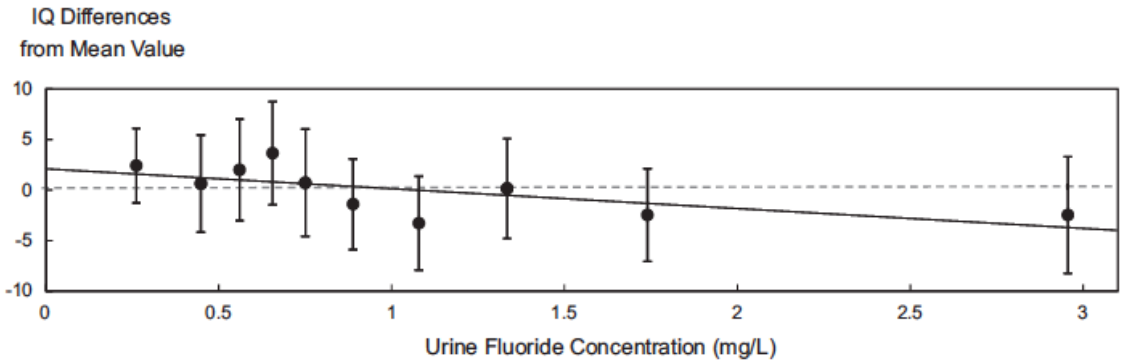

Figure 5. The relationship between IQ differences and urine fluoride concentrations. Multiple linear regression model was carried out to confirm the association of urine fluoride exposure with IQ scores ($F=9.85$, $P<0.0001$). SOURCE: Ding et al., 2011.

Ding et al. (2011) found no obvious level at which fluoride will not have some effect on IQ. Even without applying a safety margin to this finding, it seems there is no safe level that would protect all of America's children from potential interference with mental

development from fluoride exposure via the water supply. On this basis, EPA should assign an MCLG of zero for fluoride, as it has done for lead. However, as Ding et al. (2011) states that this is a preliminary finding, and that more work should be done to control for possible confounding factors, the findings of Xiang et al. (2003a; 2003b; 2010) will be employed to determine a safe reference dose for fluoride that will be adequate to protect against lowered IQ in America's children.

Turning to the significance of these brain studies for the determination of a new RfD and MCLG—if OW had used the data from Xiang et al. (2003a; 2003b) as a starting point in determining an RfD to protect all of America's children, its estimation would have been proceeded as follows:

Xiang et al. (2003a; 2003b) estimated, via linear extrapolation from all their data, that the lowest water concentration associated with a lowering of IQ (LOAEL) was 1.9 mg F/L. Because these studies only dealt with 500 children—likely with rather homogeneous genetics, lifestyles and nutritional status—we would need the full uncertainty factor of 10 to account for the full range of sensitivity expected in the whole population of children in the U.S. to arrive at an appropriate RfD for this serious end point. Thus, 1.9 mg F/day divided by 10 = 0.19 mg F/day. The necessity of an uncertainty factor of 10 could also be argued because of the use of a LOAEL, instead of a NOAEL (or we could incorporate both a UF for intraspecies variation and for use of a LOAEL, which would require an uncertainty factor of 100, resulting in an RfD of 0.019 mg/day).

In moving from an RfD to an MCLG, it is EPA policy to consider the 90th percentile water consumer. For infants 0.5 - <1 year, the consumer-only consumption of municipal water at the 90th percentile is 971 mL/day (EPA OW, 2010b, Table 3-6, p. 69). Thus for this very susceptible age group to remain at or below the RfD of 0.19 mg F/day that would reasonably protect against lowered IQ, the MCLG should be set no higher than 0.2 mg F/L, resulting in a dose of 0.02 mg F/kg/day.

However, if we consider the fluoride contribution from only one other source—fluoridated toothpaste—the situation changes. OW estimated that mean fluoride ingestion from toothpaste for children 0.5 - <1 year is 0.07 mg/day, and that for 1 - <4 year-olds is 0.34 mg/day (EPA OW, 2010b, Table 6-4, p. 94). Thus, fluoride intake from toothpaste alone contributes nearly half (for 0.5 - <1 year-olds) to twice (for 1 - <4 year-olds) the RfD of 0.19 mg/day that would reasonably protect against lowered IQ. Thus some children will already exceed the safe dose even without the fluoride contribution from water, forcing an MCLG of zero. So whether we consider the preliminary study by Ding et al. (2011) or the studies by Xiang et al. (2003a; 2003b; 2010), it is difficult to understand how the MCLG for fluoride could be set any higher than ZERO.

OW considers 0.05 mg F/kg/day to be the intake necessary to protect teeth from caries (EPA OW, 2010a, p. xiv). This means that, for the most sensitive child, the level "required" to protect their teeth may more than twice the dose that potentially damages their brain. At this point common sense should take over, and EPA should realize that any policy insisting that the health of children's teeth is more important than the health of

their brains is misguided and potentially dangerous. Thus, OPP should consider the neurological effects of fluoride exposure, as presented in the scientific literature, before concluding that "more sensitive neurotoxic effects are not expected" (EPA OCSPP, 2011b, p. 5).

3.2.2. Endocrine effects

A 2006 report by the National Research Council (NRC) of the National Academies, and commissioned by the EPA, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*, determined that fluoride is "an endocrine disruptor in the broad sense of altering normal endocrine function or response" (NRC, 2006, p. 266). Several endocrine effects have been observed at fluoride doses at or below OW's recently proposed RfD of 0.08 mg F/kg/day. These include altered thyroid function (T4 and T3 concentrations) and elevated TSH concentrations at 0.05-0.1 mg/kg/day (0.03 mg/kg/day with iodine deficiency); elevated calcitonin concentrations at 0.06-0.87 mg/kg/day; goiter prevalence >20% at 0.07-0.13 mg/kg/day (>0.01 mg/kg/day with iodine deficiency); and impaired glucose tolerance at 0.07-0.4 mg/kg/day (NRC, 2006).

According to the American Thyroid Association (ATA, 2003), 2-3% of Americans have pronounced hypothyroidism, and as many as 10-15% have subclinical hypothyroidism. Synthroid and Armour, both pharmaceuticals used to treat hypothyroidism (PubMed Health, 2008; 2011) were the 7th and 73rd top selling drugs in the United States in 2009, with over 24 million combined units sold (Drugs.com, Undated). The rate of primary (i.e. at birth) congenital hypothyroidism has increased by 75% over the past two decades in the United States, with the incidence being higher for Hispanic newborns than for white newborns (Olney et al., 2010).

NRC (2006, p. 256) states that "fluoride is likely to cause decreased melatonin production and to have other effects on normal pineal function, which in turn could contribute to a variety of effects in humans." The pineal gland is a calcifying tissue that can accumulate fluoride, with fluoride concentrations being positively related to calcification (Luke, 1997; 2001). Increased calcification of the pineal gland may be associated with a decreased number of functioning pinealocytes and with the ability to produce melatonin (Kunz et al., 1999). Higher intakes of fluoride have been associated with decreased melatonin output in pre-pubescent gerbils, and with earlier sexual maturation in the females (Luke, 1997). Schlesinger et al. (1956) reported that girls living in a fluoridated community reached menarch 5 months earlier than girls living in a non-fluoridated community, and Farkas et al. (1983) reported that postmenarcheal girls were present at younger ages in the town with higher fluoride levels compared to the low-fluoride town. Between 2004 and 2006, the onset of pubertal maturation was 8 years of age for 43% of Blacks, 31% of Hispanics, and 18% of Caucasian girls in the United States—for Caucasian girls, this is double the rate found in 1997 (Biro et al., 2010).

In light of research findings, NRC (2006) offered the following recommendation: "The

effects of fluoride on various aspects of endocrine function should be examined further, particularly with respect to a possible role in the development of several diseases or mental states in the United States." (p. 267).

3.2.3. Renal effects

Parameters of kidney function have also been found to be altered at levels within the range of that proposed by OW as the new RfD. For example, the amount of plasma membrane and endoplasmic reticulum Ca^{++}-pump protein in kidney membranes of rats showed a significant reduction associated with a plasma concentration of only 2 umol F/L (Borke and Whitford, 1999). This level is equivalent to that achieved in humans with an intake of perhaps 2.2 mg F/day (Teotia et al., 1978; NRC, 2006, p. 70), or 0.03 mg/kg/day for a 70 kg adult.

3.2.4. Skeletal effects

Development of severe dental fluorosis is only an issue for the first 8-14 years of a child's life, as it cannot occur after the permanent teeth have erupted. On the other hand, the risks of stage II skeletal fluorosis and bone fractures (particularly hip fractures) are a lifelong concern. A dose of fluoride that was insufficient to cause severe dental fluorosis in a child—if consumed on a daily basis for the rest of a person's life—might well induce permanent changes in the bones. Moreover, while an uncertainty factor of one—in our view—is not sufficient to protect against severe dental fluorosis, it most certainly is not sufficient in the case of skeletal fluorosis or bone fractures.

Fluoride accumulates in the body over a lifetime, with some authors noting that 99% of retained fluoride is found in bones and teeth (Hamilton, 1990; Kaminsky et al., 1990; WHO, 2002). Young bones are more receptive to fluoride accumulation than are older bones (Whitford, 1999), as evidenced by the greater percentage of fluoride retained by infants than by adults (Ekstrand et al, 1994). Thus, the developing skeletal system of children is likely to be more sensitive to fluoride exposure than is that of an adult. As the proportion of retained fluoride in teeth is substantially less than that retained in bone (Ayoob and Gupta, 2006), it is likely that any effects of fluoride on the developing teeth—even mild or very mild dental fluorosis—are indicators of even greater changes to the developing bones.

Several studies indicate that bone damage or bone changes may occur prior to the development of severe dental fluorosis. Research from India, where most data relating to endemic fluorosis has been generated, has found skeletal fluorosis associated with water fluoride levels of 2-3 mg/L, and as low as 0.7 mg/L (Ayoob and Gupta, 2006). The prevalence of skeletal fluorosis was found to be between 2-8% for populations with

water fluoride levels at 1.4 mg/L (Jolly, 1968; Choubisa et al., 1997, 2001; Xu et al., 1997). The Chinese government now considers any water supply containing over 1 ppm fluoride a risk for skeletal fluorosis (Bo et al., 2003). In one study, 9 of 14 villages in India had a rate of skeletal fluorosis that was at least twice that of the rate of dental fluorosis (Susheela, 2003), providing sound evidence that dental fluorosis is not always a more sensitive indicator of fluoride over-exposure. NRC (2006) indicates a lack of information on the prevalence of stage II skeletal fluorosis in the U.S., with very few reports of stage II and stage III skeletal fluorosis being reported. However, lack of evidence of harm does not indicate lack of harm, and NRC (2006) recommended more research be conducted. Presently, there are several studies that should be considered more thoroughly concerning bone changes in response to fluoride intake.

Concerning "optimally" fluoridated water supplies, Schlesinger et al. (1956) found a statistically significant doubling of cortical bone defects in the children in fluoridated Newburgh compared to non-fluoridated Kingston (12.5% versus 7.5%). The cortical bone is the lamellar structure on the outside layer of the bone, which protects against noncompressive fractures. Ironically, even though this observation was ignored as far as pursuing the issue of bone fractures among children in fluoridated communities was concerned, it was the eventual starting point for the possibility that fluoride might cause osteosarcoma in young males. According to Dr. Caffey who examined the bone X-rays, the anatomical, gender and age distribution of these defects was remarkably similar to the same distributions in osteogenic sarcoma (another name for osteosarcoma) (NRC, 1977; Connett P, et al., 2010, Ch.18). Despite the present of these bone defects, no cases of severe dental fluorosis were observed in the fluoridated community, indicating that cortical bone defects may be more sensitive to fluoride exposure than dental fluorosis.

A study of children and adults in Mexico (Alarcon-Herrera, et al., 2001) found a direct linear association between the severity of dental fluorosis and bone fractures in both children and adults. This very striking finding indicates that fractures doubled between those with no dental fluorosis and those with very mild dental fluorosis, and doubled again between those with very mild dental fluorosis and mild dental fluorosis. Clearly, such a finding negates any notion that weakening of bones will occur only after fluoride exposures have reached the point of causing severe dental fluorosis. It is interesting that no fluoridating country (including the U.S.) has ever sought to reproduce this study, nor for that matter—except for one small study by Morgan et al. (1998)—have they used the very obvious biomarker of the severity of dental fluorosis in epidemiological studies to probe fluoride's possible relationship with various other ailments.

In its recent analysis, OW set considerable store by the important bone study of Li et al. (2001), but used the study selectively and fails to identify problems with the data analysis, thereby potentially underestimating the risk fluoride poses to hip fracture in the elderly. A more critical analysis of the Li et al. data would suggest an RfD lower than that proposed for severe dental fluorosis. The Li et al. (2001) study reported bone fractures in

six Chinese villages in which the well water increased from less than 0.3 ppm to greater than 4 ppm. The authors reported (a) on the prevalence of ALL fractures and also (b) on HIP fractures only. Both the NRC (2006) and OW rated this as a strong and important study. The OW, while tabulating the results of the whole study, concentrated selectively on the total fractures, for which they provide only graphical data. These data suggested a U-shaped curve, where the fractures in the two villages with water <1 ppm (villages 1 and 2) were higher than the village at 1 ppm (village 3), but the fracture rate for villages 4, 5 and 6 increased in what looks like a linear fashion. This part of the study has been offered by some fluoridation promoters as evidence that fluoride is actually protective of bone fractures at or around 1 ppm. However, it should be noted that the apparent U-shape is much less evident and not statistically significant when data for total fractures in people over 50 years of age are considered.

It is not understood why Li et al. (2001) did not plot the fracture data on a proper numerical scale. Data were available to do not only that, but also to plot fractures against estimates of fluoride consumption, rather than merely fluoride concentration in water. Their plots have proved misleading to readers, including the OW. Figures 6 and 7 re-plot the fracture data against water consumption using data from Li et al. (2001), summarized in Tables 3 and 4.

Village	Water F (ppm)	Average Daily Intake (mg/day)	Number Surveyed	Number of All Fractures	Prevalence (%)
1	0.25 – 0.34	0.73	1,363	101	7.41
2	0.58 – 0.73	1.62	1,407	90	6.40
3	1.00 – 1.06	3.37	1,370	70	5.11
4	1.45 – 2.19	6.54	1,574	95	6.04
5	2.62 – 3.56	7.85	1,051	64	6.09
6	4.32 – 7.97	14.13	1,501	111	7.40

Table 3. All fractures (since the age of 20 years) in six Chinese villages with average fluoride intakes varying from 0.7 to 14 mg/day. Source: Li et al., 2001.

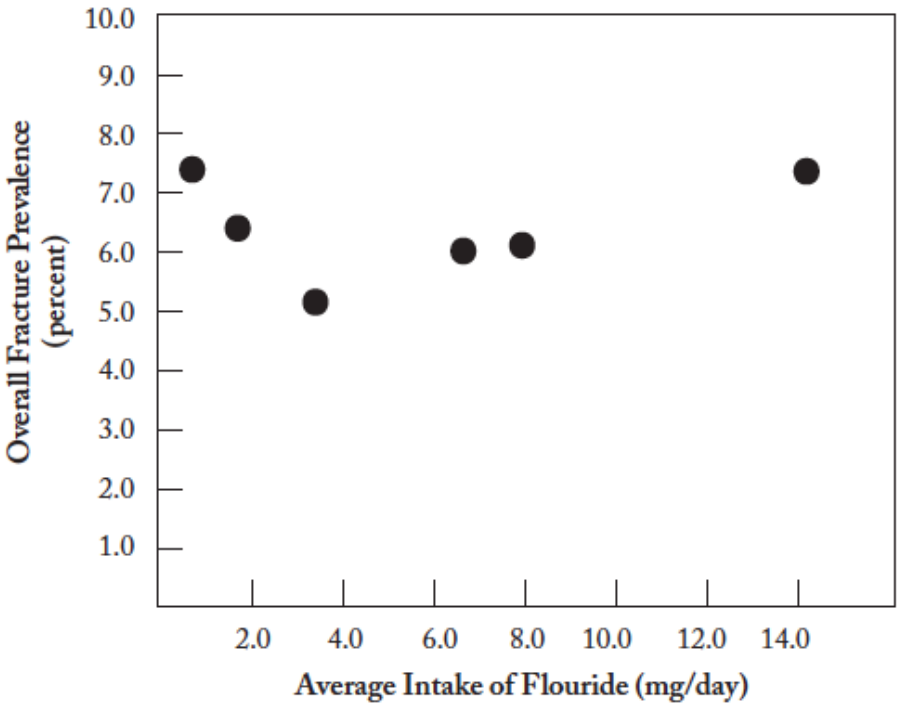

Figure 6. Prevalence of all bone fractures (since the age of 20 years) plotted against average daily fluoride intakes in six Chinese populations; data from Li et al. (2001), summarized in Table 3.

Village	Water F (ppm)	Average Daily Intake (mg/day)	Number Surveyed	Number of Hip Fractures	Prevalence (%)
1	0.25 – 0.34	0.73	1,363	5	0.37
2	0.58 – 0.73	1.62	1,407	6	0.43
3	1.00 – 1.06	3.37	1,370	5	0.37
4	1.45 – 2.19	6.54	1,574	14	0.89
5	2.62 – 3.56	7.85	1,051	8	0.76
6	4.32 – 7.97	14.13	1,501	18	1.20

Table 4. Hip fracture rates (since the age of 20 years) in six Chinese villages with average fluoride intakes varying from 0.7 to 14 mg/day. Source: Li et al., 2001.

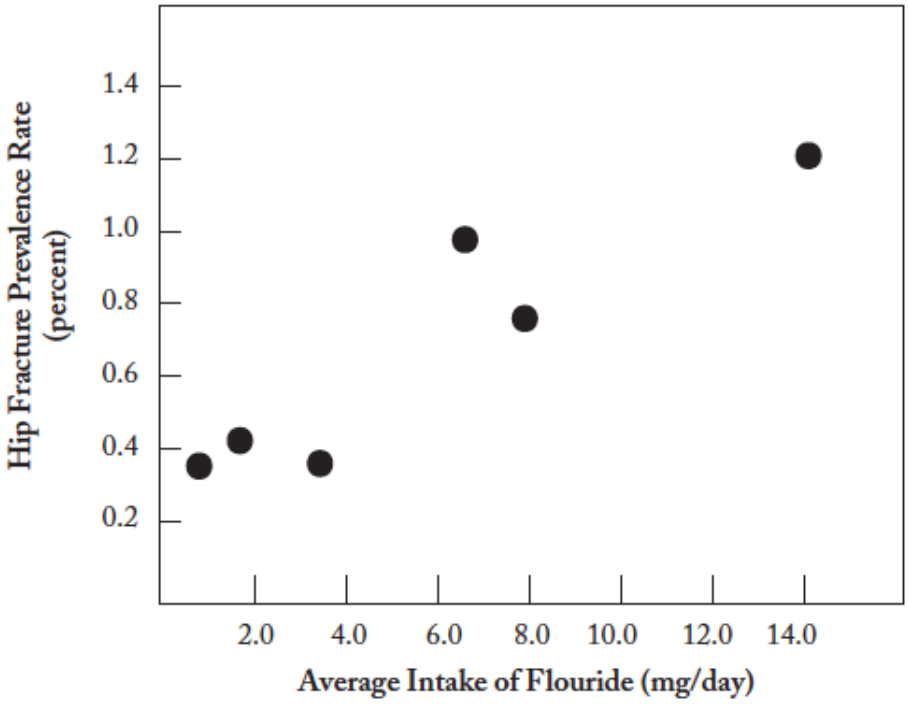

Figure 7. Prevalence of hip fractures (since the age of twenty years) plotted against average daily fluoride intakes in six Chinese populations; data from Li et al. (2001), summarized in Table 4.

The hip data (Figure 7) now look consistent with a *simple straight line relationship between fracture frequency and fluoride consumption*. A very similar relationship is seen when plotting against water fluoride concentration (plot not shown). This more orthodox presentation of what are generally considered the strongest available data puts into serious question whether there is *any threshold at all* for the fluoride effect on hip fracture. Based on the linear trend illustrated in Figure 4, hip fractures may increase at doses of 3 mg/day or even lower, and certainly at levels lower than the RfD of 5.6 mg/day (0.08 mg/kg/day) developed by OW for the end point of severe dental fluorosis.

Levy et al. (2009) observed fluoride intakes recorded from birth and compared them with bone measurements taken in children at 11 years old. Fluoride intake was significantly correlated with several bone measures, including hip and spine BMC (bone mineral content) and spine BMD (bone mineral density) in girls; hip, spine, and whole-body BMC and spine BMC in boys. When corrected for age, height, weight and Tanner stage, no significance was determined ($p<0.01$). However, consistent trends were observed. For girls, there was a negative trend for regression coefficients at all age

groupings for hip and whole-body BMC, hip and spine BMD, and at two age groupings for spine BMC. For boys, there was a positive trend for regression coefficients for all measurements at all age groupings. Despite the authors' insistence that the lack of significant findings provides "no evidence that fluoride intakes have consequences for bone outcomes at age 11 years in girls or boys within these ranges (0.54-0.81 mg F/day; 0.12-0.18 mg/kg/day for average body weights 44-45 kg), it is important to remember the accumulative nature of fluoride in bones. These consistent trends—while perhaps not capable of reaching significance at the p-value ($p<0.01$) chosen for this study—are indicative of the onset of lifelong alterations in bone structure that will not be reversed as long as intakes of fluoride, even at the relatively low levels observed in this study, are continued. Thus the trend for increased BMC and BMD found in boys may be representative of the earliest pre-clinical stages of skeletal fluorosis (NRC, 2006), while the trend for decreasing BMC and BMD found in girls may be indicative of very early onset of osteoporosis, indicated by some authors to be aggravated by fluoride, even at relatively low levels (Krishnamachari, 1986; Jacobson et al., 1990; Cooper et al., 1991; Danielson et al., 1992; Kleerekoper, 1994).

Perhaps equally important is that the types of bones affected for girls in the Levy et al. (2009) show the same patterns in this study as have consistently been observed in clinical trials—i.e. density of the trabecular-rich axial skeleton (spine) is slightly increased (albeit not significantly), while the cortical-rich appendicular bone (hip) was decreased (often significantly). This is potentially quite significant since fluoride's differential effect on bone density has been considered a causative factor in the appendicular fractures (e.g. hip fractures) consistently observed in other studies. In other words, if low-level fluoride is capable of causing a differential effect on bone density, it means that low-level fluoride can reduce the integrity of cortical bone. This, in fact, is consistent with Phipps' (2000) finding of increased wrist fractures (wrists are almost entirely comprised of cortical bone), as well as the other epidemiological findings of increased hip fractures (since the strength of the hip is primarily dependent on cortical bone).

Also worth mentioning here is that the children included in the Levy et al. (2009) study were mostly White, of higher socioeconomic status (SES), and with relatively low fluoride intakes (Levy et al., 2009). However, as will be discussed in Section 2.6., certain minority groups and people of lower SES have statistically greater intakes of fluoride, and increased rates of dental fluorosis (including the more severe forms) than do whites or people of higher SES (Beltrán-Aguilar et al., 2005). It would be interesting to determine similar bone measurements for these groups, as it is possible that more extreme morphological alterations would be revealed in response to chronic fluoride intakes.

Chachra et al. (2010) compared the fluoride content and mechanical properties of bone specimens from citizens of either Montreal (non-fluoridated) or Toronto (fluoridated). The strength of the hip bones decreased as the fluoride content increased, a finding that the authors acknowledge is "consistent with some previous animal studies." While age

may possibly explain this finding (since the older a bone is, the higher its F content will be), the authors did not verify this one way or the other. Thus, as it stands, the study should serve as a major red flag, especially given that the patients in the study had only been exposed to fluoridation for about 30 years.

While a great deal of the focus on the studies that have been performed in fluoridated countries has been on the bone itself, it should not be forgotten that the first symptoms of skeletal fluorosis (e.g. stiffness and pains in the joints) may have more to do with fluoride's interaction with the connective tissue, than with the bone itself. Joint pain and stiffness have been reported by people who claim to be sensitive to fluoridated water at 1 ppm (Waldbott, 1998, post.). In Indian villages one of the ways villagers are tested for the early stages of skeletal fluorosis is to see if they can touch their chest with their chin, or if they can reach back and touch their fingers behind their necks (Chinoy, 2000).

3.2.5. Carcinogenicity

EPA should not delay any further a weight of evidence analysis of fluoride's potential to cause osteosarcoma (a frequently fatal bone cancer) in boys and young men (Bassin et al., 2006). Such an analysis is likely to show that fluoride meets the EPA's description of a chemical that is "Likely to be carcinogenic to humans" and thus force an MCLG of zero. We expect the EPA has delayed this analysis in the hope that a paper promised by Chester Douglass (Bassin's thesis advisor) for the Summer of 2006 would negate Bassin's findings, but that paper is long overdue (by nearly 5 years) and the methodology used is not capable of refuting Bassin's central finding (Neurath and Connett, 2008). Furthermore, the NRC (2006) evaluation of Bassin's work was based on her unpublished PhD dissertation. The NRC panel indicated that "more weight would be given to an assessment of fluoride as a human carcinogen" (NRC, 2006, p. 329) with peer-reviewed publication of these findings.

The EPA may have put itself and this country through a great deal of unnecessary extra work by failing to start with an analysis of whether the weight of evidence favors classifying fluoride as a known or probable human carcinogen. Such a finding would have forced setting the MCLG for fluoride at zero, like lead and arsenic, because according to the EPA there are no safe levels for human carcinogens.

In reference to the potential of fluoride to promote cancer, NRC wrote in 2006:

> Fluoride appears to have the potential to initiate or promote cancers, particularly of the bone, but the evidence to date is tentative and mixed (Tables 10-4 and 10-5). As noted above, osteosarcoma is of particular concern as a potential effect of fluoride because of (1) fluoride deposition in bone, (2) the mitogenic effect of fluoride on bone cells, (3) animal results described above, and (4) pre-1993 publication of some positive, as well as negative, epidemiologic reports on associations of fluoride exposure with osteosarcoma risk. (p. 336)

In 2001, Else Bassin, a graduate student at the Harvard Dental School, successfully defended her doctoral thesis, which included a case-control study that found young boys were at a 5- to 7-fold increased risk for developing osteosarcoma by the age of 20 when exposed to fluoridated water between 6 and 8 years of age (Bassin, 2001).

In response to the study by Bassin, NRC (2006) stated:

> A unique feature of the analysis published in the literature so far was an exploratory analysis of ORs (odds ratios) for each specific year of age. Bassin found elevated ORs for the highest tertile compared with the lowest centering on ages 6 to 8. At age 7, the respective ORs (and 95% confidence intervals) were 7.2 (1.7 to 30.0) for males and 2.0 (0.43 to 9.28) for females. For the highest tertile, graphed results for males indicated a gradual increase and then a decrease of estimated relative risk from exposure at ages 0 to 15 with peaks at age 7, with the middle tertile, compared with the lowest, showing stable ORs across all ages…
>
> …the highest ORs at ages 6 to 8, during what the author describes as the "mid-childhood growth spurt for boys," are consistent with some previous ecologic or semiecologic studies (Hoover et al., 1991; Cohn, 1992) and with a hypothesis of fluoride as an osteosarcoma risk factor operating during these ages. A publication based on the Bassin thesis is expected in the spring/summer of 2006 (E. Bassin, personal communication, Jan. 5, 2006). If this paper provides adequate documentation and analyses or the findings are confirmed by another study, more weight would be given to an assessment of fluoride as a human carcinogen. (p. 329)

NRC (2006) also commented on a related study conducted by Bassin's thesis adviser, Chester Douglass:

> A relatively large hospital-based case-control study of osteosarcoma and fluoride exposure is under way (Douglass, 2004) and is expected to be reported in the summer of 2006 (C. Douglass, Harvard School of Dental Medicine, personal communication, January 3, 2006). (p. 329)
>
> The results of the Douglass et al. multicenter osteosarcoma study (expected in the summer of 2006) could add important data to the current body of literature on fluoride risks for osteosarcoma because the study includes bone fluoride concentrations for cases and controls. When this study is published, it should be considered in context with the existing body of evidence to help determine what follow-up studies are needed. (p. 338)

In the nearly 5 years since the NRC made these observations, Bassin has published her research (Bassin et al., 2006). Within the same issue of the journal that Bassin's research was published, Douglass included a letter repeating his claim that his related study would not support Bassin's findings (Douglass and Joshipura, 2006). Although promoters of

fluoridation in several countries have used this unpublished, and un-peer-reviewed claim to deflect attention from Bassin's finding (sometimes giving the impression that Douglass's claim in the letter to *Cancer Causes and Control* was actually a published study), as of April 2011, the Douglass study has still not been published.

Moreover, examination of the methodology described by Douglass indicates that it is highly unlikely that findings from this research could discount Bassin's conclusions, as the biometric used for fluoride exposure is bone levels at diagnosis—which, being cumulative, can not be used to ascertain fluoride exposure during the critical 6^{th} to 8^{th} years that is at the heart of Bassin's findings. Another weakness in this study design that may be a further explanation as to why it has not yet been published, is that the controls used in Douglass's study were other bone cancers. Unless Douglass can rule out the possibility that fluoride causes any of these other bone cancers, this was a highly dubious control to choose (Neurath and Connett, 2008).

Furthermore, Douglass revealed an obvious bias towards water fluoridation—and against finding a link between fluoride and osteosarcoma—in a 1991 co-authored paper published as a cover article of the *Journal of the American Dental Association* (McGuire et al., 1999). This article made it very clear how a positive finding on osteosarcoma would end the water fluoridation program, as "Linkage of fluoride ingestion and cancer initiation could result in a large-scale defluoridation of municipal water systems under the Delaney clause," an outcome the authors declared would be "detrimental to the oral health of most Americans, particularly those who cannot afford to pay for increasingly expensive restorative dental care" (McGuire et al., 1999). Such a bias brings into question Douglass's study, the regulatory agencies who selected and funded a less-than-objective oral health researcher to perform a pivotal study on osteosarcoma, and the gullibility of those who wait for such a study to rescue the water fluoridation program.

Also attempting to delay or prevent the determination of carcinogenicity for fluoride is the American Dental Association, one of the most prominent promoters of fluoridation. In March 2009 the California Office of Environmental Health Hazard Assessment solicited public comments on thirty-eight chemicals selected for prioritization for evaluation by the state's Carcinogen Identification Committee. "Fluoride and its salts" were included, and in October the state announced that fluoride was one of five chemicals selected for consideration. A January 2010 bulletin from the Executive Director of the California Dental Association (CDA), states that the American Dental Association "granted CDA $200,000 to assist in our effort *to prevent the placement* of 'fluoride and its salts' on the List of Chemicals Known to the State to Cause Cancer or Reproductive Toxicity that is produced by the State of California, Environmental Protection Agency; Office of Environmental Health Hazard Assessment (OEHHA)." (our emphasis) (CDA, 2010).

If Bassin's findings are correct, young men with osteosarcoma are dying potentially because they were exposed to fluoridated water in their childhood. Despite the low overall incidence of osteosarcoma, the death of even a single person from this horrible cancer cannot be justified by the slight reduction of dental caries claimed by the

proponents of fluoridation. More innocent young men will continue to succumb to this disease the longer it takes for the EPA to make a judgment on this matter. Delaying a decision on the carcinogenicity of fluoride to protect the water fluoridation program is completely unacceptable.

The EPA should **immediately** proceed to a weight of evidence analysis on fluoride and osteosarcoma.

Bassin's is not the only study that raises the possibility that fluoride may cause osteosarcoma (NRC, 1977; NTP, 1990; Hoover et al. 1991; Cohn, 1992; Takahashi, 2001). In the event that Bassin's study cannot be refuted, the weight of evidence should qualify fluoride in the EPA's category of "Likely to Be Carcinogenic to Humans." Here is the EPA's own criteria for establishing that description:

"Likely to Be Carcinogenic to Humans"

This descriptor is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans." Adequate evidence consistent with this descriptor covers a broad spectrum. As stated previously, the use of the term "likely" as a weight of evidence descriptor does not correspond to a quantifiable probability. The examples below are meant to represent the broad range of data combinations that are covered by this descriptor; they are illustrative and provide neither a checklist nor a limitation for the data that might support use of this descriptor. Moreover, additional information, e.g., on mode of action, might change the choice of descriptor for the illustrated examples. Supporting data for this descriptor may include:

- an agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments (see comments of NRC, 2006, above);
- an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans;
- a positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy, or an early age at onset (see Bassin et al., 2006);
- a rare animal tumor response in a single experiment that is assumed to be relevant to humans (see NTP, 1990); or
- a positive tumor study that is strengthened by other lines of evidence, for example, either plausible (but not definitively causal) association between human exposure and cancer or evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case (see Hoover et al., 1991; Cohn, 1992; Takahashi et al, 2001; Bassin et al., 2006).

Published studies on fluoride and osteosarcoma satisfy four of these five descriptors.

In addition, NRC (2006) recommended that further research be conducted on the effects of fluoride on bladder cancer risk, and suggested that in vivo human genotoxicity studies be carried out within U.S. populations or populations having similar nutritional or sociodemographic variables.

3.2.6. Psychological effects of mild/moderate fluorosis

The proposed RfD of 0.08 mg F/kg/day is based on IOM's (1997) recommended AI for fluoride (0.05 mg/kg/day) for all persons >6 months. The decision that only doses above this level would be considered as points of departure for the drinking water component of an oral RfD analysis, means that OW selectively eliminated from consideration any doses less than 0.05 mg/kg/day as the threshold dose for severe dental fluorosis (EPA OW, 2010a, p. xv). This elimination of data was not based on evidence of lack of harm from dental fluorosis, nor was it based on lack of harm from other endpoints, as indicated above. In addition, by using only severe dental fluorosis as the endpoint of concern, OW is failing to protect Americans from the likely psychological damage caused by mild and moderate dental fluorosis.

According to H. Trendley Dean (the "father" of water fluoridation), moderate dental fluorosis discolors and disfigures 100% of the tooth enamel. Moderate and severe dental fluorosis combined currently impacts 3.6% of all American children aged 12-15 (Beltrán-Aguilar et al., 2010). NRC (2006) states "the committee finds that it is reasonable to assume that some individuals will find moderate enamel fluorosis on front teeth to be detrimental to their appearance and that it could affect their overall sense of well-being." (p. 5). According to NRC (2006), "only 24.2% of parents were satisfied with the color of their children's teeth when the TSIF score was 4 or greater (moderate or severe dental fluorosis), versus 73.9% satisfaction with not dental fluorosis." An ad-hoc panel of behavioral scientists convened by the U.S. EPA and the National Institute of Mental Health in 1984 to evaluate the psychological impacts of fluorosis concluded that "individuals who have suffered impaired dental appearance as a result of moderate and severe fluorosis are probably at increased risk for psychological and behavioral problems or difficulties" (Kleck RE, cited in 50 FR 20164, EPA, 1985; NRC, 2006, p. 119).

More recently, an article published in the *New York State Dental Journal*, concluded "that children's self-esteem is harmed by even mild fluorosis" (Dincer, 2008). Similarly, a recent review of 35 studies on this issue by Chankanka et al. (2010) found little evidence of anything but a negative reaction by sufferers or observers of moderate dental fluorosis.

3.3. OPP has unreasonably reduced the FQPA Safety Factor for cryolite to 1X.

By choosing an uncertainty factor of 1 (i.e. no uncertainty) for fluoride, and thus for cryolite, OPP has sharply deviated from EPA protocol. Simply because OW has erroneously concluded that fluoride does not require a margin of safety, OPP should not blindly follow suit. OW's refusal to include an uncertainty factor in the determination of an RfD for a nonessential element like fluoride, in order to protect an ill-conceived and presently invalid Adequate Intake (AI), should be brought into question by OPP.

Section 408(b)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FFDCA) provides that "EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children" (EPA OCSPP, 2011c, p. 7).

OPP states:

> "Given the relative completeness of the fluoride toxicology database, the use of a children-specific endpoint that is the most sensitive effect and well-documented outcome in the literature, the data indicating that there is a U-shaped dose-response curve for oral health, and our understanding of the potential exposure to fluoride, the OPP is reducing the FQPA Safety Factor to 1. (EPA OCSPP, 2011b, p. 5)
>
> "The susceptible population for the critical effect, severe dental fluorosis, is children. Since the RfD was derived based on data collected from the susceptible population and the assessment is evaluating this population group, the susceptibility of infants and children is being accounted for directly" (EPA OCSPP, 2011c, p. 7).

However, OPP is ignoring that OW refused to consider prenatal exposure or children less than 6 months of age in their analysis, and that the average fluoride intake for children less than 7 years of age would routinely exceed the proposed RfD of 0.08 mg F/kg/day (Table 5)—even if the contribution from sulfuryl fluoride is eliminated (as recommended by EPA, 2011b), and the estimated fluoride intake from drinking water is reduced from an average of 0.87 mg/L (as calculated by OW) to 0.7 mg/L (as recommended by DHHS, 2011) (see Table 1).

OW's abandoning normal safety factors in deriving an RfD for severe dental fluorosis is unacceptable, and should not be repeated by OPP. OW admits that its recent analysis is riddled with uncertainties: "Various physiological factors, such as calcium deficiency, co-exposure to certain minerals, malnutrition, respiratory or metabolic acidosis or alkalosis,

and various pathological conditions affecting urinary output and kidney function, may contribute to increases in the prevalence and severity of dental fluorosis...which may, in part, account for reports of high levels of fluorosis in some populations exposed to low levels of fluoride. These factors introduce an unquantifiable degree of uncertainty in interpreting dose-response data for fluoride-induced dental fluorosis" (EPA OW, 2010a, p. 36). Yet, OW continues to tout the presumed benefits of fluoride in order to avoid dealing with these uncertainties in a traditional manner—i.e. by incorporating uncertainty factors into its calculations.

Specifically, applying an uncertainty factor of 1 (i.e. applying no margin of safety) when extrapolating from a 70 year-old study (Dean, 1942) to an RfD designed to protect the whole U.S. population today is unjustifiable. OW acknowledges a number of weaknesses in Dean's data (EPA OW, 2010a, pp. 12-13), including a serious lack of data concerning: occurrence of dental caries; potential confounding factors (e.g. unique dietary fluoride intakes); drinking water intakes; differences in dental hygiene, dietary intakes, body weights, and puberty/hormonal condition; and differences in racial or ethnic susceptibility (i.e. only white children were included in Dean's study). For the data that were available, no statistical analysis was employed.

It is precisely because vulnerabilities to toxic substances vary so widely across a human population that a safety factor is applied to the LOAEL (lowest observable adverse effect level) in deriving an RfD; a dose supposedly safe for everyone. This safety factor is sometimes called an "uncertainty factor," and Dean's data clearly contains much uncertainty as far as extrapolating to the whole population is concerned. Factors that can affect vulnerabilities to toxic substances such as fluoride include racial and ethnic differences, age, nutritional and health status, income, and level of education. The only way that OW could take into account the deficiencies in Dean's data to adequately account for the full range of vulnerability is to apply an appropriate uncertainty factor. However the OW applied NO uncertainty factor to Dean's data, and thus undermined the credibility of its whole exercise.

OW is also in violation of the SDWA, which states that an adequate margin of safety must be applied. According to SWDA:

> "Each maximum contaminant level goal . . . shall be set at the level at which no known or anticipated adverse effects on the health of persons occur and *which allows an adequate margin of safety*." (our emphasis)

By reducing the Safety Factor of cryolite to 1, OPP is disregarding *all* of the uncertainties inherent in the risk assessment and dose-response analyses for fluoride, as well as those uncertainties associated with aluminum and aluminofluoride complexes. OPP should take seriously its role as protector of not only the American people, but of the whole of the American environment, and should increase the FQPA Safety Factor for cryolite.

3.5. OPP has ignored the necessity of several required studies of cryolite based on assumptions or inadequate data.

OPP has neglected to require several studies based on assumptions, instead of on sound scientific evidence. Included among these are the assumptions that aluminofluoride complexes are not important for ecological or health risk assessments, and that severe dental fluorosis is the critical effect of fluoride exposure—thus negating the need for studies of neurotoxicity or endocrine effects of cryolite or its degratation products or complexes. OPP also refuses to require dermal testing for this pesticide, despite that no testing has ever been completed. Additionally, OPP assumes that the toxic response of terrestrial and aquatic amphibians will mimic that of birds and fish, respectively, whereas amphibians have been repeatedly shown to be much more sensitive to environmental toxins than are most other vertebrates. OPP also assumes that no chronic exposure or reproductive testing is warranted for avian species because "chronic risk to birds is not expected" (EPA OCSPP, 2011a, p. 13), but does not consider that acute maternal exposure can translate to chronic embryonic exposure for all oviparous animals. OPP also refuses to acknowledge the importance of chronic toxicity testing for both terrestrial and aquatic animals, despite the relatively short Minimum Retreatment Interval for most crops.

*3.5.1. OPP should require that testing for adverse effects include cryolite and **all** of its degradation products and complexes.*

Cryolite degrades to fluoride, aluminum, and sodium in the environment, but according to OPP, the only degradation product of concern is fluoride, and the only effect of concern is severe dental fluorosis. While OPP is requiring that free ion concentrations of Al^{3+}, F^{-}, and Na^{+} be used to estimate toxicity, OPP is ignoring the effects of complexes formed from these ions.

OPP repeatedly states that cryolite is a naturally occurring mineral as part of its rationale for not requiring certain data (e.g. chronic risk for birds, EPA OCSPP, 2011a, pp. 5-6), and while cryolite does occur as a natural mineral, OPP acknowledges that "most present day supplies of cryolite pesticide products are synthetically produced" (EPA OCSPP, 2011a, p. 9). Synthetic cryolite may contain various impurities, some of which include aluminium oxide, aluminium fluoride, lithium fluoride, magnesium fluoride, calcium fluoride, quartz, and diiron trioxide (EU Draft Risk Assessment for Cryolite, 2008). According to the Materials Safety Data Sheet (MSDS) on synthetic cryolite produced by Solvay International (Solvay, 2003), degradation products may include fluoro-complexes (at acidic pH), hydroxy-aluminum (at environmental pH) and fluorhydric acid.

While OPP states that "the dissolution of cryolite to form sodium and the aluminum fluoride complex is expected to produce no significant chronic exposure" (EPA OCSPP, 2011a, p. 11), it is also acknowledged that the Agency has no data to support this statement: "In the hydrolysis study, aluminum speciation with fluoride or hydroxide was

not determined, equilibrium constants were not measured, and the results were not compared with those from scientific literature" (EPA OCSPP, 2011a, p. 10).

Aluminofluoride complexes, which are formed spontaneously in water containing fluoride and trace amounts of aluminum, have been found to stimulate various G proteins, and thus may "mimic or potentiate the action of numerous extracellular signals and significantly affect many cellular responses" (Strunecka and Patocka, 1999). Additionally, studies have shown that animals exposed to both fluoride and aluminum have higher mortality rates, as well as higher levels of aluminum in the brain, and altered cerebrovascular and neuronal integrity (Varner et al., 1998). Elevated levels of aluminum were also reported in the kidneys. According to the authors, "Since the kidney is critical to the elimination of both sodium and aluminum, such alterations may have influenced the body burden of these elements, detoxification in general, as well as homeostasis of a variety of important ions, such as calcium" (Varner et al., 1998).

Based on this information alone, OPP should immediately require that toxicity testing of cryolite be extended to include *all* of its degradation products, including the various aluminofluoride complexes formed under different aquatic conditions

3.5.2. OPP should require neurotoxicity testing for cryolite and all of its degradation products, including aluminofluoride complexes.

Fluoride has been implicated as a potential neurotoxin (see Section 2.3.1.; Appendix A), while aluminum is a known neurotoxin (e.g. Forbes et al., 2002; Savory et al., Unpublished; Bondy, 2010). OPP has unfortunately relied on OW's use of severe dental fluorosis as the most sensitive endpoint for fluoride exposure, stating that "more sensitive neurotoxic effects are not expected" (EPA, 16 Mar 2011, p. 5). However, OW was irresponsible in its analysis, in that it failed to consider the voluminous evidence of fluoride's potential to harm the developing brain, even at doses below that which cause severe dental fluorosis. Thus, OPP should also require that cryolite and its degradation products and complexes immediately be subjected to neurotoxicity testing.

OPP states that "Acute and subchronic neurotoxicity studies are not available for cryolite. However, neurotoxicity was not observed in the available cryolite studies" (EPA OCSPP, 2011b, p. 5). As neurological status can only be established by a combination of morphological, physiological and behavioral observations, simply assuming that neurotoxicity was not present because it was not readily observed in non-neurological tests is a major fallacy.

3.5.3. OPP should consider the endocrine disrupting potential of cryolite's degradation products and complexes.

That fluoride exposure can affect endocrine function is known (NRC, 2006), yet OPP has ignored these effects in its analysis. According to NRC (2006), fluoride is "an endocrine

disruptor in the broad sense of altering normal endocrine function" (p. 266), and aluminum has similarly been implicated as such (e.g. Correia et al., 2010) This altered function can be involve the thyroid, parathyroid, and pineal glands, as well as the adrenals, the pancreas, and the pituitary (NRC, 2006). Fluoride exposure in humans can lead to "elevated TSH with altered concentrations of T3 and T4, increased calcitonin activity, increased PTH activity, secondary hyperparathyroidism, impaired glucose tolerance, and possible effects on timing of sexual maturity." (NRC, 2006, p. 260). Several of these effects are associated with average intakes of 0.05 to 0.10 mg/kg/day (0.03 mg/kg/day with iodine deficiency)—the range wherein the OW's proposed RfD of 0.08 mg/kg/day lies.

OPP is obviously waiting for cryolite to be nominated for screening under the Endocrine Disruptor Screening Program (EDSP) prior to giving any consideration to fluoride's endocrine disrupting potential. While FFDCA sec. 408(p) states that EPA must screen all pesticide chemicals, neither cryolite nor fluoride are among the initial or secondary groups of pesticide active ingredients to be screened under the EDSP (EPA OCSPP, 2011b, p. 9), and we predict that their inclusion will not be forthcoming. OPP should no longer delay testing for endocrine disruption for cryolite or any of its degradation products or complexes, but should require that such tests be required as part of the Registration Review for cryolite.

3.5.4. OPP has failed to consider dermal routes of exposure.

OPP claims that there is no evidence to suggest a dermal route of exposure for cryolite. However, lack of evidence does not equate with lack of harm. OPP's failure to consider the potential for dermal exposure—especially among those directly handling the chemical—is negligent. According to the Material Safety Data Sheets (MSDS) for Prokil Cryolite 96 and Kryocide, two of the main cryolite products used in the United States, this chemical is "Harmful if…absorbed through skin" (Gowan, 2007; Cerexagri-Nisso, 2006), and that "Inhalation and skin contact are expected to be the primary routes of exposure to this material" (Cerexagri-Nisso, 2006). ATSDR (2003) states that "Dermal application of hydrofluoric acid results in rapid penetration of the fluoride ion into the skin" and that "reports suggest that hydrogen fluoride is quickly absorbed into the body following dermal exposure," although "these studies did not provide useful information concerning the extent of fluoride absorption, or information on absorption of smaller doses" (p. 139).

Despite that the European Union's Risk Assessment for Cryolite (2008) states there were "no data available" for dermal exposures in either human or animal studies, this risk assessment employed a "value of 10% for risk characterization by the dermal uptake route for animals and humans" (EU Risk Assessment for Cryolite, 2008, p. 88). OPP should follow this example, and use the Precautionary Principle regarding dermal exposure when determining if cryolite should be considered "safe" for the entire population.

3.5.5. OPP has failed to include amphibians in the Ecologial Risk Assessment.

As indicated by serious global population declines, amphibians are some of the most susceptible organisms to ecological perturbations. Scientists recognize amphibians as "valuable indicators of environmental stress" as they "experience both aquatic and terrestrial stressors; have moist, permeable skin and unshelled eggs that are directly exposed to soil, water, and sunlight and that readily absorb toxic substances" (Blaustein and Wake, 1995; Blaustein et al., 2003). Adverse effects have been observed for amphibians exposed to even low levels of pesticides. For example, repeated applications of the lowest concentration of malathion caused larger impacts on many of the response variables of *R. pipiens* than did single "pulse" applications 25 times greater (Relyea and Diecks, 2008). Yet OPP (and EPA in general) has failed to require toxicity testing for amphibians, despite that pesticides may play a significant role in amphibian reproductive abnormalities and population declines (Wake, 1991; Ouellet et al., 1997; Davidson et al., 2001; Sparling et al., 2001; Kiesecker et al., 2001; Blaustein et al., 2003; Blaustein and Bancroft, 2007; Davidson and Knapp, 2007; McCoy et al., 2008).

Studies have found that "the values for LC50, EC50, and minimal concentrations to inhibit growth (MCIG) of sodium fluoride met the limits established for a teratogen in frog embryos, showing that sodium fluoride is a direct acting teratogen on developing embryos" (Goh and Neff, 2003). Low dose endocrine disrupting effects, as observed in mammals exposed to fluoride (see NRC, 2006), "have not been addressed extensively in amphibians" (Hayes et al., 2002). Thus, "exposed animals could suffer impaired reproductive function [and] exposed populations could decline and even go extinct without any recognition of the developmental effects on individuals" (Hayes et al., 2002).

The teratogenicity of fluoride to amphibians is serious enough, but when these animals are also exposed to increased levels of aluminum—as results from the degradation of cryolite, especially in acidic environments—the results may be catastrophic. Studies have shown that aluminum often acts synergistically with pH to cause embryo mortality in embryos (Blaustein et al., 2003)—e.g. aluminum as low as 10-20 μg/L at pH 4.7 can cause reduced hatching success of *B. americanus* and *R. sylvatica* eggs (Clark and LaZerte, 1987)

3.5.6. OPP should require reproductive/developmental toxicity/teratogenicity testing for terrestrial and aquatic species.

OPP states that "avian reproduction data are not available for cryolite" (EPA OCSPP, 2011a, p. 5), but that none are required. OPP assumes that because cryolite is "practically nontoxic to avian species on an acute oral and sub-acute dietary basis" and is "no more than slightly toxic to small mammals on an acute oral basis" (EPA OCSPP, 2011a, p. 13), that chronic risk to birds and small mammals is not expected. As stated in the 1996 Reregistration Eligibility Decision (RED), "chronic risk is not a concern in this case as cryolite is not acutely toxic to birds and it is a naturally occurring mineral that is soluble in water." However, OPP acknowledges that "most present day supplies of cryolite

pesticide products are synthetically produced" (EPA OCSPP, 2011a, p. 9). Furthermore, while OPP states that "Toxicity of the introduced elements of cryolite (Al and F) is expected to be washed off food items into the soil" (EPA OCSPP, 2011b), the MSDS for synthetic cryolite states that bioconcentration of cryolite is possible, with "accumulation into vegetable leafs (fluorides)" (Solvay, 2003).

As it is well known that developing embryos and fetuses are much more vulnerable to toxins than is the adult form, and that fluoride is an endocrine disruptor (NRC, 2006) that may impact reproductive function, OPP should require reproductive/developmental toxicity/teratogenicity testing for all representative terrestrial and aquatic species exposed to cryolite and all of its degradation products and complexes.

OPP does not require reproductive testing for mammals based on "no increased fetal sensitivity noted in three developmental studies," and "no quantitative sensitivity" in the two-generation reproductive toxicity study (despite that qualitative sensitivity was noted) (EPA OCSPP, 2011b, p. 5). However, the European Union (EU) has taken a more active stance. According to EU's 2008 Draft Risk Assessment for Trisodium Hexafluoroaluminate (cryolite), "On the basis of the data submitted (two-generation reproduction toxicity study with rats) cryolite needs to be classified and labeled as a reproductive toxicant. The critical adverse effects that had been revealed were impairment of postnatal growth evidenced by significantly decreased pup body weights during lactation as well as gross pathological changes in several organs (kidney, liver, heart) of the pups resulting from dose levels without any significant systemic toxicity." (EU Risk Assessment for Cryolite, 2008).

For all oviparous species—including invertebrates, fish, amphibians, reptiles, and birds—acute exposure to cryolite (and its degradation products and complexes) of the female at the time of ovulation and fertilization potentially establishes a situation of chronic exposure for the duration of embryological development. Thus, although cryolite is considered "practically nontoxic" to adult avian species, a sub-acute level deposited into the egg could potentially expose the embryo to that same level throughout its critical development—a level that could significantly impact embryological development.

3.5.7. OPP should require chronic toxicity testing for aquatic animals.

OPP states that "Freshwater and marine fish and invertebrate chronic studies (e.g. early life-stage/life cycle tests) are not required because there are currently no registered aquatic uses" (EPA OCSPP, 2011a, p. 11). However, this discounts several factors inherent in the nature of cryolite application that may contribute to chronic aquatic exposure.

Cryolite is registered to be applied aerially, and thus "may reach estuarine/marine and freshwater environments through drift" (EPA OCSPP, 2011a, p. 11). Dissolution of cryolite in soil may also lead to its degradation products and complexes reaching water bodies via runoff/erosion or leaching into groundwater (EPA, 2010b, Figure 2, p. 17).

Most applications of cryolite occur during the active growing season, which includes the late spring and summer months. This time frame generally corresponds with decreased frequency of rainfall events and increased ambient temperatures, resulting in increased evaporation from water bodies. Thus, water bodies that consistently receive input from agricultural applications of cryolite, and which do not have another substantial and consistent source of inflow (e.g. some lakes, reservoirs, ponds, wetlands, and irrigation ditches) may experience increased concentrations of cryolite's degradation products and complexes, exposing aquatic animals to higher than expected levels. However, even low levels of pesticides (separate and combined) may dramatically impact wetland communities (Relyea, 2009).

Another factor that must be considered by OPP is that the Minimum Retreatment Interval (MRI) for the application of cryolite on most crops listed is only seven days (EPA, 2010a). For grapes, which constitute approximately 92% of all cryolite used in the United States (GfK Kynetec, 1998-2008, cited in EPA OCSPP, 2011a, p. 2), the MRI is 14 days (EPA, 2010a, pp.1-2). Thus, for the vast majority of cryolite applications, re-exposure of water bodies could potentially take place every 7-14 days. This would certainly constitute chronic exposure for organisms living in such aquatic environments, especially concerning those water bodies lacking constant flow.

3.6. OPP has failed to adequately consider Environmental Justice concerns.

According to OPP (EPA OCSPP, 2011b, p. 9), "The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S. (including different ages, regions, and ethnicities), and people who may be exposed when harvesting crops." However, there are a number issues regarding fluoride exposure that fall within the realm of environmental justice concerns that OPP has not addressed. Several sub-populations have been shown to be disproportionately harmed by fluoride's toxicity, including low-income people, certain minority groups, and infants and children.

OPP's recent aggregate risk assessment for fluoride was based on OW's analysis of fluoride, which included flawed methodology, inappropriate assumptions, and refusal to consider the voluminous scientific evidence indicating that the harmful effects of fluoride exposure extend beyond just the teeth. The decision by OPP to reduce the FQPA Safety Factor for fluoride to 1X was determined via similar parameters, based largely on OW's findings.

However, as discussed in Section 2.4., OW's use of a safety factor of 1 is scientifically unjustified. OW defends their use of an uncertainty factor of 1 as follows:

> In establishing an estimated oral RfD for fluoride, data on nutritional benefit were assessed in combination with the data on severe dental fluorosis to define a level that provides anticaries protection without causing severe dental fluorosis when consumed daily for a lifetime. Conventional application of uncertainty factors is not always appropriate when carrying out a risk assessment for nutrients and other beneficial substances, especially when there is a relatively small difference between the levels that satisfy need and those that cause adverse effects. For this reason the total uncertainty factor applied was 1. (EPA OW, 2010a, p. 105)

By using a safety factor of 1, OW is claiming that the full range of sensitivity to fluoride among the American population in 2011—with its vast spectrum of racial, ethnic, and socioeconomic groups—was completely accounted for by a study of approx 5000 children in the 1930s. This is quickly countered by the fact that all children in the Dean (1942) study were white. However, numerous studies indicate that black children are more susceptible to dental fluorosis (and probably other harmful effects of fluoride) than are white children. Using an uncertainty factor of 1 here is tantamount to perpetrating environmental *in*justice against black children.

The National Research Council 1993 Review (NRC, 1993) reported four earlier studies showing that ethnicity plays a role in the effects of fluoride:

• Russell (1962), in the Grand Rapids fluoridation study, noted that fluorosis was twice as prevalent among African-American children as white children.
• In the Texas surveys in the 1980s, the odds ratio for African-American children having dental fluorosis, compared with Hispanic and non-Hispanic white children, was 2.3 (Butler et al., 1985).
• Dental fluorosis also tended to be more severe among African-American children than white children in the Georgia study (Williams and Zwemer, 1990), although the difference was not statistically significant.
• In Kenya, prevalence and number of severe cases were unexpectedly high when related to fluoride concentrations in drinking water (Manji et al., 1986), although nutritional factors could have confounded these results. The reasons for these findings are unknown and do not seem to have been explored further.

Data published in CDC's Morbidity and Mortality Weekly Report in 2005 (Beltrán-Aguilar et al., 2005) show that Black and Mexican Americans have significantly higher levels of the worst forms of dental fluorosis than do Whites, as shown in Table 5.

	Unaffected		Questionable		Very mild		Mild		Moderate/Severe	
Characteristic	%†	SE§	%	SE	%	SE	%	SE	%	SE
Age group (yrs)										
6–11	59.81	4.07	11.80	2.50	19.85	2.12	5.83	0.73	2.71	0.59
12–15	51.46	3.51	11.96	1.84	25.33	1.98	7.68	0.93	3.56	0.59
16–19	58.32	3.30	10.21	1.70	20.79	1.78	6.65	0.67	4.03	0.77
20–39	74.86	2.28	8.83	1.23	11.15	1.22	3.34	0.58	1.81	0.39
Sex										
Male	67.65	2.63	9.99	1.45	15.65	1.52	4.58	0.54	2.12	0.39
Female	66.97	2.84	9.83	1.34	15.58	1.36	4.84	0.61	2.78	0.49
Race/Ethnicity¶										
White, non-Hispanic	69.69	3.13	10.43	1.62	14.09	1.56	3.87	0.60	1.92	0.48
Black, non-Hispanic	56.72	3.30	10.40	2.16	21.21	2.16	8.24	0.82	3.43	0.54
Mexican-American	65.25	3.89	8.95	1.29	15.93	2.24	5.05	0.72	4.82**	1.81
Poverty status††										
<100% FPL	68.02	3.21	10.67	1.64	14.28	1.73	4.07	0.69	2.97	0.66
100%–199% FPL	66.92	2.91	9.11	1.79	16.11	1.46	5.21	0.78	2.65	0.56
≥200% FPL	66.88	2.75	10.73	1.33	15.56	1.56	4.83	0.50	2.00	0.37
Total	**67.40**	**2.65**	**9.91**	**1.35**	**15.55**	**1.37**	**4.69**	**0.49**	**2.45**	**0.40**

* Using Dean's index. All estimates are adjusted by age (single years) and sex to the U.S. 2000 standard population, except sex, which is adjusted only by age.
† Weighted prevalence estimates.
§ Standard error.
¶ Calculated using "other race/ethnicity" and "other Hispanic" in the denominator.
** Unreliable estimate: the standard error is 30% the value of the point estimate, or greater.
†† Percentage of the Federal Poverty Level (FPL), which varies by income and number of persons living in the household.

Table 5. Enamel fluorosis* among persons aged 6-39 years, by selected characteristics—United States, National Health and Nutrition Examination Survey, 1999-2002. Source: Beltrán-Aguilar et al., 2005.

While EPA acknowledges the results of a study by Sohn et al. (2001) that "Fluid intake was significantly associated with age, sex, socioeconomic status, and race and ethnicity," OW failed to include this association in its risk assessment (EPA OW, 2010a). Sohn et al. (2001) states "The effect of race or ethnicity and socioeconomic status (SES) on fluid consumption were particularly noticeable," with African American children consuming significantly more plain water and less milk than other racial or ethnic groups (white

children consumed the least amount of total fluid and plain water), and children from the low SES group consuming significantly more plain water and less milk than higher SES groups. A paper in the 2009 *Journal of Public Health Dentistry* reviewed the available research and concluded that "African-American children, and/or children of lower SES, are ingesting significantly more fluoride than children who are higher on the social scale. They may be therefore at higher risk for fluorosis." (Sohn et al., 2009)

There may be several reasons why black children are more susceptible to developing dental fluorosis than white children. In addition to ingesting more fluoride (as indicated above) it may also reflect dietary differences. Some black children are lactose intolerant and therefore have less protective calcium and less vitamin D in their diets. Dark pigmentation reduces the synthesis of Vitamin D in the skin at a given level of sunlight, and reduction of sunlight by inner-city pollution may be a further factor. Another possible association was raised by Leite et al. (2011). In this study the authors found that rats treated with both lead and fluoride had worse dental fluorosis than rats treated with fluoride alone. Thus it is possible that children from inner city areas that have already been compromised with lead exposure will be more susceptible to developing dental fluorosis. One can only assume that OW did not recognize the lack of Environmental Justice inherent in its use of an uncertainty factor of 1. However, whether it realized it or not, in developing this RfD in this manner, OW simply failed to protect vulnerable minorities in the population. This is clearly in violation of a U.S. Executive Order (12898, 1994) and one of the stated goals of EPA administrator Lisa Jackson (EPA, 2011a).

OPP should be aware that there are gross disparities in the racial and socioeconomic demographics of agricultural laborers—those most directly affected by the application of cryolite to crops. Approximately 97% of all agricultural usage of cryolite in the United States is in California (GfK Kynetec, 1998-2008; EPA OCSPP, 2010, p. 2). According to the National Agricultural Workers Survey of 2005, 99% of all farmworkers interviewed in California were Hispanic. Forty-three percent of all individual farmworkers, and 30% of farmworker families earned less than $10,000 per year, and 22% of California farmworkers had annual incomes below the federal poverty level (Aguirre International, 2005).

4. Conclusions

For the many reasons submitted above, FAN calls for a phase out of the use of cryolite as a pesticide on food. The most important reason is that the OPP has itself established that children under 7 years of age are already exceeding the newly proposed RfD for fluoride (a known residue left with cryolite applications) from a combination of existing sources. As FAN believes that this RfD of 0.08 mg/kg/day was derived by OW with inadequate and sometimes inappropriate assumptions, and that this RfD should and will be lowered, the situation with cryolite will become even more untenable. The only possible way that this situation may be relieved is for the major source of fluoride—namely, the practice of water fluoridation—to be eliminated.

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Appendix A

Selected studies published since the release of the National Research Council report, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*, in March 2006.
Also available at http://www.fluoridealert.org/since-nrc.html

Year	Rough Category	Study	Journal
2011	Apoptosis	Wang Z, et al. 2011. Sodium fluoride suppress proliferation and induce apoptosis through decreased insulin-like growth factor-I expression and oxidative stress in primary cultured mouse osteoblasts. "**All the tested NaF inhibited proliferation and arrested cell cycle at S phase in osteoblasts, and further demonstrated to induce apoptosis in osteoblasts. On the other hand, we found that NaF increased oxidative stress and decreased protein expression of IGF-I.** Our study herein suggested that NaF caused proliferation suppression, and apoptosis may contribute to decrease IGF-I expression and increased oxidative stress damage by NaF in the primary mouse osteoblasts."	Arch Toxicol. 2011 Apr 2. [Epub ahead of print] Abstract
2011	Apoptosis	Rocha RA, et al. 2011. Arsenic and fluoride induce **neural progenitor cell** apoptosis.	Toxicol Lett. Mar 22. [Epub ahead of print] Abstract
2011	Apoptosis	Sun Z, et al. 2011. Fluoride-induced apoptosis and gene expression profiling in **mice sperm in vivo**.	Arch Toxicol. 2011 Feb 22. [Epub ahead of print] Abstract
2011	Apoptosis	Andrade-Vieira LF, et al. 2011. Spent Pot Liner (SPL) induced **DNA damage** and nuclear alterations in root tip cells of Allium cepa as a consequence of programmed cell death.	Ecotoxicol Environ Saf. 2011 Jan 11. [Epub ahead of print] Abstract
2011	Apoptosis	Yan X, et al. 2011. Fluoride induces apoptosis and alters collagen I expression in **rat osteoblasts.**	Toxicol Lett. 200(3):133-8. Feb 5. Abstract
2011	Apoptosis	Xu B, et al. 2011. Effects of the Fas/Fas-L pathway on fluoride-induced apoptosis in **SH-SY5Y cells**.	EnvironToxicol. 26(1):86-92. Feb. Abstract
2011	Apoptosis	Madusudanan Rao S, et al. 2011. Morphometry of buccal mucosal cells in fluorosis - a new paradigm. "Conclusions: **Fluorosis induces oxidative stress, DNA damage and apoptosis** which can be the reasons for the increase in the nuclear size and decrease in the cell size."	Hum Exp Toxicol. Mar 15. [Epub ahead of print] Abstract
2010	Apoptosis	Gutiérrez-Salinas J, et al. 2010. Exposure to	Int J Mol Sci. 11(9):3610-
2010	Apoptosis	Gutiérrez-Salinas J, et al. 2010. Exposure to sodium fluoride produces signs of apoptosis in **rat leukocytes**.	Int J Mol Sci. 11(9):3610-22. Sept. 27. Full Text Article

2010	Apoptosis	Jacinto-Alemán LF, et al. 2010. In vitro effect of sodium fluoride on antioxidative enzymes and apoptosis during **murine odontogenesis**.	J Oral Pathol Med. 39(9):709-14. Oct. Abstract
2010	Apoptosis	Gutowska I, et al. 2010. Fluoride as a pro-inflammatory factor and inhibitor of ATP bioavailability in differentiated human THP1 monocytic cells. "The incubation of macrophages in fluoride solutions significantly decreased the amount of synthesized cellular ATP and **increased formation of ROS and apoptosis in a dose-dependent pattern**."	Toxicology Letters 196: 74-9. Abstract
2010	Apoptosis	Lu J, et al. 2010. Proteomics analysis of liver samples from puffer fish Takifugu rubripes exposed to excessive fluoride: an insight into molecular response to fluorosis. "… Consistent with their previously known functions, **these identified proteins seem to be involved in apoptosis and other functions associated with fluorosis**. These results will greatly contribute to our understanding of the … **toxicological mechanism of fluoride causing fluorosis in both fish and human**."	J Biochem Mol Toxicol. 24(1):21-8. Jan-Feb. Abstract
2010	Apoptosis	Salgado-Bustamante M, et al. 2010. Pattern of expression of apoptosis and inflammatory genes in **humans exposed to arsenic and/or fluoride**.	Sci Total Environ. 408(4):760-7. Jan 15. Abstract
2009	Apoptosis	Karube H, et al. 2009. NaF activates MAPKs and induces apoptosis in **odontoblast-like cells**.	J Dent Res. 88(5):461-5. May. Abstract
2009	Apoptosis	Yan X, et al. 2009. Effects of sodium fluoride treatment in vitro on cell proliferation, apoptosis and caspase-3 and caspase-9 mRNA expression by **neonatal rat osteoblasts**.	Arch Toxicol. 83(5):451-8. May. Abstract
2009	Apoptosis	Herai M, et al. 2009. Induction of apoptosis in **human gingival epithelial cells** by sodium fluoride.	Fluoride 42(1):3-8. Jan–March. Full Report
2009	Apoptosis	Wang H, et al. 2009. Effects of dietary protein and calcium on **thymus** apoptosis induced by fluoride in **female rats (**Wistar rats).	Environ Toxicol. 24(3):218-24. June. Abstract
2008	Apoptosis	Lee JH, et al. 2008. Involvement of both mitochondrial- and death receptor-dependent apoptotic pathways regulated by Bcl-2 family in sodium fluoride-induced apoptosis of the **human gingival fibroblasts**.	Toxicology 243(3):340–7. Jan 20. Abstract
2008	Apoptosis	Tsai CL, et al. Wu PC. 2008. Induction of apoptosis in **rabbit oral mucosa** by 1.23% acidulated phosphate fluoride gel.	Arch Toxicol. 82(2):81-7. Feb. Abstract

2008	Apoptosis	Chouhan S, et al. 2008. Effects of fluoride on the tissue oxidative stress and apoptosis in **rats**: biochemical assays supported by IR spectroscopy data.	Toxicology 5;254(1-2):61-7. Dec. Abstract
2007	Apoptosis	Yan Q, Zhang Y, Li W, Denbesten PK. 2007. Micromolar fluoride alters **ameloblast lineage cells** in vitro.	J Dent Res. 86(4):336-40. April. Abstract
2007	Apoptosis	Liu K, et al. 2007. Fluoride-mediated apoptosis and disordering of cell cycle distributions during in vitro organ culture of **mouse fetal long bones**.	Fluoride 40(1):19–23. Jan-March. Full Report
2007	Apoptosis	Guney M, et al. 2007. Effect of fluoride intoxication on **endometrial** apoptosis and lipid peroxidation in rats: role of vitamins E and C.	Toxicology. 231(2-3):215-23. March 7. Abstract
2007	Apoptosis	Huang C, et al. 2007. Toxic effects of sodium fluoride on **reproductive function in male mice**.	Fluoride 40(3):162-8. July-Sept. Full Report
2007	Apoptosis	Matsui H, et al. 2007. Some characteristics of fluoride-induced cell death in **rat thymocytes**: Cytotoxicity of sodium fluoride.	Toxicol in Vitro 21(6):1113-20. Sept. Abstract
2007	Apoptosis	Zhang M, et al. 2007. Effects of fluoride on the expression of NCAM, oxidative stress, and apoptosis in **primary cultured hippocampal neurons**.	Toxicology 236(3):208-16. July 17. Abstract
2006	Apoptosis	Yu RA, et al. 2006. Effects of selenium and zinc on **renal** oxidative stress and apoptosis induced by fluoride in rats.	Biomed Environ Sci. 19(6):439-44. Dec. Abstract
2006	Apoptosis	Xu H, et al. 2006. Effect of sodium fluoride on the expression of bcl-2 family and osteopontin in rat **renal** tubular cells.	Biol Trace Elem Res. 109(1):55-60. Jan. Abstract
2006	Apoptosis	He LF, Chen JG. 2006. DNA damage, apoptosis and cell cycle changes induced by fluoride in **rat oral mucosal cells and hepatocytes**.	World J Gastroenterol. 12(7):1144-8. Feb 21. Full Report
2006	Apoptosis	Ge Y, et al. 2006. Apoptosis in **brain cells of offspring rats** exposed to high fluoride and low iodine.	Fluoride 39(3);173-8. July-Sept. Full Report
2005	Apoptosis	Otsuki S, et al. 2005. Possible link between **glycolysis** and apoptosis induced by sodium fluoride.	J Dent Res. 84(10):919-23. Oct. Abstract
2005	Apoptosis	Sun G, Zhang Y, Sun X. 2005. Experimental study of fluoride toxicity **onosteoblasts during bone formation**. Paper presented at the XXVIth. ISFR conference in Wiesbaden, Germany.	Fluoride 38(3). Sept. See Abstract No. 48.
2005	Apoptosis	Sun G, Zhang Y, Sun X. 2005. Experimental study of fluoride toxicity **onosteoblasts during bone formation**. Paper presented at the XXVIth. ISFR conference in Wiesbaden, Germany.	Fluoride 38(3). Sept. See Abstract No. 48.

2005	Apoptosis	Jiang CX, et al. 2005. [**Relationship between spermatogenic cell apoptosis and serum estradiol level** in rats exposed to fluoride]	Wei Sheng Yan Jiu. 34(1):32-4. January. [Article in Chinese] Abstract
2011	Asthma	Donoghue AM, et al. 2011. Occupational asthma in the aluminum smelters of Australia and New Zealand: 1991-2006. "RESULTS: The incidence of occupational asthma across all smelters combined was highest in 1992 at 9.46/1,000/year, declining to 0.36/1,000/year in 2006; a 96.2% reduction. **The incidence of occupational asthma was correlated with geometric mean total fluoride concentration**, measured as personal samples from employees undertaking anode changing (r(s) □=□0.497, P□<□0.001)."	Am J Ind Med. 54(3):224-31. Mar. Abstract
2010	Asthma	Abramson MJ, et al. 2010. Is potroom asthma due more to sulphur dioxide than fluoride? An inception cohort study in the Australian aluminium industry. "… SO(2) exposure was significantly associated with these symptoms, bronchial hyper-responsiveness (BHR) to methacholine (a feature of asthma), airflow limitation (reduced forced expiratory volume in 1 second/forced vital capacity ratio) and longitudinal decline in lung function. Fluoride exposure was associated with the same outcomes, but less strongly… further modelling suggested that of the known respiratory irritants, SO(2) was more likely than fluoride to be primarily responsible for the symptoms observed. **Fluoride, inhalable dust and SO(2) were the most important airborne contaminants associated with effects on lung function**."	Occup Environ Med. Oct;67(10):679-85. Abstract
2006	Asthma	Taiwo OA, et al. 2006. Incidence of asthma among **aluminum workers**.	J Occup Environ Med. 48(3):275-82. March. Abstract
2011	Blood	Amini H, et al. 2011. Drinking Water Fluoride and Blood Pressure? An Environmental Study. "… **Statistically significant positive correlations were found between the mean concentrations of F in the GWRs [ground water resources] and the hypertension prevalence of males** (r□=□0.48, p□=□0.007), females (r□=□0.36, p□=□0.048), and overall (r□=□0.495, p□=□0.005). Also, statistically significant positive correlations between the mean concentrations of F in the GWRs and the mean SBP [systolic blood pressure] of males (r□=□0.431, p□=□0.018)…"	Biol Trace Elem Res. Apr 12. [Epub ahead of print] Abstract
2011	Blood	Amini H, et al. 2011. Drinking Water Fluoride and Blood Pressure? An Environmental Study. "… **Statistically significant positive correlations were found between the mean concentrations of F in the GWRs [ground**	Biol Trace Elem Res. Apr 12. [Epub ahead of print] Abstract

2010	Blood	Sawan RMM, et al. 2010. **Fluoride increases lead concentrations** in whole blood and in calcified tissues from lead-exposed rats.	Toxicology 271(1-2): 21-6. April 30. Abstract
2010	Blood	Gutiérrez-Salinas J, et al. 2010. Exposure to sodium fluoride produces signs of apoptosis in **rat leukocytes**.	Int J Mol Sci. 11(9):3610-22. Sept 27. Abstract
2010	Blood	Feng P, et al, 2010. Influence of selenium and fluoride on blood antioxidant capacity of rats. "**Fluorosis could induce the decline of blood antioxidant capacity and the fluidity of erythrocyte membrane, as evident in this study,** and Se at different levels possess some antagonistic effects on blood induced by fluoride."	Exp Toxicol Pathol. Dec 10. [Epub ahead of print] Abstract
2009	Blood	Gutowska I, et al. 2009. Changes in the concentration of fluoride and biogenic elements in the **serum** and bones **of female rats** with stretozotocin-induced diabetes. "In our research we observed a **statistically significant increase in the concentration of F in the bones of the diabetic rats, with a simultaneous decrease in the concentration of this element in serum**."	Fluoride 42(1):9-16. Jan-March. Full Report
2007	Blood	Grucka-Mamczar E, et al. 2007. Influence of extended exposure to sodium fluoride and caffeine on the activity of carbohydrate metabolism enzymes in **rat blood serum and liver**. "… Glycolysis in extra-hepatic tissues (serum), under the influence of F, was slightly inhibited; however, it was markedly intensified by caffeine. **Overall, a more profound influence by caffeine on carbohydrate enzyme activity was observed in blood serum (extra-hepatic tissues) than in the liver**."	Fluoride 40(1)62–66. Jan-March. Full Report
2006	Blood	Opydo-Szymaczek J, et al. 2006. Variations in concentration of fluoride in blood plasma of **pregnant women** and their possible consequences for amelogenesis in a fetus. "… Mean value of fluoride concentration in the samples of blood plasma from the 28th week of pregnancy was lower than the mean concentration detected in the 33rd week of pregnancy (**3.29 and 3.73mumol/l, respectively**). These values suggest that apart from drinking water, there were other important sources of fluoride in the examined sample. **The results indicate that a reliable assessment of fluoride exposure in a given population cannot be based solely on the**	Homo. 57(4):295-307. Abstract
2006	Blood	Opydo-Szymaczek J, et al. 2006. Variations in concentration of fluoride in blood plasma of **pregnant women** and their possible consequences for amelogenesis in a fetus. "… Mean value of fluoride concentration in	Homo. 57(4):295-307. Abstract

2006	Blood	Shanthakumari D, et al. 2006. Antioxidant defense systems in **red blood cell lysates of men with dental fluorosis** living in Tamil Nadu, India.	Fluoride 39(3):231–9. July-Sept. Full Report
2005	Blood	Connett M. 2005. Blood fluoride levels as a **tool for assessing risk of fluoride toxicity**. Paper presented at the XXVIth. ISFR conference in Wiesbaden, Germany, September.	Fluoride 38(3):226. See Abstract Number 9
2005	Blood	Ruiz-Payan A, et al. 2005**. Chronic effects** of fluoride on growth, **blood chemistry**, and thyroid hormones in adolescents residing in northern Mexico. Paper presented at the XXVIth Conference of the International Society for Fluoride Research (September 26-29).	Fluoride 38(3):246. Full Article (see Abstract Number 37)
2005	Blood	Xiang Q, et al. 2005. **Serum fluoride and skeletal fluorosis** in two villages in Jiangsu Province, China.	Fluoride 38(3):178–84. Full Report
2011	Bone	Chen L, et al. 2011. Medication-induced periostitis in lung transplant patients: periostitis deformans revisited. " We report five cases of **diffuse periostitis resembling hypertrophic osteoarthropathy** and **perostitis deformans** in lung transplantation patients **on chronic voriconazole, a fluoride-containing compound**…"	Skeletal Radiol. 40(2):143-8. Feb. Abstract
2011	Bone	Wang Z, et al. 2011. Sodium fluoride suppress proliferation and induce apoptosis through decreased insulin-like growth factor-I expression and oxidative stress in primary cultured mouse osteoblasts. "**All the tested NaF inhibited proliferation and arrested cell cycle at S phase in osteoblasts, and further demonstrated to induce apoptosis in osteoblasts. On the other hand, we found that NaF increased oxidative stress and decreased protein expression of IGF-I.** Our study herein suggested that NaF caused proliferation suppression, and apoptosis may contribute to decrease IGF-I expression and increased oxidative stress damage by NaF in the primary mouse osteoblasts."	Arch Toxicol. 2011 Apr 2. [Epub ahead of print] Abstract
2011	Bone	Yan X, et al. 2011. Fluoride induces apoptosis and alters collagen I expression in **rat osteoblasts.**	Toxicol Lett. 200(3):133-8. Feb 5. Abstract
2010	Bone	Sawan RMM, et al. 2010. **Fluoride Increases Lead Concentrations in Whole Blood and in Calcified Tissues from Lead-Exposed**	Toxicology 271(1–2): 21–26. Abstract
2010	Bone	Sawan RMM, et al. 2010. **Fluoride Increases Lead Concentrations in Whole Blood and in Calcified Tissues from Lead-Exposed Rats**.	Toxicology 271(1–2): 21–26. Abstract

2010	Bone	Itai K, et al. 2010. Serum ionic fluoride concentrations are related to renal function and menopause status but not to age in a Japanese general population. "Conclusion: SIF [serum ionic fluoride] concentrations in middle-aged healthy subjects were increased with an age-related degeneration in renal function. **SIF concentrations in post-menopausal women arise from the increased fluoride release from bone after menopause. Age is not related to SIF concentrations."**	Clinica Chimica Acta 411: 263–266. Abstract
2010	Bone	Tu J, et al. 2010. Interactive effect of fluoride burden with calcitonin receptor gene polymorphisms on the risk of **F bone injury**. "In this **case-control study, a total of 119 cases and 126 controls were enrolled from 2 aluminum plants in Hubei province**. F burden (UF) was measured by F ion-selective electrode method… RESULTS: The odds of developing F bone injury for participants in the moderate F burden group versus the mild F burden group were 4.1 (95% CI: 1.9, 8.7); the heavy F burden group versus the mild F burden group were 14.1 (95% CI: 6.5, 30.6). The odds of developing F bone injury for participants with the TC & TT genotypes versus the CC genotype were 2.6 (95% CI: 1.4, 4.7). The interactions between TC & TT genotypes and moderate, heavy F burden were significant (OR = 14.4; OR = 40.3). CONCLUSION: The interactive effect of F burden and CTR genotype was significant, which increased the F bone injury risk."	Int Arch Occup Environ Health. Nov 25. [Epub ahead of print] Abstract
2010	Bone	Song YE, et al. 2010. Effect of fluoride exposure on **bone metabolism indicators ALP, BALP, and BGP**.	Environ Health Prev Med. 2010 Oct 2. [Epub ahead of print] Abstract
2010	Bone	Shalina TI, Vasil'eva LS. 2010. [**Femoral bone morphogenesis in human fetuses** in the area of environmental fluoride pollution]. "… In the town of Shelekhov, located closely to the pollution source, the **growth of bones in both length and width, is delayed**. The bone growth was active till week 16, however, **during weeks 18-29, osteoresorption prevailed over the osteosynthesis, the bone thickness decreased, while the activity of their growth in length remained reduced**."	Morfologiia. 137(1):54-7. [Article in Russian] Abstract
2010	Bone	Xu H, et al. 2010. Activation of PERK signaling through fluoride-mediated	Toxicology 277(1-3):1-5. Nov 9.
2010	Bone	Xu H, et al. 2010. Activation of PERK signaling through fluoride-mediated endoplasmic reticulum stress in OS732 cells. "… **This study proved that PERK signaling play major roles in action of fluoride on**	Toxicology 277(1-3):1-5. Nov 9. Abstract

2009	Bone	Levy SM, et al. 2009. **Associations of fluoride intake with children's bone measures at age 11**. "… In gender-stratified, and body size- and Tanner stage-adjusted linear regression analyses, associations between girls' bone outcomes and fluoride intake for girls were almost all negative; **associations for boys were all positive and none was statistically significant when using an alpha = 0.01 criterion**…"	Community Dent Oral Epidemiol. 37(5):416-26. Oct. Abstract
2009	Bone	Gutowska I, et al. 2009. Changes in the concentration of fluoride and biogenic elements in the serum and **bones of female rats** with stretozotocin-induced diabetes. "In our research we observed a **statistically significant increase in the concentration of F in the bones of the diabetic rats, with a simultaneous decrease in the concentration of this element in serum**."	Fluoride 42(1):9-16. Jan-March. Full Report
2008	Bone	Qu W, et al. 2008. Sodium fluoride modulates **caprine osteoblast proliferation and differentiation**.	J Bone Miner Metab 26(4):328-34. July. Abstract
2007	Bone	Tamer MN, et al. 2007. **Osteosclerosis** due to endemic fluorosis.	Sci Total Environ. 373(1):43-8. Feb 1. Abstract
2007	Bone	Tang Q, et al. 2007. Effect of fluoride on expression of pura gene and CaM gene in **newborn rat osteoblasts**.	Fluoride 40(1):31-6. Jan-March. Full Report
2007	Bone	Chavassieux P, et al. 2007. Insights into material and structural basis of bone fragility from diseases associated with fractures: how determinants of the biomechanical properties of bone are compromised by disease. **"fluorosis and osteomalacia"**	Endocrine Reviews 28(2):151–64. Abstract
2007	Bone	Hallanger Johnson JE, et al. 2007. **Fluoride-related bone disease** associated with habitual tea consumption. Figure 1. Lateral lumbar spine showing advanced osteosclerosis of the vertebral bodies, with absence of usual marrow space radiolucency	Mayo Clin Proc. 82(6):719-24. June. • Erratum in: Mayo Clin Proc. 2007 Aug;82(8):1017. dosage error in text. Full Text
2007	Bone	Kakei M, et al. 2007. Effect of fluoride ions on **apatite crystal formation in rat hard tissues**.	Ann Anat. 189(2):175-81. Abstract
2006	Bone	Bouletreau PH, et al. 2006. Fluoride exposure and **bone status** in patients with **chronic**	Am J Clin Nutr. 83(6):1429-37. June.
~~2006~~	~~Bone~~	Bouletreau PH, et al. 2006. Fluoride exposure and **bone status** in patients with **chronic intestinal failure** who are receiving home parenteral nutrition. • TABLE 3. Spinal bone status	Am J Clin Nutr. 83(6):1429-37. June. Full Article

2006	Bone	Claassen H, et al. 2006. Extracellular matrix changes in **knee joint cartilage** following bone-active drug treatment.	Cell Tissue Res. 324(2):279-89. May. Abstract
2006	Bone	Harinarayan CV, et al. 2006. **Fluorotoxic metabolic bone disease:** an osteo-renal syndrome caused by excess fluoride ingestion in the tropics.	Bone 39(4):907-14. Oct. Abstract
2006	Bone	Clarke E, et al. 2006. **Fluorosis as a probable cause of chronic lameness in free ranging eastern grey kangaroos** (Macropus giganteus). "… The significant lesions observed were: osteophytosis of the distal tibia and fibula, tarsal bones, metatarsus IV, and proximal coccygeal vertebrae; osteopenia of the femur, tibia, and metatarsus IV; incisor enamel hypoplasia; stained, uneven, and abnormal teeth wear; abnormal bone matrix mineralization and mottling; increased bone density; and elevated bone fluoride levels. Microradiography of affected kangaroos exhibited "**black osteons**," which are a known manifestation of fluorosis. Collectively, these lesions were consistent with a diagnosis of fluorosis."	J Zoo Wildl Med. Dec;37(4):477-86. Abstract
2005	Bone	Nyman JS, et al. 2005. Effect of ultrastructural **changes on the toughness of bone**.	Micron 36(7-8):566-82. Abstract
2005	Bone	Roos J, Dumolard A, Bourget S, Grange L, Rousseau A, 2005. [**Osteofluorosis caused by excess use of toothpaste**.] [Article in French].	Presse Med. 34(20 Pt 1):1518-20. Nov. Abstract
2011	Brain: *Animal Studies*	Ge Y, et al. 2011. **Proteomic Analysis of Brain Proteins of Rats Exposed to High Fluoride and Low Iodine**.	Archives of Toxicology Arch Jan;85(1):27-33. Abstract
2011	Brain: *Animal Studies*	Pereira M, et al. 2011. **Memory Impairment** Induced by Sodium Fluoride Is Associated with Changes in Brain Monoamine Levels.	Neurotoxicity Research 19(1):55-62. Jan. Abstract
2011	Brain: *Animal Studies*	Zhu W, et al. 2011. Effects of Fluoride on Synaptic Membrane Fluidity and PSD-95 Expression Level in **Rat Hippocampus**.	Biological Trace Element Research 139, no 2, 197-203. Feb. Abstract
2010	Brain: *Animal Studies*	Narayanaswamy M, et al. 2010. Effect of maternal exposure of fluoride on biometals and oxidative stress parameters in **developing CNS of rat**. "The results confirm that the fluoride provoked oxidative stress and biometal deformations are	Biol Trace Elem Res. 133(1):71-82. Jan. Abstract
2010	Brain: *Animal Studies*	Narayanaswamy M, et al. 2010. Effect of maternal exposure of fluoride on biometals and oxidative stress parameters in **developing CNS of rat**. "The results confirm that the fluoride provoked oxidative stress and biometal deformations are	Biol Trace Elem Res. 133(1):71-82. Jan. Abstract

2010	Brain: *Animal Studies*	Basha PM, et al. 2010. Evaluation of Fluoride-Induced Oxidative Stress in Rat Brain: A **Multigeneration Study**.	Biol Trace Elem Res. Jul 24. [Epub ahead of print] Abstract
2010	Brain: *Animal Studies*	Basha PM, et al. 2010. Pre and Post Natal Exposure of Fluoride Induced Oxidative Macromolecular Alterations in **Developing Central Nervous System of Rat** and Amelioration by Antioxidants.	Neurochemical Research, 1017–28. Mar. Abstract
2010	Brain: *Animal Studies*	Bouaziz H, et al. 2010. Fluoride-Induced **Brain Damages in Suckling Mice**.	Pesticide Biochemistry and Physiology 96: 24–29.
2010	Brain: *Animal Studies*	Chouhan S, et al. 2010. Fluoride-induced Changes in Haem Biosynthesis Pathway, Neurological Variables and Tissue Histopathology of Rats. "… changes were accompanied by depletion in GSH:GSSG ratio, **whole brain biogenic amine levels** and a dose-dependent increase in fluoride concentration. **Interestingly and most significantly, these changes were more pronounced at lower concentrations of fluoride compared with higher fluoride dose**…"	Journal of Applied Toxicology 30(1): 63–73. Abstract
2010	Brain: *Animal Studies*	Gui C Z, et al. 2010. Changes of Learning and Memory Ability and **Brain Nicotinic Receptors** of Rat Offspring with Coal Burning Fluorosis.	Neurotoxicology and Teratology 32(5):536-41. Sep-Oct. Abstract
2010	Brain: *Animal Studies*	Kaoud H and Kalifa B. 2010. Effect of **Fluoride, Cadmium and Arsenic Intoxication on Brain and Learning-Memory Ability in Rats**.	Toxicology Letters 196, suppl. 1 (2010): S53 (abstract from the XII International Congress of Toxicology).
2010	Brain: *Animal Studies*	Li H, et al. 2010. Toxic Effects of Fluoride on **Rat Cerebral Cortex Astrocytes** in Vitro.	Wei Sheng Yan Jiu 39(1): 86–88. Abstract (Article in Chinese)
2010	Brain: *Animal Studies*	Liu YJ, et al. 2010. Alterations of nAChRs and ERK1/2 in the Brains of Rats with Chronic Fluorosis and Their Connections with the **Decreased Capacity of Learning and Memory**.	Toxicology Letters 192(3): 324–29. Abstract
2010	Brain: *Animal Studies*	Zhang J, et al. 2010. Effect of Fluoride on Calcium Ion Concentration and Expression of Nuclear Transcription Factor Kappa-B Rho65 in **Rat Hippocampus**.	Experimental and Toxicologic Pathology [in press; available online March 19, 2010].
2009	Brain:	Bharti VK and Srivastava RS. 2009**. Fluoride-**	Biological Trace Element
2009	Brain: *Animal Studies*	Bharti VK and Srivastava RS. 2009**. Fluoride-induced Oxidative Stress in Rat's Brain** and Its Amelioration by Buffalo (Bubalus Bubalis) Pineal Proteins and Melatonin.	Biological Trace Element Research 130(2): 131–40. Abstract

2009	Brain: *Animal Studies*	Flora SJ, et al. 2009. **Co-exposure to Arsenic and Fluoride on Oxidative Stress**, Glutathione Linked Enzymes, Biogenic Amines and DNA Damage in Mouse Brain.	Journal of the Neurological Sciences 285(1–2): 198–205. Abstract
2009	Brain: *Animal Studies*	Gao Q, et al. 2009. **Decreased Learning and Memory Ability in Rats with Fluorosis: Increased Oxidative Stress and Reduced Cholinesterase Activity**.	Fluoride 42(4): 277–85. Full Report
2009	Brain: *Animal Studies*	Kaur T, et al. 2009. **Effect of Concurrent Chronic Exposure of Fluoride and Aluminum on Rat Brain**.	Drug and Chemical Toxicology 32(3):215–21. Abstract
2009	Brain: *Animal Studies*	Madhusudhan N, et al. 2009. Fluoride-induced Neuronal Oxidative Stress Amelioration by Antioxidants in Developing Rats.	Fluoride 42(3):179–87. Full Report
2009	Brain: *Animal Studies*	Niu R, et al. 2009. **Decreased Learning Ability and Low Hippocampus Glutamate in Offspring** Rats Exposed to Fluoride and Lead.	Environmental Toxicology and Pharmacology 28:254–58.
2009	Brain: *Animal Studies*	Whitford GM, et al. 2009. Appetitive-based Learning in Rats: Lack of Effect of Chronic Exposure to Fluoride. Note: This is the **only study reported "no significant effect on appetitive-based learning."**	Neurotoxicology and Teratology 31(4):210–15. Abstract
2008	Brain: *Animal Studies*	Chioca LR, et al. 2008. Subchronic Fluoride Intake Induces **Impairment in Habituation and Active Avoidance Tasks** in Rats.	European Journal of Pharmacology 579(1–3):196–201. Abstract
2008	Brain: *Animal Studies*	Chouhan S, et al. 2008. Effects of Fluoride on the **Tissue Oxidative Stress and Apoptosis** in Rats: Biochemical Assays Supported by IR Spectroscopy Data.	Toxicology 254(1–2):61–67. Abstract
2008	Brain: *Animal Studies*	Niu R, et al. 2008. Effects of Fluoride and Lead on Locomotor Behavior and Expression of **Nissl Body in Brain of Adult Rats**.	Fluoride 41(4):276–82. Full Report
2008	Brain: *Animal Studies*	Sun ZR, et al. 2008. Effects of High Fluoride Drinking Water on the **Cerebral Functions** of Mice.	Fluoride 41(2):148–51 . Full Report
2008	Brain: *Animal Studies*	Wu N, et al. 2008. Behavioral Teratology in Rats exposed to Fluoride. "Brain slices in the 25 mg/L group also showed **a significantly lower average cerebral cortex thickness than in the control group** (10.97 μm vs. 11.70 μm).]	Fluoride 41(2):129–133 Full Report
2008	Brain: *Animal Studies*	Zhang M, et al. 2008. Effects of Fluoride on DNA Damage, S-phase Cell-cycle Arrest and the Expression of NF-KappaB in **Primary Cultured Rat Hippocampal Neurons**.	Toxicology Letters 179(1):1–5. Abstract

2008	Brain: *Animal Studies*	Zhang Z, et al. 2008. Effect of Fluoride Exposure on **Synaptic Structure of Brain Areas Related to Learning-memory in Mice**.	Fluoride 41(2):139–43. Full Report
2007	Brain: *Animal Studies*	Bera I, et al. 2007. **Neurofunctional Effects** of Developmental Sodium Fluoride Exposure in Rats.	European Review for Medical and Pharmacological Sciences 11(44):211–24. Abstract
2007	Brain: *Animal Studies*	Chirumari K and Reddy PK. 2007. Dose-Dependent Effects of Fluoride on Neurochemical Milieu in the **Hippocampus and Neocortex** of Rat Brain.	Fluoride 40(2):101–10. Full Report
2007	Brain: *Animal Studies*	Ge Y, et al. 2007. Apoptosis in Brain Cells of Offspring Rats **Exposed to High Fluoride and Low Iodine**.	Fluoride 39(3):173–78. Full Report
2007	Brain: *Animal Studies*	Xia T, et al. 2007. Effects of Fluoride on Neural Cell Adhesion Molecules mRNA and Protein Expression Levels in **Primary Rat Hippocampal Neurons**.	Zhonghua Yu Fang Yi Xue Za Zhi 41(6):475–78. (Article in Chinese) Abstract
2007	Brain: *Animal Studies*	Zhang M, et al. 2007. Effects of Fluoride on the Expression of NCAM, Oxidative Stress, and Apoptosis in **Primary Cultured Hippocampal Neurons** [rat].	Toxicology 236(3):208–16. Abstract
2006	Brain: *Animal Studies*	Bhatnagar M, et al.. 2006. **Biochemical Changes in Brain** and Other Tissues of Young **Adult Female Mice** from Fluoride in their Drinking Water.	Fluoride 39(4):280–84. Full Report
2005	Brain: *Animal Studies*	Ge Y, Ning H, Wang S, and Wang J. 2005. Comet Assay of **DNA Damage in Brain Cells** of Adult Rats Exposed to High Fluoride and Low Iodine.	Fluoride 38(3):209–14. Full Report
2005	Brain: *Animal Studies*	Krechniak J and Inkielewicz I. 2005. Correlations Between Fluoride **Concentration and Free Radical Parameters** in Soft Tissues of Rats.	Fluoride 38(4):293–96. Full Report
2005	Brain: *Animal Studies*	Tsunoda M, et al. 2005. Changes in **Fluoride Levels** in the Liver, Kidney, and Brain and in Neurotransmitters of Mice after Subacute Administration of Fluorides.	Fluoride 38(4):284–92. Full Report
2008	Brain: ***Human Fetal Studies***	Du L, et al. 2008. **The Effect of Fluorine on the Developing Human Brain**.	Fluoride 41(4):327–30. Full Report
2008	Brain: *Human Fetal*	He H, et al. 2008. **Effects of Fluorine on the Human Fetus.**	Fluoride 41(4):321–26. Full Report
2008	Brain: *Human Fetal Studies*	He H, et al. 2008. **Effects of Fluorine on the Human Fetus.**	Fluoride 41(4):321–26. Full Report

2008	Brain: *Human Fetal Studies*	Yu Y, et al. 2008. Neurotransmitter and Receptor **Changes in the Brains of Fetuses** from Areas of Endemic Fluorosis.	Fluoride 41(2):134–38. Full Report
2009	Brain: ***Children Study***	Rocha-Amador D, et al. 2009. Use of the Rey-Osterrieth Complex Figure Test for **neurotoxicity evaluation of mixtures in children**. "…The highest proportion of children (89%) with Copy performance below _1 SD was observed in **children from F–As area**. Approximately 9 out of 10 children were unable to copy the ROCF as expected for their age. For example, the expected score on Copy for a 6-year-old child is 9.94 _ 2.28 points. A child classified in the category below _1 SD means that his score was lower than 7.66. In the F–As area children had z-scores as low as _5 SD (scoring only two points on the test). For Immediate Recall, the proportion of children in the lowest category was 59% and almost 6 out of 10 children were unable to draw the figure as expected for their age after 3 min had elapsed. Following the same example of a 6-year-old child, the expected value for drawing the figure from memory is 7.26 _ 2.45. One child classified in the _1 SD category had a score below 4.81 points. Fluoride correlated inversely with Copy and Immediate Recall r = _0.29 and r = _0.27 (adjusted values). In the F–As area, the mean of FU was 5.6 _ 1.7 and the proportion of children with FU levels over 2 mg/gcrt was 97.5%. **All children had some degree of dental fluorosis as an indicator of chronic exposure to fluoride**…"	Neurotoxicology 30(6):1149-54. Nov. Abstract
2008	Brain: ***Infant Study***	Li J, et al. 2008. Effects of High Fluoride on Neonatal Neurobehavioral Development.	Fluoride 41(2):165–70. Full Report
2008	Brain: ***Workers Study***	Z. Guo Z, et al. 2008. Research on the Neurobehavioural Function of Workers Occupationally Exposed to Fluoride.	Fluoride 41(2):152–55. Full Report
2011	Brain: *Human IQ Studies*	Ding Y, et al. 2011. The **relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas** in Hulunbuir, Inner Mongolia, China.	Journal of Hazardous Materials 186:1942–1946. Abstract
2010	Brain: *Human IQ Studies*	• *Xiang Q, et al. 2010. **Serum Fluoride Level and Children's Intelligence Quotient** in Two Villages in China.* *Note: this is good paper initially accepted for publication by EHP and put online Dec 17. However, EHP withdrew the report because certain data was published by the lead author in another publication.*	*Accepted for publication in Environmental Health Perspectives, and pre-published online December 17.* *- available from FAN.*
2008	Brain: *Human IQ Studies*	Chen Y, et al. 2008. Research on the **Intellectual Development of Children in High Fluoride Areas**	Fluoride 41(2):120–24. Full Report

2008	Brain: *Human IQ Studies*	Guo X, et al. 2008. A Preliminary Investigation of the **IQs of 7–13 Year Old Children** from an Area with Coal Burning-Related Fluoride Poisoning.	Fluoride 41(2):125–28. Full Report
2008	Brain: *Human IQ Studies*	Hong F, et al. 2008. Research on the Effects of Fluoride on **Child Intellectual Development** Under Different Environmental Conditions.	Fluoride 41(2):156–60. Full Report
2008	Brain: *Human IQ Studies*	Liu S, et al. 2008. Report on the **Intellectual Ability of Children Living in High-Fluoride Water Areas**.	Fluoride 41(2):144–47. Full Report
2008	Brain: *Human IQ Studies*	Qin L, et al. 2008. Using the Raven's Standard Progressive Matrices to Determine the Effects of the Level of Fluoride in Drinking Water on the **Intellectual Ability of School-Age Children**.	Fluoride 41(2):115–19. Full Report
2008	Brain: *Human IQ Studies*	Ren D, et al. 2008. A Study of **the Intellectual Ability of 8–14 Year-Old Children** in High Fluoride, Low Iodine Areas.	Fluoride 41(4):319–20. Full Report
2008	Brain: *Human IQ Studies*	Wang G, et al. 2008. A Study of the **IQ Levels of Four- to Seven-Year-Old Children** in High Fluoride Areas.	Fluoride 41(4): 340–43. Full Report
2008	Brain: *Human IQ Studies*	Wang S, et al. 2008. The Effects of Endemic Fluoride Poisoning Caused by Coal Burning on the **Physical Development and Intelligence of Children**.	Fluoride 41(4): 344–48. Full Report
2007	Brain: *Human IQ Studies*	Rocha-Amador D, et al. 2007. **Decreased Intelligence in Children and Exposure to Fluoride and Arsenic** in Drinking Water.	Cadernos de Saúde Pública 23(suppl. 4): S579–87. Full Report
2007	Brain: *Human IQ Studies*	Seraj B, et al. 2007. **Effect of High Fluoride Concentration in Drinking Water on Children's Intelligence**.	Journal of Dental Medicine 19(2):80–86. English translation (from lead author).
2007	Brain: *Human IQ Studies*	Trivedi MH, et al. 2007. Effect of High Fluoride Water on Intelligence of School Children in India.	Fluoride 40(3):178–83, Full Report
2007	Brain: *Human IQ Studies*	Wang SX, et al. 2007**. Arsenic and Fluoride Exposure in Drinking Water: Children's IQ and Growth** in Shanyin County, Shanxi Province, China.	Environmental Health Perspectives 115(4):643–47. Full Report
2007	Brain: *Human IQ Studies*	Fan ZX, et al. 2007. Effect of **High Fluoride Exposure on Children's Intelligence**.	Huan Jing Yu Jian Kang Za Zhi 24(10): 802–3. (Article in Chinese)
2011	Brain: ***Other***	Xu B, et al. 2011. Effects of the **Fas/Fas-L pathway** on fluoride-induced apoptosis in SH-SY5Y cells.	Environ Toxicol. 26(1):86-92. Feb. Abstract
2010	Brain: ***Other***	Lockwood G. 2010. Theoretical context-sensitive elimination times for **inhalation anaesthetics**.	Br J Anaesth. 104(5):648-55. May. Abstract
2010	Brain: ***Other***	Lockwood G. 2010. Theoretical context-sensitive elimination times for **inhalation anaesthetics**.	Br J Anaesth. 104(5):648-55. May. Abstract

Note from FAN: Desflurane, Sevoflurane and Isoflurane all break down to the fluoride ion

2009	Brain: ***Other***	Wann BP, et al. 2009. Effect of Olfactory Bulbectomy on **Adenylyl Cyclase Activity in the Limbic System**.	Brain Research Bulletin 79(1):32–36. Abstract
2009	Brain: ***Other***	García-Montalvo EA, et al. 2009. Fluoride Exposure Impairs Glucose Tolerance Via Decreased Insulin Expression and Oxidative Stress. "Interestingly, **values of F− in soft rat tissues (kidney, liver, brain and testis) were similar to those in urine (312 µmoll−1).** According to this information, urinary F− level is a good indicator of the F− concentration in soft tissues. In cases of subchronic exposure, the level of F− in the plasma probably does not reflect the levels of F− distributed in soft tissues."	Toxicology 263:75–83. Abstract
2008	Brain: ***Other***	Gao Q, et al. 2008. Oxidative Stress Might Be a Mechanism Connected with the Decreased Alpha 7 **Nicotinic Receptor** Influenced by High-Concentration of Fluoride in **SH-SY5Y Neuroblastoma Cells**.	Toxicology in Vitro 22(4):837–43. Abstract (Corrigendum in Toxicology in Vitro 22: 1814. The concentrations of fluoride should have been given as mM, instead of µM.)
2008	Brain: ***Other***	Liu M, et al. 2008. Effect of endemic fluorosis on **children's intelligence development: a Meta analysis**. [Article in Chinese]	Zhongguo Dang Dai Er Ke Za Zhi.10(6):723-5. Dec. Abstract
2009	Co-exposure: Aluminum	Kaur T, et al. 2009. Effect of Concurrent Chronic Exposure of Fluoride and Aluminum on Rat Brain. **Effects were "more pronounced in animals given fluoride and aluminum together** …it can be concluded that **aluminum appears to enhance the neurotoxic hazards caused by fluoride**."	Drug Chem Toxicol. 32(3):215-21. Abstract
2009	Co-exposure: Aluminum	Kant V, et al. 2009. Alterations in biochemical parameters during subacute toxicity of fluoride alone and in conjunction with aluminum sulfate in goats. "… On the basis of results, it could be concluded that **sodium fluoride alone and in conjunction with aluminum sulfate produced significant alterations in the various biochemical parameters of the body**."	Biol Trace Elem Res. Jul;130(1):20-30. Abstract
2006	Co-exposure: Aluminum	Lubkowska A, et al. 2006. The effect of alternating administration of aluminum chloride and sodium fluoride in drinking water on the concentration of fluoride in serum and	Ann Acad Med Stetin. 52 Suppl 1:67-71. [Article in Polish] Abstract
2006	Co-exposure: Aluminum	Lubkowska A, et al. 2006. The effect of alternating administration of aluminum chloride and sodium fluoride in drinking water on the concentration of fluoride in serum and its content in bones of rats.	Ann Acad Med Stetin. 52 Suppl 1:67-71. [Article in Polish] Abstract

2007	Co-exposure: Aluminum	Manoharan V, et al. 2007. Interactive effects of soil acidity and fluoride on soil solution aluminium chemistry and barley (Hordeum vulgare L.) root growth. *Note from FAN: this is relevant in regards to Dow AgroSciences 2010 proposal to use sulfuryl fluoride as a soil fumigant.* "Increasing rates of F additions to soil significantly increased the soil solution concentrations of aluminium (Al) and F irrespective of the initial adjusted soil pH, which ranged from 4.25 to 5.48… The results suggested that continuous input of F to soils, and increased soil acidification, may become an F risk issue in the future."	Environ Pollut. Feb;145(3):778-86. Abstract
2011	Co-exposure: Arsenic	Flora SJ, et al. 2011. **Interactive effect of arsenic and fluoride on cardio-respiratory disorders in male rats**: possible role of reactive oxygen species.	Biometals. Jan 18. [Epub ahead of print] Abstract
2011	Co-exposure: Arsenic	Rocha RA, et al. 2011. **Arsenic and fluoride induce neural progenitor cell apoptosis**.	Toxicol Lett. Mar 22. [Epub ahead of print] Abstract
2010	Co-exposure: Arsenic	Kaoud H and Kalifa B. 2010. Effect of **Fluoride, Cadmium and Arsenic Intoxication on Brain and Learning-Memory Ability in Rats**. "… These results suggest that learning-memory ability and brain function in rats are affected by HiF, HiCd and HiAs and that oxidative stress in the brain may be one of the causes of this damage."	Toxicology Letters 196, suppl. 1 (2010): S53 (abstract from the XII International Congress of Toxicology).
2010	Co-exposure: Arsenic	Salgado-Bustamante M, et al. 2010. **Pattern of expression of apoptosis and inflammatory genes in humans exposed to arsenic and/or fluoride**.	Sci Total Environ. 408(4):760-7. Jan 15. Abstract
2009	Co-exposure: Arsenic	Flora SJ, et al. 2009. **Co-exposure to Arsenic and Fluoride on Oxidative Stress**, Glutathione Linked Enzymes, Biogenic Amines and DNA Damage in Mouse Brain.	Journal of the Neurological Sciences 285(1–2): 198–205. Abstract
2007	Co-exposure: Arsenic	Rocha-Amador D, et al. 2007. **Decreased Intelligence in Children and Exposure to Fluoride and Arsenic in Drinking Water**.	Cadernos de Saúde Pública 23(suppl. 4): S579–87. Full Report
2007	Co-exposure: Arsenic	Wang SX, et al. 2007**. Arsenic and Fluoride Exposure in Drinking Water: Children's IQ and Growth** in Shanyin County, Shanxi Province, China.	Environmental Health Perspectives 115(4):643–47. Full Report
2006	Co-exposure: Arsenic	Mittal M and Flora SJ. 2006. Effects of individual and combined exposure to sodium arsenite and sodium fluoride on tissue	Chem Biol Interact. 25;162(2):128-39. Aug. Abstract
2006	Co-exposure: Arsenic	Mittal M and Flora SJ. 2006. Effects of individual and combined exposure to sodium arsenite and sodium fluoride on tissue oxidative stress, **arsenic and fluoride levels in male mice**.	Chem Biol Interact. 25;162(2):128-39. Aug. Abstract

2011	Co-exposure: Lead	Leite GA, et al. 2011. Exposure to lead exacerbates dental fluorosis. "This study shows that **lead exacerbates dental fluorosis in rodents, suggesting that co-exposure to lead may affect the degree of fluorosis**."	Arch Oral Biol. 2011 Jan 24. [Epub ahead of print] Abstract
2010	Co-exposure: Lead	Sawan RMM, et al. 2010. **Fluoride increases lead concentrations** in whole blood and in calcified tissues from lead-exposed rats.	Toxicology 271(1-2): 21-6. April 30. Abstract
2009	Co-exposure: Lead	Niu R, et al. 2009. **Decreased Learning Ability and Low Hippocampus Glutamate in Offspring** Rats Exposed to Fluoride and Lead.	
2008	Co-exposure: Lead	Liu H, et al. 2008. **Changes caused by fluoride and lead** in energy metabolic enzyme activities in the reproductive system of **male offspring rats**.	Fluoride 41(3):184-91. July-Sept. Full Article
2007	Cytotoxicity	Matsui H, et al. 2007. Some characteristics of fluoride-induced cell death in **rat thymocytes:** cytotoxicity of sodium fluoride.	Toxicol In Vitro. 21(6):1113-20. Sept. Abstract
2005	Cytotoxicity	Satoh R, et al. 2005. Changes in fluoride sensitivity during in vitro senescence of normal **human oral cells**.	Anticancer Res. 25(3B):2085-90. May-June. Abstract
2009	Dental Caries	Warren JJ, et al. 2009. Considerations on optimal fluoride intake and dental caries outcomes--a longitudinal study. "… These findings suggest that achieving a caries-free status may have relatively little to do with fluoride *intake*, while fluorosis is clearly more dependent on fluoride intake … CONCLUSIONS: Given the overlap among caries/fluorosis groups in mean fluoride intake and extreme variability in individual fluoride intakes, firmly recommending an "optimal" fluoride intake is problematic."	J Pub Health Dent 69(2): 111-115. Abstract
2007	Dental Caries	Broffitt L, et al. 2007. **An investigation of bottled water use and caries in the mixed dentition**.	Journal of Public Health Dentistry 67(3):151-8. Abstract
2007	Dental Caries	Cheng KK, et al. 2007. Adding fluoride to	British Medical Journal

2007	Dental Caries	Maupomé G, et al. 2007. A comparison of dental treatment utilization and costs by HMO members living in fluoridated and nonfluoridated areas. In the largest region examined in the study, representing over 75% of the HMO members surveyed (the Portland metro area of Oregon), fewer children and adults in the non-fluoridated areas required treatment than children and adults in the fluoridated areas. Moreover, the children and adults in the non-fluoridated area who sought treatment accrued lower total costs over the 5-year period than those in the fluoridated area. As noted by the authors, the "**Portland metro had lower treatment costs for the NF (Non-Fluoridated) area**..."	Journal of Public Health Dentistry 67(4):224-33.
2007	Dental Caries	Pizzo G, et al. 2007. **Community water fluoridation and caries prevention: a critical review.** "For the past 50 years, CWF (Community Water Fluoridation) has been considered the most cost-effective measure for the control of caries at the community level. However, it is now accepted that systemic fluoride plays a limited role in caries prevention. Several epidemiologic studies conducted in fluoridated and nonfluoridated communities clearly indicated that CWF may be unnecessary for caries prevention, particularly in the industrialized countries where the caries level has [become] low."	Clinical Oral Investigations 11(3):189-93.
2006	Dental Caries	Burt BA, et al. 2006. Dietary patterns related to caries in a **low-income adult population**. "This population had severe caries, poor oral hygiene, and diets that are high in sugars and fats and low in fruits and vegetables… **Interventions to promote oral health are unlikely to be successful without improvements in the social and physical environment**."	Caries Res. 40(6):473-80. Abstract
2005	Dental Caries	Neurath C. 2005. Tooth decay **trends in nonfluoridated and fluoridated countries.**	Fluoride 38(4):324–5. Nov. Full Report
2011	Dental Fluorosis	Leite GA, et al. 2011. Exposure to lead exacerbates dental fluorosis. "This study shows that **lead exacerbates**	Arch Oral Biol. 2011 Jan 24. [Epub ahead of print] Abstract
2011	Dental Fluorosis	Leite GA, et al. 2011. Exposure to lead exacerbates dental fluorosis. "This study shows that **lead exacerbates dental fluorosis in rodents, suggesting that co-exposure to lead may affect the degree of**	Arch Oral Biol. 2011 Jan 24. [Epub ahead of print] Abstract

2011	Dental Fluorosis	Riksen EA, et al. 2011. Fluoride reduces the expression of enamel proteins and cytokines in an ameloblast-derived cell line. "Conclusions. **These results indicate that fluoride may impact on the expression of structural enamel proteins and the protease responsible for processing these proteins during the secretory stage of amelogenesis** and go some way to explaining the mineralization defect that characterises fluorotic enamel."	Arch Oral Biol. 56(4): 324-330. April. Abstract
2011	Dental Fluorosis	Jiménez-Farfán MD, et al. 2011. Fluoride consumption and its impact on oral health. "CONCLUSIONS: Data from our study show that**, despite values of excretion within an optimal fluoride intake range, the prevalence of caries was significant in both groups, and 60% of the 11- to 12-year-old children presented with dental fluorosis**. In addition, **variable fluoride concentrations in products frequently consumed by children were found**."	Int J Environ Res Public Health. 8(1):148-60. Jan. Full Article
2010	Dental Fluorosis	Beltran-Aguilar ED, et al. 2010. Prevalence and severity of dental fluorosis in the United States, 1999-2004. See Table 23. **Mexican-Americans and Black Americans had significantly higher levels of moderate dental fluorosis compared to White Americans** and **Mexican-Americans had significantly higher levels of severe dental fluorosis** compared to Black or White Americans.	NCHS data brief, no 53. Hyattsville, MD: National Center for Health Statistics. Full Report (See Table 23)
2010	Dental Fluorosis	Choubisa SL, et al. 2010. Osteo-dental fluorosis in relation to age and sex in tribal districts of Rajasthan, India. "… **males showed relatively a higher incidence of dental and skeletal fluorosis compared to their counterparts**…"	J Environ Sci Eng. 52(3):199-204. July. Abstract
2010	Dental Fluorosis	Levy SM, et al. 2010. Associations between fluorosis of permanent incisors and fluoride intake from infant formula, other dietary sources and dentifrice during early childhood. "CONCLUSIONS: **Greater fluoride intakes from reconstituted powdered formulas (when participants were aged 3-9 months) and other water-added beverages (when participants were aged 3-9 months) increased fluorosis risk**, as did higher	Journal of the American Dental Association 141(10):1190-1201. Abstract
2010	Dental Fluorosis	Levy SM, et al. 2010. Associations between fluorosis of permanent incisors and fluoride intake from infant formula, other dietary sources and dentifrice during early childhood. "CONCLUSIONS: **Greater fluoride intakes**	Journal of the American Dental Association 141(10):1190-1201. Abstract

2010	Dental Fluorosis	Martinez-Mier EA, et al. 2010. **Differences in exposure and biological markers of fluoride among White and African American children**.	Journal of Public Health Dentistry 70:234–240. Abstract
2010	Dental Fluorosis	Verkerk RH. 2010. The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. "Conventional risk assessment on fluoride as undertaken by European and US authorities is explored in detail, and **it is shown that risk management, if applied by public authorities in a manner which is consistent with that used for other nutrients, would make public drinking water fluoridation programmes unfeasible in light of dental fluorosis risk to children**."	Toxicology 278(1):27-38. Nov 28. Abstract
2009	Dental Fluorosis	Sohn W, et al. 2009. Fluoride ingestion is related to fluid consumption patterns. "…African-American children ingested significantly more fluoride than White children in bivariate analysis. This association remained significant after accounting for fluid consumption pattern and other confounding factors in the model. CONCLUSION: Our results raise concerns that some children are ingesting significantly more fluoride than others depending on sociodemographic factors and fluid consumption patterns. Additional research is warranted to investigate the variation in the amounts of fluoride ingestion by these factors and **its impact on fluorosis** prevalence in different population groups.	J Public Health Dent. 2069(4):267-75. Fall. Abstract
2009	Dental Fluorosis	Warren JJ, et al. 2009. Considerations on optimal fluoride intake assessing dental fluorosis and dental caries outcomes - **a longitudinal study**. "CONCLUSIONS: Given the overlap among caries/fluorosis groups in mean fluoride intake and extreme variability in individual fluoride intakes, **firmly recommending an "optimal" fluoride intake is problematic.**"	J Public Health Dent. 69(2):111-5. Spring. Abstract
2009	Dental Fluorosis	Nyvad B, et al. 2009. Diagnosing dental caries in populations with different levels of dental fluorosis [in Denmark]. "**The prevalence of dental fluorosis was**	Eur J Oral Sci. 117(2):161-8. April. Abstract
2009	Dental Fluorosis	Nyvad B, et al. 2009. Diagnosing dental caries in populations with different levels of dental fluorosis [in Denmark]. "**The prevalence of dental fluorosis was 45% in the 1.1 ppm fluoride area and 21%**	Eur J Oral Sci. 117(2):161-8. April. Abstract

2008	Dental Fluorosis	Sharma R, et al. 2008. Fluoride induces endoplasmic reticulum stress and **inhibits protein synthesis** and secretion. "CONCLUSIONS: These data suggest that F(-) initiates an ER stress response in ameloblasts that interferes with protein synthesis and secretion. Consequently, ameloblast function during enamel development may be impaired, and this may culminate in dental fluorosis."	Environ Health Perspect. 116(9):1142-6. Sept. Full Report
2008	Dental Fluorosis	Dincer E. 2008. Why do I have white spots on my front teeth? "Because their swallowing reflex is not fully developed, **children under the age of 6 can swallow between 25% and 33% of fluoridated toothpaste with each brushing**. In order to better educate parents about fluorosis and its effect on children's teeth, it is worth revisiting the guidelines for toothpaste use."	NY State Dent J. 74(1):58-60. Jan. Abstract
2008	Dental Fluorosis	Wurtz T, et al. 2008. **Fluoride at non-toxic dose** affects odontoblast gene expression in vitro.	Toxicology 249(1):26-34. July 10. Abstract
2007	Dental Fluorosis	Xiong X, et al. 2007. Dose–effect relationship between drinking water fluoride levels and **damage to liver and kidney functions in children**. "… our results suggest that drinking water fluoride levels over 2.0 mg/L can cause damage to liver and kidney functions in children and that the **dental fluorosis was independent of damage to the liver but not the kidney**."	Environ Res. 103(1):112-6. Jan. Abstract
2007	Dental Fluorosis	Vandana KL, et al. 2007. Periodontal changes in fluorosed and nonfluorosed teeth **by Scanning Electron Microscopy**.	Fluoride 40(2):128–33. April-June. Full Report
2007	Dental Fluorosis	Waidyasekera PG, et al. 2007. **Caries susceptibility** of human fluorosed enamel and dentine. "CONCLUSIONS: Moderately fluorosed enamel showed a significant caries resistance. In contrast, **mild and moderately fluorosed dentine was significantly caries susceptible in vitro**."	J Dent. 35(4):343-9. April. Abstract
2007	Dental Fluorosis	Ruan JP, et al. 2007. Dental fluorosis **in children in areas with fluoride-polluted air, high-fluoride water, and low-fluoride water**	Acta Odontol Scand. 65(2):65-71. April. Abstract
2007	Dental Fluorosis	Ruan JP, et al. 2007. Dental fluorosis **in children in areas with fluoride-polluted air, high-fluoride water, and low-fluoride water as well as low-fluoride air**: a study of deciduous and permanent teeth in the Shaanxi province, China.	Acta Odontol Scand. 65(2):65-71. April. Abstract

2006	Dental Fluorosis	Lyaruu DM, et al. 2006. **Short exposure to high levels of fluoride induces** stage-dependent structural changes in ameloblasts and **enamel mineralization**.	Eur J Oral Sci 114 (Suppl. 1):111–5. Abstract
2005	Dental Fluorosis	Bharati P, et al. 2005. Clinical symptoms of **dental and skeletal fluorosis** in Gadag and Bagalkot Districts of Karnataka.	J. Hum. Ecol. 18(2):105-7.
2005	Dental Fluorosis	Cunha-Cruz J, et al. 2005. **Dental fluorosis increases caries risk**.	Journal of Evidence Based Dental Practice 5:170-1.
2005	Dental Fluorosis	Beltran-Aguilar ED et al. 2005. Surveillance for Dental Caries, Dental Sealants, Tooth Retention, Edentulism, and **Enamel Fluorosis** --- United States, 1988--1994 and 1999—2002. **See Table 23.**	MMWR. Surveillance Summaries. 54(03);1-44. August 26. Full Article
2005	Dental Fluorosis	Heikens A, et al. 2005. The impact of the hyperacid Ijen Crater Lake: **risks of excess fluoride** to human health. "**Based on the total daily intake, the lowest F concentration in drinking water that poses a risk of developing fluorosis is approximately 0.5 mg/l for dental fluorosis and 1.1 mg/l for skeletal fluorosis**."	Sci Total Environ. 346(1-3):56-69. June 15. Abstract
2010	Developmental	Flace P, et al. 2010. Effects of developmental fluoride exposure on rat ultrasonic **vocalization, acoustic startle reflex and pre-pulse inhibition**.	Eur Rev Med Pharmacol Sci. 14(6):507-12. June. Abstract
2007	Developmental	Wang SX, et al. 2007**. Arsenic and Fluoride Exposure in Drinking Water: Children's IQ and Growth** in Shanyin County, Shanxi Province, China. "… The statistically significant differences were found in the following comparisons: **Children's height in the control group was significantly higher than that in high-fluoride group ($p < 0.05$)**… It is less surprising that exposure to fluoride affected children's growth function, especially height. Previous studies have demonstrated multiple effects of exposure to high concentrations of fluoride on children's morphology, growth and development, and on bones and teeth (Qian et al. 1989; Xu and Huo 2000). This is because fluoride accumulates in bone and reduces calcium uptake, thereby influencing growth."	Environmental Health Perspectives 115(4):643–47. Full Report
2011	DNA	Andrade-Vieira LF, et al. 2011. Spent Pot Liner (SPL) induced **DNA damage** and nuclear alterations in root tip cells of Allium cepa **as a consequence of programmed cell death**.	Ecotoxicol Environ Saf. 2011 Jan 11. [Epub ahead of print] Abstract

2011	DNA	Andrade-Vieira LF, et al. 2011. Spent Pot Liner (SPL) induced **DNA damage** and nuclear alterations in root tip cells of Allium cepa **as a consequence of programmed cell death**.	Ecotoxicol Environ Saf. 2011 Jan 11. [Epub ahead of print] Abstract
2011	DNA	Madusudanan Rao S, et al. 2011. Morphometry of buccal mucosal cells in fluorosis - a new paradigm. "Conclusions: … **Fluorosis induces oxidative stress, DNA damage and apoptosis** which can be the reasons for the increase in the nuclear size and decrease in the cell size…"	Hum Exp Toxicol. Mar 15. [Epub ahead of print] Abstract
2010	DNA	Li H, et al. 2010. [Toxic effects of fluoride on **rat cerebral cortex astrocytes in vitro**]. "Conclusion: **NaF can induce cell cycle arrest from S to G2/M and inhibit activities of 5'-NT,SDH and ACP in astrocytes**."	Wei Sheng Yan Jiu. 39(1):86-8. Jan. [Article in Chinese] Abstract
2010	DNA	Shashi A, et al. 2010. Histochemical pattern of gastrocnemius muscle in fluoride toxicity syndrome. "Conclusions: **The findings of present study demonstrate that certain concentrations of fluoride can induce muscle lesions and damage DNA, RNA, and protein in muscle cells** and excessive intake and accumulation of fluoride is therefore a serious risk factor for muscular abnormalities in fluorosis."	Asian Pacific Journal of Tropical Medicine 3(2):136-140. Feb.
2009	DNA	Zhang R, et al. 2009. A stable and sensitive testing system for potential carcinogens based on DNA damage-induced **gene expression in human HepG2 cell**. "The results showed that all 20 [including **sodium fluoride**] tested known carcinogenic and genotoxic agents were able to induce gadd153-Luc expression at a sublethal dose."	Toxicol In Vitro. 23(1):158-65. Feb. Abstract
2008	DNA	Jia L, et al. 2008. DNA damage induced by fluoride in **rat kidney** cells.	Fluoride 41(4):297-300. October-December. Full Report
2008	DNA	Zhang M, et al. 2008. Effects of fluoride on DNA damage, S-phase cell-cycle arrest and the expression of NF- B in **primary cultured rat hippocampal neurons**.	Toxicology Letters 179(1):1–5. Abstract
2006	DNA	He LF, Chen JG. 2006. DNA damage, apoptosis and cell cycle changes induced by fluoride in **rat oral mucosal cells and**	World J Gastroenterol. 12(7):1144-8. February 21.

2006	DNA	Zhang Y, et al. 2006. DNA damage induced by fluoride in **rat osteoblasts**.	Fluoride 39(3)191–4. July-Sept. Full Report
2005	DNA	Ge Y, et al. 2005. Comet assay of **DNA damage in brain cells of adult rats** exposed to high fluoride and low iodine.	Fluoride 38(3):209-14. Full Report
2005	DNA	Ge Y, et al. 2005. DNA damage in **thyroid gland cells of rats** exposed to long-term intake of high fluoride and low iodine.	Fluoride 38(4):318–23. November. Full Report
2008	Dyspepsia	Spittle B. 2008. Dyspepsia associated with fluoridated water.	Fluoride 41(1):89-92. Jan-March. Full Report
2008	Enzymes	Moolenburgh H. 2008. Fluoride and **serum cholinesterase**. Letter.	Fluoride 41(3): 227. July-Sept. Full Report
2005	Enzymes	Adamek E, et al. 2005. In vitro and in vivo effects of fluoride ions on enzyme activity.	Ann Acad Med Stetin. 51(2):69-85.
2011	Exposure	Vernacchio L, et al. 2011. Vitamin, Fluoride, and Iron **Use among US Children Younger than 12 Years of Age**: Results from the Slone Survey 1998-2007. "…Between February 1998 and April 2007, there were 2,857 children 0 to 11 years of age enrolled from the 48 contiguous United States … The response rate to the survey was 61%… **Overall, fluoride was used by 3.3% of participants** and iron by 9.7%… **Use of each was highest in the 2- to 5-year-old age group for both (4.3% for fluoride** and 12.4% for iron).	J Am Diet Assoc. 111:285-289.
2010	Exposure	Lockwood G. 2010. Theoretical context-sensitive elimination times for inhalation anaesthetics. *Note from FAN: Desflurane, Sevoflurane and Isoflurane all break down to the fluoride ion in the body.* "After 4 h of anaesthesia, the model **predicted body content** to be 28 g nitrous oxide, **26 g desflurane, 14 g sevoflurane, or 15 g isoflurane**, and **99.9% brain elimination times were** then 9 h for nitrous oxide, **33 h for desflurane, 52 h for sevoflurane, and 71 h for isoflurane. At this stage of elimination,**	Br J Anaesth. 104(5):648-55. May. Abstract
2010	Exposure	Lockwood G. 2010. Theoretical context-sensitive elimination times for inhalation anaesthetics. *Note from FAN: Desflurane, Sevoflurane and Isoflurane all break down to the fluoride ion*	Br J Anaesth. 104(5):648-55. May. Abstract

2010	Exposure	Mansfield P. 2010. Fluoride consumption: the effect of water fluoridation. Mansfield re-analyzed data from the 2000-2003 UK National Diet and Nutrition Survey. Using a revised calculation to estimate fluoride intake (i.e. 45% fluoride excretion rate based on current literature, instead of 100% excretion rate as was originally proposed), the author found that the original estimate of those exceeding the Safe Intake (SI) level for fluoride (0.05 mg/kg body weight/day, as established by the Committee on the Medical Aspects of Food Policy) was an order of magnitude too low--**25% of the UK population is now estimated to exceed the SI for fluoride, and nearly two-thirds of those living in fully fluoridated areas exceed the SI for fluoride**.	Fluoride 43(4): 223-231. Full Report
2010	Exposure	Mason SC, et al. 2010. Evaluation of salivary fluoride retention from a new high fluoride mouthrinse. **Single-use treatment with the new mouthrinse containing 450 ppm fluoride resulted in statistically significantly higher salivary fluoride levels throughout the 120 min test period. Total fluoride retention (AUC_{0-120}) was also statistically significantly greater** versus comparator rinse treatments.	J Dent. 38(Suppl 3):S30-S36. Nov. Abstract
2009	Exposure	Rodrigues MH, et al. 2009. Dietary fluoride intake by children receiving different sources of systemic fluoride. "The aim of this study was to estimate the dietary F intake by children receiving F from artificially fluoridated water (AFW-Brazil, 0.6-0.8 mg F/L), naturally fluoridated water (NFW-Brazil, 0.6-0.9 mg F/L), fluoridated salt (FS-Peru, 180-200 mg F/Kg), and fluoridated milk (FM-Peru, 0.25 mg F). Children (n=21-26) aged 4-6 yrs old participated in each community. A non-fluoridated community (NoF) was evaluated as the control population... **The results indicate that the dietary F intake must be considered before a systemic method of fluoridation is implemented**."	J Dent Res. 88(2):142-5. Feb. Abstract
2009	Exposure: Children	Sohn W, et al. 2009. Fluoride ingestion is related to fluid consumption patterns. "There was substantial variation in the estimated amount of fluoride ingestion depending on the children's fluid consumption patterns as well as age, gender, and	J Public Health Dent. 2069(4):267-75. Fall. Abstract
2009	Exposure: Children	Sohn W, et al. 2009. Fluoride ingestion is related to fluid consumption patterns. "There was substantial variation in the estimated amount of fluoride ingestion depending on the children's fluid consumption	J Public Health Dent. 2069(4):267-75. Fall. Abstract

2007	Exposure	Opydo-Szymaczek J, et al. 2007. Transplacental passage of fluoride in pregnant Polish women assessed on the basis of fluoride concentrations in maternal and cord blood plasma.	Fluoride 40(1):46-50. Full Report
2007	Exposure	Kanbak M, et al. 2007. Renal safety and extrahepatic defluorination of **sevoflurane** in hepatic transplantations.	Transplant Proc. 39(5):1544-8. June.
2006	Exposure	Hong L, et al. 2006. **Fluoride intake levels in relation to fluorosis development** in permanent maxillary central incisors and first molars. "… As part of the longitudinal Iowa Fluoride Study, subjects were followed from birth to 36 months... Cumulatively from birth to 36 months, average daily intake of 0.04 mg F/kg BW or less carried relatively low risk for fluorosis (12.9% for maxillary central incisors, 6.8% for first molars). Average daily intake of 0.04-0.06 mg F/kg BW showed a significantly elevated risk for fluorosis (23.0% for maxillary central incisors, 14.5% for first molars), while fluorosis risk was even higher for average intake above 0.06 mg F/kg BW (38.0% for maxillary central incisors, 32.4% for first molars)."	Caries Res. 40(6):494-500. Abstract
2006	Exposure	Hong L, et al. 2006. **Timing of fluoride intake** in relation to development of fluorosis on maxillary central incisors. "… The **first two years of life were most important** to fluorosis development in permanent maxillary central incisors; however, this study also suggests the importance of other individual years."	Community Dent Oral Epidemiol. 34(4):299-309. Abstract
2006	Exposure	Krook LP, Justus C. 2006. Fluoride poisoning of **horses** from artificially fluoridated drinking water.	Fluoride 39(1)3-10. Jan-Mar. Full Report
2006	Exposure	ADA (American Dental Association). 2006. Interim Guidance on **Reconstituted Infant Formula**. 2006.	American Dental Association, ADA,eGRAM. Nov 9.
2005	Exposure	Erdal S, et al. 2005. A quantitative look at fluorosis, fluoride exposure, and **intake in children** using a health risk assessment approach.	Environ Health Persp113:111-7. Full Report
2006	Exposure	Pagliari AV, et al. 2006. Analysis of fluoride concentration in **mother's milk substitutes**.	Braz Oral Res. 20(3):269-74. Abstract
2005	Exposure	Zuanon ACC, Aranha AMF. 2005.	J Clin Pediatr Dent
2005	Exposure	Zuanon ACC, Aranha AMF. 2005. **Mouthwash ingestion** by preschool children.	J Clin Pediatr Dent 30(1):15-18.

2010	Exposure: Tea	Pehrsson PR, et al. 2010. The fluoride content of select brewed and microwave-brewed black teas in the United States. "Conclusions: **… on average, the dry tea contributes 3–4 times as much fluoride to the brewed tea as does the water. The fluoride provided by brewed tea may contribute significantly amounts of F, and should be considered when assessing total daily intake."**	Journal of Food Composition and Analysis. Published ahead of print. Dec 27.
2010	Exposure: Tea	Joshi S, et al. 2010. **Skeletal fluorosis due to excessive tea** and toothpaste consumption.	Osteoporos Int. Oct 9. [Epub ahead of print] Abstract
2010	Exposure: Tea	Cressey P, et al. 2010. Estimated dietary fluoride intake for New Zealanders. "Intake of fluoride was driven by consumption of dietary staples (bread, potatoes), beverages (**particularly tea**, soft drinks, and beer), and the fluoride status of drinking water."	J Public Health Dent. 70(4):327-36. Fall. Abstract
2009	Exposure: Tea	de Lourdes Azpeitia-Valadez M, et al. 2009. [Risk factors for dental fluorosis in children between 6 and 15 years old]. "Prepared gaseous drink and **tea consumption**, age in relation to the exhibition of periodic applications of fluoride and the area of residence are the **main risk factors for dental fluorosis."**	Rev Med Inst Mex Seguro Soc. May-47(3):265-70. June. [Article in Spanish] Abstract
2008	Exposure: Tea	Whyte MP, et al. 2008. **Skeletal fluorosis from instant tea**. "CONCLUSIONS: **SF [skeletal fluorosis] from habitual consumption of large volumes of extra strength instant tea calls for recognition and better understanding of a skeletal safety limit for this modern preparation of the world's most popular beverage**."	J Bone Miner Res. 23(5):759-69. May. Abstract
2008	Exposure: Tea	Yi J, Cao J. 2008. **Tea and fluorosis**. "… Long-term consumption of high fluoride tea could result in chronic fluoride intoxication. This review summarized those data of the fluoride content in various tea commodities, and estimated the risk of fluorosis caused by high fluoride tea commodities. We also introduced fluorosis caused by tea from case reports, epidemiology observations and animal models… **it is urgent that governmental and international agencies adopt safe standards of fluoride content in tea**	Journal of Fluorine Chemistry 129:76-81.
2008	Exposure: Tea	Yi J, Cao J. 2008. **Tea and fluorosis**. "… Long-term consumption of high fluoride tea could result in chronic fluoride intoxication. This review summarized those data of the fluoride content in various tea commodities, and estimated the risk of fluorosis caused by	Journal of Fluorine Chemistry 129:76-81.

2007	Exposure: Tea	Hallanger Johnson JE, et al. 2007. **Fluoride-related bone disease** associated with habitual tea consumption. Figure 1. Lateral lumbar spine showing advanced osteosclerosis of the vertebral bodies, with absence of usual marrow space radiolucency	Mayo Clin Proc. 82(6):719-24. June. • Erratum in: Mayo Clin Proc. 2007 Aug;82(8):1017. dosage error in text. Full Text
2006	Exposure: Tea	Whyte MP. 2006. **Fluoride Levels in Bottled Teas**. Letter to Editor.	American Journal of Medicine, 119(2):189-90. February.
2005	Exposure: Tea	Whyte MP, et al. 2005. **Skeletal fluorosis** and instant tea. "CONCLUSIONS: SF [skeletal fluorosis] from habitual consumption of large volumes of extra strength instant tea calls for recognition and better understanding of a skeletal safety limit for this modern preparation of **the world's most popular beverage**."	Am J Med. 118(1):78-82. Jan. Abstract
2005	Exposure: Tea	Pehrsson P et al. 2005. The **fluoride content of brewed and microwave brewed black teas** .	U.S. Department of Agriculture. Full Article
2005	Exposure: Tea	Sun DJ et al. 2005. Dose-response relationship between **dental fluorosis and fluoride in brick tea**. Presented at the 26th International Society for Fluoride Research in Wiesbaden, Germany (September).	Fluoride 38(3):253. Full Article (see Abstract 47)
2006	Fetotoxicity	Helal M, El Dakdoky M. 2006. **Fetotoxicity of fluoride in rats** alleviated by some antioxidants.	Fluoride 39(3):202–10. July-Sept. Full Report
2007	Fluoridation	Cheng KK, et al. 2007. **Adding fluoride to water supplies**. "…If fluoride is a medicine, evidence on its effects should be subject to the standards of proof expected of drugs, including evidence from randomized trials... In the case of fluoridation, people should be aware of the limitations of evidence about its potential harms and that **it would be almost impossible to detect small but important risks (especially for chronic conditions) after introducing fluoridation**…"	British Medical Journal 335(7622):699-702. Full Report
2007	Fluoridation	Limeback H, Thiessen K, Isaacson R, Hirzy W. 2007. The EPA MCLG for fluoride in drinking water: new recommendations. "**Our results indicated that in all**	Society of Toxicology 46th Annual Meeting, Charlotte, North Carolina, March 25-29.
2007	Fluoridation	Limeback H, Thiessen K, Isaacson R, Hirzy W. 2007. The EPA MCLG for fluoride in drinking water: new recommendations. "**Our results indicated that in all calculations the new MCLG for fluoride in**	Society of Toxicology 46th Annual Meeting, Charlotte, North Carolina, March 25-29.

2007	Free Radicals	Shanthakumari D, et al. 2007. Effect of fluoride intoxication on the levels of **intestinal antioxidants studied in rats**.	Methods Find Exp Clin Pharmacol. 29(2):93-9. Abstract
2005	Free Radicals	Krechniak J, Inkielewicz I. 2005. Correlations between fluoride concentrations and free radical parameters in **soft tissues of rats**.	Fluoride 38(4)293–6. Nov. Full Report
2011	Genotoxicity	Podder S, et al. 2011. Reduction in fluoride-induced genotoxicity in **mouse bone marrow cells** after substituting high fluoride-containing water with safe drinking water.	J Appl Toxicol. 2011 Mar 5. doi: 10.1002/jat.1644. Abstract
2010	Genotoxicity	Podder S, et al. 2010. Fluoride-induced genotoxicity in **mouse bone marrow cells**: effect of buthionine sulfoximine and N-acetyl-l-cysteine.	J Appl Toxicol. 2010 Dec 10. doi: 10.1002/jat.1605. [Epub ahead of print] Abstract
2008	Genotoxicity	Podder S, et al. 2008. Differential *in vivo* genotoxic effects of lower and higher concentrations of fluoride in **mouse bone marrow cells**.	Fluoride 41(4):301-7. Oct-Dec. Full Report
2008	**Genotoxicity**	**Podder S, et al. 2008. *In vivo* suppression by fluoride of chromosome aberrations induced by mitomycin-C in mouse bone marrow cells.**	**Fluoride 41(1):40–3. Jan-March.**
2005	Genotoxicity	Velazquez-Guardarrama, et al. 2005. Genotoxic evaluation of sodium fluoride and sodium perborate in **mouse bone marrow cells**.	Bull Environ Contam and Toxicol. 74: 566-72.
2010	Haem Biosynthesis Pathway	Chouhan S, et al. 2010. Fluoride-induced changes in haem biosynthesis pathway, neurological variables and tissue histopathology of rats. "This study intended to determine the effects of various concentrations of fluoride (1, 10, 50 and 100 ppm) in drinking water for a period of 12 weeks on changes in haem biosynthesis pathway, oxidative stress and neurological variables supported by histopathological observations and fluoride in rats… **Interestingly and most significantly, these changes were more pronounced at lower concentrations of fluoride compared with higher fluoride dose**…These changes support our earlier findings regarding the role of decreased ionic mobility of fluoride ion at higher concentrations, leading to less pronounced toxicity."	J Appl Toxicol. 30(1):63-73. Jan. Abstract
2011	Heart: *Study on children*	Karademir S, et al. 2011. Effects of fluorosis on QT dispersion, heart rate variability and echocardiographic **parameters in children** - Original Investigation.	Anadolu Kardiyol Derg. 11(2):150-5. Full Report
2011	Heart: *Study on children*	Karademir S, et al. 2011. Effects of fluorosis on QT dispersion, heart rate variability and echocardiographic **parameters in children** - Original Investigation. "… We found **statistically significant low**	Anadolu Kardiyol Derg. 11(2):150-5. Full Report

2011	Heart	Flora SJ, et al. 2011. **Interactive effect of arsenic and fluoride on cardio-respiratory disorders in male rats**: possible role of reactive oxygen species.	Biometals. Jan 18. [Epub ahead of print] Abstract
2010	Heart	Varol E, et al. 2010. Impact of chronic fluorosis on **left ventricular diastolic and global functions**.	Science of the Total Environment 408(11): 2295-8. Abstract
2010	Heart	Varol E, et al. 2010. **Aortic elasticity** is impaired in patients with endemic fluorosis.	Biol Trace Elem Res. 133:121-7. Abstract
2010	Heart	Yang E, et al. 2010. Fluoride induces **vascular contraction through activation of RhoA/Rho kinase pathway in isolated rat aortas**.	Environ Toxicol Pharmacol. 29(3):290-296. May.
2006	Heart	Jeon SB, et al. 2006. A role for **Rho kinase in vascular contraction** evoked by sodium fluoride.	Biochem Biophys Res Commun. 343(1):27-33. April 28. Abstract
2005	Heart	Cicek E, et al. 2005. Effects of chronic ingestion of sodium fluoride on myocardium in a **second generation of rats**.	Hum Exp Toxicol. 24(2):79-87. Feb. Abstract
2011	Immune System / Human study	Hernández-Castro B, et al. 2010. **Effect of fluoride exposure on different immune parameters in humans**. "*Context:* T regulatory (Treg) cells play an important role in the modulation of the immune response, and are implicated in the pathogenesis of autoimmune diseases… *Conclusion*: Our data suggest that F exposure exerts a complex and relevant effect on Treg cells in humans."	Immunopharmacology and Immunotoxicology, 33(1):169-77. March. Abstract
2011	Insulin	Lupo M, et al. 2011. Effect of fluoridated water on plasma insulin levels and glucose homeostasis in rats with renal deficiency. "… It is concluded that the consumption of fluoridated water from water supply did not affect plasma glucose levels even in cases of animals with renal disease. However, **a resistance to insulin action was demonstrated**."	Biol Trace Elem Res. 140(2):198-207. May. Abstract
2009	Insulin	García-Montalvo EA, et al. 2009. Fluoride exposure **impairs glucose tolerance** via decreased insulin expression and oxidative stress.	Toxicology 263(2-3):75-83. Sept 19. Abstract
2008	Insulin	Chehoud KA, et al. 2008. Effects of fluoride intake on **insulin sensitivity and insulin**	Fluoride 41(4):270-5. Oct-Dec.

2008	Insulin	Chehoud KA, et al. 2008. Effects of fluoride intake on **insulin sensitivity and insulin signal transduction**.	Fluoride 41(4):270-5. Oct-Dec. Full Article
2008	Insulin	Menoyo I, et al. 2008. Fluoride-**induced resistance to insulin in the rat**.	Fluoride 41(4):260–9. Oct-Dec. Full Article
2005	Insulin	Menoyo I et al. 2005. Effect of fluoride on the **secretion of insulin in the rat**.	Arzneimittelforschung 55:455-60. Abstract
2011	Iodine	Ge Y, et al. 2011. **Proteomic Analysis of Brain Proteins of Rats Exposed to High Fluoride and Low Iodine**.	Archives of Toxicology Arch Jan;85(1):27-33. Abstract
2009	Iodine	Wang J, et al. 2009. Chapter 67 - DNA Damage in Brain and Thyroid Gland Cells **due to High Fluoride and Low Iodine**.	Comprehensive Handbook of Iodine, Pages 643-649. Edited by: Victor R. Preedy, Gerard N. Burrow and Ronald Watson. ISBN: 978-0-12-374135-6. Elsevier Inc.
2008	Iodine	Ren D, et al. 2008. A Study of **the Intellectual Ability of 8–14 Year-Old Children** in High Fluoride, **Low Iodine Areas**.	Fluoride 41(4):319–20. Full Report
2007	Iodine	Voronych-Semchenko NM. 2007. Characteristics of hypothyroidism correction and lipid metabolism disorder in iodine deficiency. "… It has been revealed that hypothyrosis has negative influence on lipid metabolism indexes. "Iodid- 100" usage stabilized hormonal and lipid status. **Excessive intake of chlorine and fluorine ions by the organism decreased the effectiveness of iodine containing drugs**."	Fiziol Zh. 53(3):38-42. [Article in Ukrainian] Abstract
2006	Iodine	Ge Y, et al. 2006. Apoptosis in **brain cells of offspring rats** exposed to **high fluoride and low iodine.**	Fluoride 39(3);173-8. July-Sept. Full Report
2005	Iodine	Ge Y, et al. 2005. Comet assay of **DNA damage in brain cells of adult rats** exposed to high **fluoride and low iodine**.	Fluoride 38(3):209-14. Full Report
2005	Iodine	Ge Y, et al. 2005. DNA damage in **thyroid gland cells of rats** exposed to long-term intake of high fluoride and low iodine.	Fluoride 38(4):318–23. November. Full Report
2005	Iodine	Gas'kov AIu, et al. 2005. [The specific features of the development of **iodine deficiencies in children living under environmental**	Gig Sanit. Nov-Dec;(6):53-5. Full Article - English

2011	Kidney	Yang K and Liang X. 2011. Fluoride in Drinking Water: Effect on Liver and Kidney Function. "Abstract. … high level of fluoride in drinking water is harmful to the living system. Chronic fluoride intoxication causes damages to osseous tissue (teeth and bone) and soft tissues (liver, kidney, brain, etc.). **Liver and kidney are the target organs markedly attacked by excessive amount of fluoride. High doses of fluoride intake lead to changes of structure, function, and metabolism in liver and kidney."**	Encyclopedia of Environmental Health (Editor-in-Chief: Jerome O. Nriagu, Elsevier B.V.), Pages 769-775.
2011	Kidney	Chattopadhyay A, et al. 2011. Fluoride-induced histopathology and synthesis of stress protein in liver and kidney of mice. "Selective low (15 mg sodium fluoride (NaF)/L) and relatively high (150 mg NaF/L) doses of in vivo fluoride (F) treatment to Swiss albino mice through drinking water elicited organ-specific toxicological response. **All the F-exposed groups showed severe alterations in both liver and kidney architectures**"	Arch Toxicol. 85(4):327-35. April. Abstract
2011	Kidney	Chandrajith R, et al. 2011. Dose-dependent Na and Ca in fluoride-rich drinking water--another major cause of **chronic renal failure** in tropical arid regions.	Sci Total Environ. 409(4):671-5. Jan 15. Abstract
2010	Kidney	Itai K, et al. 2010. Serum ionic fluoride concentrations are related to renal function and menopause status but not to age in a Japanese general population. **"Conclusion: SIF [Serum ionic fluoride] concentrations in middle-aged healthy subjects were increased with an age-related degeneration in renal function. SIF concentrations in post-menopausal women arise from the increased fluoride release from bone after menopause. Age is not related to SIF concentrations."**	Clinica Chimica Acta 411: 263–266. Abstract
2010	Kidney	Błaszczyk I, et al. 2011. Influence of methionine upon the activity of antioxidative enzymes in the kidney of rats exposed to sodium fluoride.	Biol Trace Elem Res. 33(1):60-70. Jan. Abstract
2010	Kidney	Błaszczyk I, et al. 2011. Influence of methionine upon the activity of antioxidative enzymes in the kidney of rats exposed to sodium fluoride. "… Among the factors inducing intensified free	Biol Trace Elem Res. 33(1):60-70. Jan. Abstract

2010	Kidney	Al Omireeni, et al. 2010. Biochemical and histological studies on the effect of sodium fluoride on rat kidney collagen. "Abstract: The present study was carried out to study the effect of acute doses of sodium fluoride on the collagen content of the rat kidneys. Five groups of rats were studied: (i) control rats and (ii) rats divided into four subgroups according to the dose of NaF. Results showed that higher doses of sodium fluoride 10, 20 and 30 mg of NaF/kg body weight **caused a significant decrease in the collagen content of the kidneys when compared to the control rats.** Electron microscope studies supported these results and showed the sodium fluoride doses 10, 20 and 30 mg of NaF/kg body weight **caused disruption of ordered collagen fibrils of the rat kidneys**."	J of Saudi Chemical Society. 14(4):413-416. Full Report
2009	Kidney	Kobayashi CAN, et al. 2009. **Proteomic analysis of kidney in rats** chronically exposed to fluoride.	Chem Biol Interact. 180(2):305-11. July 15. Abstract
2008	Kidney	Jia L, et al. 2008. **DNA damage** induced by fluoride in **rat kidney cells**.	Fluoride 41(4):297-300. Oct-Dec. Full Report
2008	Kidney	Tang Q, et al. 2008. In vitro hormesis effects of sodium fluoride on kidney cells of **three-day old male rats**.	Fluoride 41(4):292-6. Oct-Dec. Full Article
2007	Kidney	Xiong X, et al. 2007. Dose–effect relationship between drinking water fluoride levels and **damage to liver and kidney functions in children**. "… **our results suggest that drinking water fluoride levels over 2.0 mg/L can cause damage to liver and kidney functions in children and that the dental fluorosis was independent of damage to the liver but not the kidney**."	Environ Res. 103(1):112-6. Jan. Abstract
2007	Kidney	Xu H, et al. 2007. Effects of fluoride on the intracellular free Ca2+ and Ca2+-ATPase of kidney. "To sum up, the effect of fluoride on Ca2+-ATPase is a similar to a dose-effect relationship phenomenon characterized by low-dose stimulation and high-dose inhibition, **and the increase of [Ca2+]i probably plays a key role on the mechanism of renal injury in fluorosis**."	Biol Trace Elem Res. 116(3):279-88. June. Abstract
2006	Kidney	Bober J, et al. 2006. Fluoride **aggravation of oxidative stress in patients with chronic renal failure**.	Fluoride 39(4):302–9. Oct-Dec. Full Article

2006	Kidney	Bansal R, Tiwari SC. 2006. Back pain in **chronic renal failure**. "…Definitive diagnosis was reached with estimation of **fluoride levels in blood and urine, which were 0.291 mg/l and 0.962 mg/l** (15.3 and 50.6 µmol/l), respectively. **Her drinking water source**, ground water from a tubewell, was found to contain **3.910 mg/l** (205.9 µmol/l) of fluoride."	Nephrology Dialysis Transplantation 21:2331-2. Full Article
2006	Kidney	Harinarayan CV, et al. 2006. Fluorotoxic metabolic bone disease: an **osteo-renal syndrome** caused by excess fluoride ingestion in the tropics.	Bone 39(4):907-14. Abstract
2006	Kidney	Ayoob S, Gupta AK. 2006. Fluoride in drinking water: a review on the status and **stress effects**.	Critical Reviews in Environmental Science and Technology 36:433–87.
2006	Kidney	Zhan XA, et al. Toxic effects of fluoride on kidney function and histological structure in **young pigs**.	Fluoride 39(1):22–6. Jan-Mar. Full Report
2005	Kidney	Liu JL, et al. 2005. [The dose-effect relationship of water fluoride levels and **renal damage in children**] "CONCLUSION: **Over 2.0 mg/L fluoride in drinking water can cause renal damage in children, and the damage degree increases with the drinking water fluoride content**. Renal damage degree is not related to whether the children suffered from dental fluorosis and mainly due to water fluoride concentration."	Wei Sheng Yan Jiu. 34(3):287-8. May. [Article in Chinese]. Abstract
2005	Kidney	Grucka-Mamczar E, et al. 2005. Disturbances of **kidney function in rats with fluoride-induced hyperglycemia** after acute poisoning by sodium fluoride.	Fluoride 38(1):48–51. Full Report
2005	Kidney	Xu H, et al. 2005. **Proteomic analysis** of kidney in fluoride-treated **rat**.	Toxicol Lett. 60(1):69-75. Dec 30. Abstract
2010	Lipid Peroxidation	Chauhan SS, et al. 2010. Modulation of lipid peroxidation and antioxidant defense systems in rat intestine by subchronic fluoride and ethanol administration. "**These findings suggest that fluoride and ethanol exposure induces considerable changes in lipid peroxidation, antioxidant defense, and morphology of rat intestine,**	Alcohol, [Epub ahead of print] Abstract

2007	Lipid Peroxidation	Kalyanalakshmi P, et al. 2007. Oxidative stress in **males with skeletal fluorosis** in Andhra Pradesh, India.	Fluoride 40(1):42–5. Full Report
2007	Lipid Peroxidation	Oncu M, et al. 2007. Effect of long-term fluoride exposure on lipid peroxidation and histology of **testes in first- and second-generation rats**.	Biol Trace Elem Res. 118(3):260-8. Sept. Abstract
2006	Lipid Peroxidation	Oncu M, et al. 2006. Effect of chronic fluorosis on lipid peroxidation and histology of **lung tissues in first and second generation rats**.	Toxicol Ind Health. 22(9):375-80. Oct. Abstract
2005	Lipid Peroxidation	Bouaziz H, et al. 2005. Toxic effects of fluoride by maternal ingestion on **kidney function of adult mice and their suckling pups**. "Lipid peroxidation increased in the treated mice, as revealed by high kidney malondialdehyde levels, while plasma and urinary uric acid levels showed a significant decline."	Fluoride 38(1):23–31. Full Report
2004	Lipid Peroxidation	Karaoz E, et al. 2004. Effect of chronic fluorosis on lipid peroxidation and histology of **kidney tissues in first- and second-generation rats**.	Biol Trace Elem Res. 102(1-3):199-208. Winter. Abstract
2011	Liver	Yang K and Liang X. 2011. Fluoride in Drinking Water: Effect on Liver and Kidney Function. "Abstract. … high level of fluoride in drinking water is harmful to the living system. Chronic fluoride intoxication causes damages to osseous tissue (teeth and bone) and soft tissues (liver, kidney, brain, etc.). **Liver and kidney are the target organs markedly attacked by excessive amount of fluoride. High doses of fluoride intake lead to changes of structure, function, and metabolism in liver and kidney."**	Encyclopedia of Environmental Health (Editor-in-Chief: Jerome O. Nriagu. Elsevier B.V.), Pages 769-775.
2011	Liver	Chattopadhyay A, et al. 2011. Fluoride-induced histopathology and synthesis of stress	Arch Toxicol. 85(4):327-35. April.
2011	Liver	Chattopadhyay A, et al. 2011. Fluoride-induced histopathology and synthesis of stress protein in liver and kidney of mice. "Selective low (15 mg sodium fluoride (NaF)/L) and relatively high (150 mg NaF/L)	Arch Toxicol. 85(4):327-35. April. Abstract

2010	Liver	Iano FG, et al. 2010. Chronic Toxicity of Fluoride in the Liver Antioxidant Defense. "… The enzyme CAT was significantly reduced and SOD significantly increased, respectively, in the 15 ppm F group when compared to control and 5 ppm F group. In summary, clear changes in the antioxidant parameters in relation with the level of administered F was observed. **These results show that chronic F administration alters the antioxidant systems of rats**."	Free Radical Biology and Medicine 49(Suppl 1):S221. July.
2009	Liver	Birkner E, et al. 2009. The Influence of rich-in-cholesterol diet and fluoride ions contained in potable water upon the concentration of malondialdehyde and the activity of selected antioxidative enzymes in **rabbit liver**.	Biol Trace Elem Res. 129(1-3):137-42. Summer. Abstract
2007	Liver	Xiong X, et al. 2007. Dose–effect relationship between drinking water fluoride levels and **damage to liver and kidney functions in children**.	Environ Res. 103(1):112-6. Jan. Abstract
2007	Liver	Grucka-Mamczar E, et al. 2007. Influence of extended exposure to sodium fluoride and caffeine on the activity of carbohydrate metabolism enzymes in **rat blood serum and liver**. "… **Glycolysis in extra-hepatic tissues (serum), under the influence of F, was slightly inhibited; however, it was markedly intensified by caffeine.** Overall, a more profound influence by caffeine on carbohydrate enzyme activity was observed in blood serum (extra-hepatic tissues) than in the liver."	Fluoride 40(1)62–66. Jan-March. Full Report
2005	Liver	Guo X, et al. 2005. [Effect of fluoride on activities of **enzyme and ultrastructure in primary cultured rat hepatocytes**]	Wei Sheng Yan Jiu. 34(1):35-7. January. [Article in Chinese] Abstract
2009	Lung	Ridley W, Matsuoka M. 2009. Fluoride-induced cyclooxygenase-2 expression and prostaglandin E(2) production in A549 **human pulmonary epithelial cells**.	Toxicol Lett. 188(3):180-5. Aug10. Abstract
2008	Lung	Refsnes M, et al. 2008. Fluoride-induced IL-8 release in **human epithelial lung cells**: relationship to EGF-receptor-, SRC- and MAP-kinase activation.	Toxicol Appl Pharmacol. 227(1):56-67. Feb 15. Abstract
2006	Lung	Oncu M, et al. 2006. Effect of chronic fluorosis on lipid peroxidation and histology of **lung tissues in first and second generation rats**.	Toxicol Ind Health. 22(9):375-80. Oct. Abstract

2006	Lung	Oncu M, et al. 2006. Effect of chronic fluorosis on lipid peroxidation and histology of **lung tissues in first and second generation rats**.	Toxicol Ind Health. 22(9):375-80. Oct. Abstract
2003	Lung	Aydin G, et al. 2003. Histopathological and biochemical changes in lung tissues of rats following administration of fluoride over several generations. "… This multigenerational evaluation of the long-term effect of different doses of fluoride intake through drinking water on lung damage shows that the lung tissues were damaged, there was **emphysema and inflammation of lung parenchyma associated with loss of alveolar architecture and the degree of lung damage seemed to correlate with the increased dosage of fluoride.** A similar relationship was observed between the degree of lung damage, body and lung weight and serum fluoride levels according to the fluoride dose."	J Appl Toxicol. 23(6):437-46. Nov-Dec. Abstract
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2008	Oxidative Stress	Inkielewicz I, Czarnowskia W. 2008. Oxidative stress parameters in **rats** exposed to fluoride and aspirin.	Fluoride 41(1):76–82. Jan-March. Full Report
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2005	Reproductive	Pushpalatha T, et al. 2005. Exposure to high fluoride concentration in drinking water will affect **spermatogenesis and steroidogenesis in male albino rats**.	Biometals. 18(3):207-12. June. Abstract

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2011	Thyroid	Karademir S, et al. 2011. Effects of fluorosis on QT dispersion, heart rate variability and echocardiographic **parameters in children** - Original Investigation. "… We found **statistically significant low**	Anadolu Kardiyol Derg. 11(2):150-5. Full Report

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2005	Thyroid	Ge Y, et al. 2005. **DNA damage in thyroid gland cells of rats** exposed to long-term intake of high fluoride and low iodine.	Fluoride 38(4):318–23. Nov. Full Article
2005	Thyroid	Ruiz-Payan A, et al. 2005. Chronic effects of fluoride on growth, blood chemistry, and **thyroid hormones in adolescents** residing in northern Mexico. Paper presented at the XXVIth Conference of the International Society for Fluoride Research (September 26-29).	Fluoride 38(3):246. Full Article (see Abstract Number 37)

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"There was substantial variation in the estimated amount of fluoride ingestion depending on the children's fluid consumption patterns as well as age, gender, and race/ethnicity. African-American children ingested significantly more fluoride than White children in bivariate analysis. This association remained significant after accounting for fluid consumption pattern and other confounding factors in the model.
CONCLUSION: Our results raise concerns that some children are ingesting significantly more fluoride than others depending on sociodemographic factors and fluid consumption patterns. Additional research is warranted to investigate the variation in the amounts of fluoride ingestion by these factors and its impact on fluorosis prevalence in different population groups.