Comments on
the U.S. EPA's Report
Fluoride: Exposure and Relative Source Contribution Analysis

Prepared for the
U.S. Environmental Protection Agency

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1. Introduction

On 7 January 2011 the Environmental Protection Agency's (EPA) Office of Water (OW) released a new analysis for fluoride exposure for populations in the United States. This was in response to recommendations set forth by a National Research Council (NRC) panel, as detailed in the 2006 report *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*. Both the maximum contaminant level (MCL) and the maximum contaminant level goal (MCLG) for fluoride in drinking water are currently set at 4 mg/L, a level that the NRC panel determined is not protective of human health and "should be lowered" (NRC, 2006, p.10).

OW analyzed exposure and relative source contribution to estimate "total exposures for children during the period of sensitivity to severe dental fluorosis (six months to 14 years)" and to "develop an exposure estimate for the adult population" (EPA, 2010a). Unfortunately, several policies that are used by OW in calculating the exposure and relative source contribution analysis are flawed. Using only the 90th percentile of water consumption for estimates of fluoride exposure ignores the 10% of the U.S. population (approximately 31 million Americans) that are above-average water drinkers. Using the mean concentration of fluoride in drinking water (0.87 mg/L) ignores perhaps half of the population whose drinking water contains higher levels. Using the average body weight of each age group of interest negates the impact that fluoride exposure has on the lower percentiles of body weight—especially for infants and children.

In addition, OW has failed to adequately consider a number of sensitive subpopulations in its analysis. These include pregnant women and embryos/fetuses, infants less than 6 months old, above-average water consumers, diabetics, those with renal dysfunction, minorities, low-income families, those with inadequate diets, those with differences in food consumption patterns (e.g. excessive tea consumers), heavy smokers, residents of heavily industrialized areas, those with occupational exposures, and those with fluoride sensitivity. OW has also failed to adequately consider a number of potentially important sources of fluoride in its exposure analysis. These include various dental products, dietary supplements, pharmaceuticals, and ambient air.

By ignoring entire subsets of Americans, OW is potentially underestimating the fluoride exposures of a substantial proportion of the American population. As OW has refused to include any margin of safety in its determination of a safe RfD (EPA, 2010a), it is especially important that all possible uncertainties are accounted for in its Exposure and Relative Source Contribution Analysis, such that even more people are not neglected when moving from the proposed RfD to a new MCLG.

2. Response to EPA's Exposure and Relative Source Contribution Analysis

2.1. The policies used to calculate fluoride exposures are flawed, especially when no margin of safety is applied.

Several of the policies used by OW in determining total fluoride exposures have inherent weaknesses that must be addressed by either a) a change in OW policy, or b) application of uncertainty factors greater than 1, as are currently used. These policies include the use of only the 90th percentile for water consumption, use of the mean water fluoride concentration, use of the average body weight, and use of theoretical consumption information instead of a more accurate measure of fluoride intake (e.g. urine fluoride levels).

2.1.1. OW's policy of using the 90th percentile for water consumption ignores 10% of the U.S. population—nearly 31 million people.

As OW has refused to incorporate *any* margin of safety into its calculations, it should use the absolutely most conservative estimates of exposure possible to ensure that the vast majority of the American people are protected from fluoride's adverse effects. However, as per EPA protocol, OW has only considered fluoride exposures for the 90th percentile water consumer, meaning that those Americans consuming more than 2 L of water per day are completely ignored.

Among the above-average consuming groups are some already extremely sensitive subpopulations that are also being outright ignored by OW, including diabetics (especially when not adequately controlled), pregnant and lactating women, and those with renal dysfunction (EPA, 2000; NRC, 2006). People with high activity levels (e.g. athletes, workers with physically demanding duties, military personnel) and people living in very hot or dry climates (especially outdoor workers) are also likely to be above average water consumers.

In addition, a number of factors and conditions can increase thirst, and thus increase water consumption to above-average intakes. Some of these include dehydration, hormone imbalances (e.g. hyperthyroidism, hyperadrenalism), hypernatremia, psychogenic polydipsia, and damage to the hypothalamus. Also at risk for increased thirst are those taking certain drugs, including anticholinergics, demeclocycline, phenothiazines, and diuretics (Medline, 2011). Several of the top 200 selling drugs in 2009 are included in the list of those known to increase thirst (Drugwatch.com), including Effexor (13.7 million prescriptions in 2009), Actos (11.7 million prescriptions), Seroquel (11.1 million prescriptions), Zyprexa (3.6 million prescriptions), and Protonix (3.1 million prescriptions) (Drugs.com, Undated).

As per NRC (2006, p. 429), "Individuals at the upper levels of water intake from EPA's estimates could have fluoride intakes in excess of 1 mg/day at the lowest levels of fluoridation up to about 6 mg/day for some adults, depending on age and level of water fluoridation. Persons in the high water intake groups…could have even higher intakes."

2.1.2. OW's policy of using the mean drinking water fluoride concentration ignores as much as half of the population whose drinking water has higher fluoride levels.

OW's use of the mean fluoride concentration of 0.87 mg/L is even less protective than use of the 90th percentile for water consumption. OW claims that the proposed RfD is an exposure that would protect against severe dental fluorosis "in 99.5% of the children who drink water with 0.87 mg/L F at a 90th percentile intake level and have average intakes from other media during the period of secondary tooth formation" (EPA, 2010b, p. 104). However, this completely ignores those children whose drinking water contains more than 0.87 mg F/L. Again, owing to OW's refusal to incorporate any margin of safety for fluoride, it should be compelled to use the most conservative estimates possible to ensure safety of the American people.

It is disturbing that OW acknowledges that children will likely be over exposed to fluoride, yet does not seem to be concerned by this. Not only will children whose drinking water contains more than 0.87 mg F/L be over exposed—

> "some children drinking water at the 90th percentile intake level up to about age 7 are being exposed to fluoride on a daily basis at levels at or higher than estimated acceptable intake levels when the concentration of fluoride in their drinking water is at or above 0.87 mg/L" (EPA, 2010b, p. 104).

but many children with "average" intakes from all sources will also be over exposed to fluoride—

> "Children with average intake of all media in the younger age groups would still be slightly over exposed if the drinking water concentration were 0.87 mg/L" (EPA, 2010b, p. 105).

If it is the goal of OW to account for at least 90% of the population in its exposure analysis, then it is necessary that *at least* the 90th percentile for drinking water fluoride concentration be used for exposure calculations.

2.1.3. OW's policy of using the average body weight of the population of interest ignores as much as half of the population in the lower 50th percentile for weight.

OW's use of the average body weight of the group of interest (EPA, 2010b, p.104) does not adequately represent the majority of Americans. As fluoride exposure is most accurately expressed on a mg/kg/day scale, OW should use an estimated body weight that would be more inclusive of the entire population, especially when considering the susceptibility of infants and young children. If it is OW's goal that 90% of the population should be protected, then the 10th percentile for weight for each group of interest should be used in place of an average weight.

Age Range (years)	Mean Weight (kg)	10^{th} Percentile Weight (kg)
<0.5	6	3
0.5 - <1	9	7
1 - <4	14	10
4 - <7	21	16
7 - <11	32	22
11 – 14	51	35
Adult females	65	51
Adult males	79	63

Table 1. Comparison of mean weight (as used by OW) to the 10^{th} percentile weight (which would include 90% of the population) for age groups of interest. Weight data from EPA, 2004.

The disparity between the mean and 10^{th} percentile weights is great, and could be of significance when calculating weight-specific fluoride intakes for each age group.

Age Range (years)	Intake Estimate (mg/day)	By Mean Weight (mg/kg/day)	By 10^{th} Percentile Weight (mg/kg/day)	Difference (% Increase from Mean)
<0.5	1.11*	0.185	0.370	100%
0.5 - <1	1.21	0.134	0.173	29%
1 - <4	1.58	0.113	0.158	40%
4 - <7	2.03	0.097	0.127	31%
7 - <11	2.16	0.068	0.098	44%
11 – 14	2.41	0.047	0.069	47%
Adult females	2.91	0.045	0.057	27%
Adult males	2.91	0.037	0.046	24%

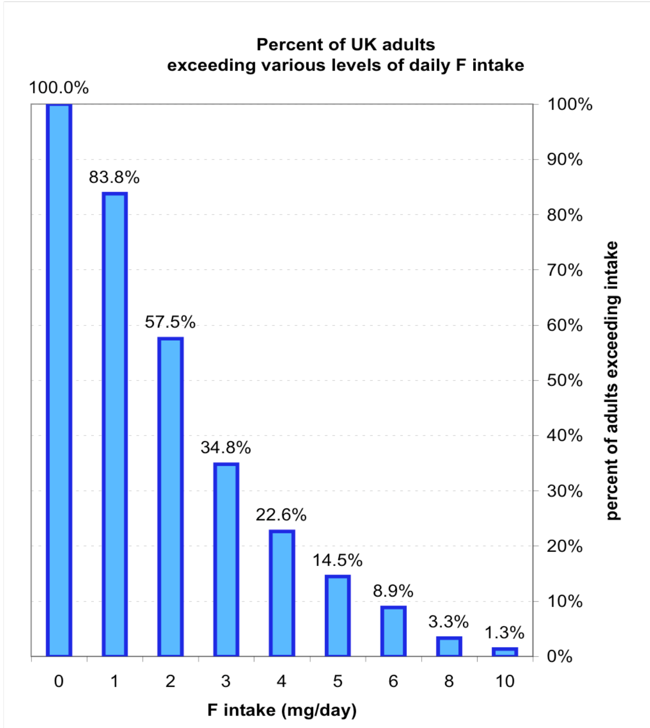
Table 2: Comparison of weight-specific fluoride intake estimates by mean weight (as used by OW) and 10^{th} percentile weight (which would include 90% of the population). Weight data from EPA, 2004. Intake estimates from EPA, 2010b (p. 104), except for the age group <0.5 years*, which was calculated according to EPA guidelines (EPA, 2010b, p.97), with data from EPA, 2008.

If OW considered children to the 10^{th} percentile of weight (thus accounted for 90% of this population of interest), nearly all would have intakes that greatly exceed the proposed RfD of 0.08 mg/kg/day—some (those <0.5 years) by nearly a factor of 5. Even with OW's flawed use of average weights, children at the 90^{th} percentile for consumption of drinking water at the average of 0.87 mg/L F will still be exceeding the proposed RfD of 0.08 mg/kg/day, and thus will be chronically over exposed to fluoride. The refusal by OW to incorporate any margin of safety for fluoride exposure should require that the most conservative estimates be used in order to protect the population from fluoride's detrimental effects.

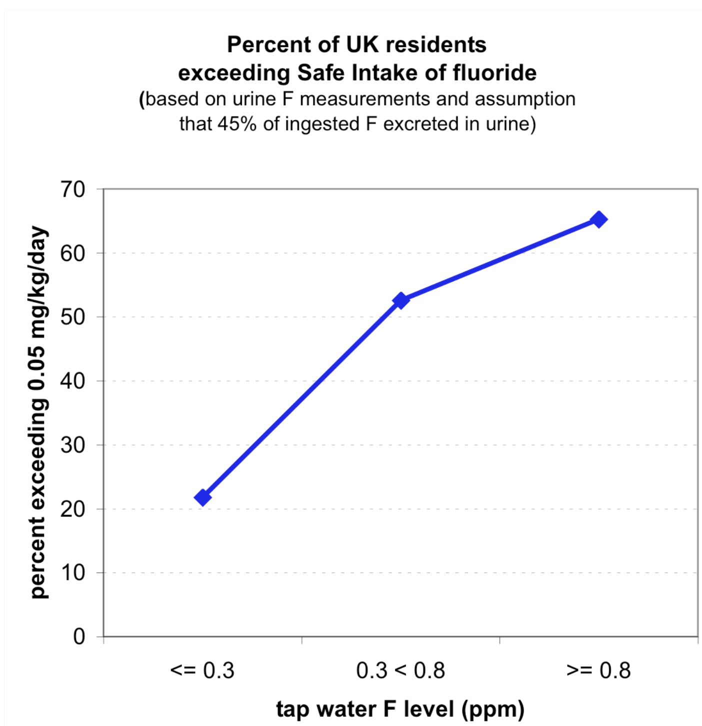
2.1.4. OW has failed to consider studies of urinary fluoride excretion as an estimate of total fluoride intake.

OW has failed to consider evidence from studies of urinary excretion of fluoride, which is likely to provide a more accurate estimate of total fluoride intake from all sources and pathways than any theoretical calculations based on consumption information and population average weights. To date, the best source of urine fluoride measurements covering an entire population is that done in the U.K. as part of a nationwide health and nutrition survey, similar to the NHANES surveys in the U.S. (Henderson et al., 2003) Over a thousand subjects provided 24 hour urine samples for fluoride analysis. They also completed questionnaires, which provided information such as age and weight, as well as detailed dietary information including source of drinking water.

A recent publication (Mansfield, 2010) has reanalyzed this data, using a corrected method of extrapolating from urinary fluoride excretion back to the likely total fluoride intake. The originally issued report incorrectly assumed that 99% of fluoride intake was excreted in urine, whereas the generally accepted value is roughly 45% (90% of ingested fluoride absorbed and 50% of that excreted in urine, for a urine excretion proportion of 45%). This correction doubles the estimated fluoride intake from those originally published. The corrected levels of fluoride intake are higher than OW has estimated, suggesting that OW has underestimated the true intake of fluoride. For example, the U.K. data show that 3.3% of adults have exposures above 8 mg F/day. This is a level that, even by OW's previous laxer safe intake standards, would put these people at risk of crippling skeletal fluorosis. Furthermore, 1.3% of adults exceeded 10 mg F/day, which the OW considers the threshold for risk of crippling skeletal fluorosis over the course of 10-20 years, let alone a lifetime of exposure. See figure below for details.



The study also found that over 65% of residents who had fluoridated water (>0.8 mg F/L) exceeded a proposed U.K. Safe Intake level, equivalent to the OW's RfD (see figure below). These estimates took into account the body weight of the individuals, so they are the most accurate way of estimating total fluoride dosage (mg/kg/day), which is most relevant to determining whether people are exceeding an RfD.



While it is conceivable the U.S. population has lower *average* fluoride intake, it is likely that this U.K. data does encompass the extremes that will also be experienced in the U.S. It is important to note that even for those with water between 0.3 and 0.8 mg F/L, which is similar or lower than the newly proposed HHS level of 0.7 mg F/L for fluoridation, over 50% of adults exceeded a Safe Intake of 0.05 mg F/kg/day, as recommended by U.K. authorities. Clearly, lowering fluoridation levels to 0.7 mg F/L will not reduce total exposure enough to prevent a very large proportion of American adults from exceeding a safe dosage. This is from actual individual biomarker data, rather than calculations. The OW exposure assessment suggests that very few people drinking water with 0.7 mg F/L will exceed the RfD. The U.K. data shows the opposite, bringing this conclusion into question.

We understand that OW has recently conducted urine fluoride sampling and analysis of U.S. subjects. If this is true, then these data are critically important for assessing the accuracy of the exposure assessment estimates and needs to be made public and applied before the OW exposure assessment is finalized. In the meantime, the U.K. data must be considered as the best available check on the assumptions and data used for the OW exposure assessment. They suggest OW has underestimated the true exposure levels.

2.2. OW's has failed to consider fluoride exposures for several of the most sensitive groups—pregnant women, embryos/fetuses, and infants 0-6 months.

OW's exposure analysis has disregarded several groups that are generally recognized as the most sensitive to exposure from any contaminant, including the pregnant woman, the embryo/fetus and the infant.

It is well documented that fluoride readily crosses the placenta (Shen and Taves, 1974; Ron et al., 1986; Caldera et al., 1988; Forestier et al., 1990; Gupta et al., 1993; Malhotra et al., 1993; Chlubek et al., 1994; Shimonovitz et al., 1995; Montherrat-Carret et al, 1996; Opydo-Szymaczek and Borysewicz-Lewicka, 2007). Thus the maternal burden of fluoride passes to her unborn child, which can then pass through the blood-brain barrier and damage the developing brain.

In addition to increased fluoride levels in the brain (Du et al., 2008; He et al., 2008; Yu et al., 2008), various significant neurological alterations have been observed in fetuses of mothers residing in endemic fluorosis areas (Du et al., 2008; He et al., 2008; Yu et al., 2008). Additionally, neonates of mothers residing in areas with high ($\geq$1.7 mg/L) fluoride levels in the drinking water were found to have impaired neurobehavioral capability and agonistic muscle tension, and thus a significantly lower overall neonatal behavioral neurological assessment (NBNA) score compared to those from low (<1.0 mg/L) fluoride areas (Li et al., 2008). At least 24 studies have indicated an association between increasing levels of fluoride and reduced IQ in children (Connett et al., 2010), with fourteen published after the NRC report was released in March 2006 (see Appendix A). As the developing embryo and fetus are undoubtedly the most susceptible of all life stages to environmental toxins, special consideration should be given to this group when estimating fluoride exposure and relative source contribution.

Another highly susceptible group that has been excluded by OW from its analyses are infants less than 6 months of age. OW's rationale for this is based on the flawed assumption that the period of sensitivity to severe dental fluorosis is from 6 months to 14 years (EPA 2010b, p xiii). Not only are children younger than 6 months also vulnerable to dental fluorosis, but are likely the most sensitive subpopulation regarding all other adverse effects of fluoride, include damage to the brain, bones, thyroid, kidneys, pineal gland, and other tissues and organ systems. That OW has declared that severe dental fluorosis the only endpoint of concern for infants and children is irrational and unfounded.

Despite OW's assertion, many children's permanent teeth begin mineralization prior to 6 months of age. NRC (2006, p.4) explains that enamel fluorosis "is permanent after it develops in children during tooth formation, a period ranging from birth until about age 8." IOM (1997) identifies the period of sensitivity for developing fluorosis from 0 to 8 years. Levy et al. (2010), citing several references (El Nesr and Avery, 1994; Bårdsen, 1999; Evans and Darvell, 1995; Hong et al, 2006) similarly state that the "critical period for development of fluorosis…is during the period from birth".

Human breast milk contains very low concentrations of fluoride, averaging less than 0.01 mg/L F, even in fluoridated communities (EPA, 2010b; NRC, 2006). Infants consuming formula made with fluoridated water could receive up to 250 times as much fluoride as a breast-fed infant. NRC (2006, p. 429) states "An average consumer below the age of 6 months would have an intake of 0.06-0.1 mg/kg/day from fluoridated water (0.7-1.2 mg/L)." Intakes for higher percentile water consumers would be even more extreme, up to 0.288 mg/kg/day for the 99th percentile consumer at a water fluoridation level of 1.2 mg/L (NRC, 2006, Table B-13, p. 432).

The OW's proposed RfD of 0.08 mg/kg/day, already not protective of infant's health, will certainly be exceeded by formula fed infants, especially those less than 6 months of age. Despite recommendations from leading health authorities that infants be exclusively breast fed through 6 months of age, OW cannot assume that this is occurring for all American infants. In fact, by 6 months of age the incidence of exclusive breastfeeding is less than 15%, and more than 40% of breast-fed babies are at least occasionally supplemented with formula (CDC, 2010). OW is being extremely negligent in refusing to consider differences in fluoride intakes between formula- and breast-fed infants, and in not factoring in a margin of safety to protect the health of formula-fed infants.

2.3. OW has failed to adequately consider racial, ethnic, regional, and socioeconomic differences in food and beverage consumption patterns.

In addition to the differences in breast- and formula-feeding patterns of infants between racial groups, there are also substantial differences in food and beverage consumption patterns among children and adults of different racial and ethnic populations in the United States.

Tea is one example of a fluoride-containing beverage that has wide variations in consumption patterns. Tea consumption has increased "over three-fold in the past two decades, primarily from ready-to-drink teas but also from brewed black teas" (Pehrsson, 2011). The average daily consumption of tea considered by NRC (2006, pp. 60-61) as a component of background food is ½ cup brewed tea, but data from the National Health and Nutrition Examination Survey (NHANES, 2003) suggests that Americans consume twice this amount (Pehrsson, 2011).

Certain populations drink substantially more tea than others, and must not be ignored when considering fluoride exposure rates. As tea contains relatively high levels of fluoride (up to 5 mg/L F; NRC, 2006, p. 40), and has a bioavailability close to that of sodium fluoride (EPA, 2010b, p. 10), "A habitual tea drinker, especially for brewed tea, can be expected to significantly exceed" the consumption rates presented in Table 2-9 (NRC, 2006, p. 60-61). In the United Kingdom, for example, people can consume up to 9 mg F/day (Jenkins, 1991). According to the Tea Association of the U.S.A., "In 2010, Americans consumed well over 65 billion servings of tea, or over 3 billion gallons. On a regional basis, the South and Northeast have the greatest concentration of tea drinkers." (Tea Association, Undated).

Cow's milk (≤0.07 mg/L F; NRC, 2006) generally contains less fluoride than water. However, not all Americans consume the same proportions of milk, water, and other beverages. For example, African Americans and Mexican Americans have been found to have a significantly higher intake of water and lower intake of milk than Caucasians (Sohn et al, 2001, 2009). Certain racial groups are more likely to be lactose intolerant than others. Included among these are Central and East Asians (80-100% lactose intolerant; de Vrese, 2001), Native Americans (80-100% lactose intolerant; National Institute of Child Health and Human Development, 2006), African Americans (75% lactose intolerant), and Southern Indians (70% lactose intolerant; de Vrese, 2001). The elevated incidence of lactose intolerance may indicate lower rates of milk consumption, and higher water consumption rates than North American Anglos (21% lactose intolerant; Scrimshaw and Murray, 1988). Thus these groups may be more heavily exposed to fluoride in water and other beverages than are Caucasian Americans.

Also of interest when considering differences in milk consumption is calcium intake. Calcium deficiency leads to more severe effects of fluoride, metabolic bone diseases, and bone deformities (Teotia et al., 1998; NRC, 2006). Thus lower fluoride intakes are required to produce toxic effects when calcium deficiency exists (Teotia et al, 1998; NRC, 2006). Certain groups, including African Americans (data from NHANES III, Alaimo et al, 1994; NRC, 1989) and low-income persons are at a higher risk for calcium deficiency. USDA reports that participants in the Food Stamp Program "consumed a significantly smaller percentage of the AI (Adequate Intake) for calcium than…higher-income non-participants (73% vs. 83%) (Fox and Cole, 2004).

Certain groups, especially low-income families, consume substantially less fresh fruits and vegetables—and thus more processed foods—than other groups. Many processed foods, including mechanically separated chicken, generally have higher levels of fluoride (Heilman et al., 1997; Fein and Cerklewski, 2001; USDA, 2005), as food processing often concentrates fluoride (Warren and Levy, 2003).

Certain groups consume substantially more fish and shellfish, which contain the highest concentrations of fluoride of all solid foods analyzed (ATSDR, 2003; EPA, 2010b, p. 21). In particular, fish consumption rates are higher for some Asian populations, Blacks, Native Americans, and other minority groups (OEHHA, 1987).

Unless OW can verify that all racial, ethnic, socioeconomic, and regional populations were adequately represented in each of the studies and "Market Basket" collections reviewed, OW cannot claim to have identified fluoride exposure patterns representative of all Americans. In addition, while the USDA (2005) database on foods is stated to be the "most comprehensive source of information on the concentrations of fluoride in foods", OW admits that it is "incomplete because many foods found in an average U.S. diet are not included." (EPA, 2010b, p. 20).

2.4. OW has ignored several sources of fluoride as contributors to total intake.

OW claims that the "RSC for fluoride has been developed using human health AWQC (Ambient Water Quality Criteria) methodology framework" (EPA, 2010b, p. 3). According to AWQC methodology, "All known exposure routes and media are considered" (EPA, 2010b, p. 3), yet OW has ignored several sources of fluoride exposure that may contribute immensely to total exposure. These include various dental products, dietary supplements, pharmaceuticals, ambient air, occupational exposures, cigarette smoke, and dermal exposures. According to OW, "these sources make minimal contributions to daily intakes during the period of dental fluorosis vulnerability." (EPA, 2010b, p. 88). However, this rationale is severely flawed, and the refusal to consider these sources as part of the exposure calculation may result in OW underestimating fluoride exposures for many in the population.

Several of these sources are neglected because it is claimed that they are not likely to occur during the period of dental fluorosis vulnerability. For example, OW states that the "major chronic-use, fluoride-containing pharmaceuticals do not include young children among their target population" (EPA, 2010b, p. 89). However, despite that OW's stated endpoints of concern for these analyses are severe dental fluorosis (for children up to 14 years) **and** stage II skeletal fluorosis **and** increased risk of bone fracture (for children over 14 years and for adults), no further reference is made for these (or any) fluoride-containing pharmaceuticals for adult exposure estimates.

2.4.1. OW has ignored fluoride exposures from several dental products, including professionally applied topical fluorides, mouthwashes, and various dental devices.

While OW claims that several sources of fluoride, including professional dental treatment products "make minimal contributions to daily intakes during the period of dental fluorosis vulnerability" (EPA, 2010b, p. 88), NRC (2006, p. 43) states that they "could be important with respect to short-term or peak exposures."

Relatively high amounts of fluoride are swallowed during fluoride gel treatments (Whitford et al, 1987), perhaps as much as 0.5 mg F per treatment (Larsen et al, 1985). Ingestion of high-concentration fluoride gel leads to a sharp increase in plasma fluoride levels, and acute symptoms of dizziness and nausea follow (Ekstrand and Koch, 1980). For young children, the amount of fluoride swallowed from professional gel treatments may be sufficient to cause dental fluorosis (Whitford et al, 1987).

Acute exposures to high amounts of fluoride may "lead to nausea, abdominal pain, vomiting and diarrhea, and in more severe cases, generalized weakness spasms of the extremities, drop in blood pressure, convulsions and death" (Zuanon and Aranha, 2005).

OW admits that "Use of fluoride-containing mouthwashes, particularly by children in the 1-7 year age group…could measurably increase the total estimates (EPA, 2010b, p. 101), and that "Use of fluoridated mouth washes on a daily basis in the home setting is likely to increased the daily dose of fluoride from dental products" (EPA, 2010b, p. 80), yet no effort has been made to quantify this route of exposure to fluoride among children or adults. Fluoridated mouthwashes contain between 230-500 mg F/L (for daily use) and 900-1000 mg F/L (for weekly or biweekly use) (WHO, 2002), and thus a large amount of fluoride could potentially be ingested from these products on a daily or weekly basis. However, OW has failed to include this potentially significant source of fluoride due to a claimed "lack of data" (EPA, 2010b, p. 101).

Contrary to this claim, within the same document OW states that "Several studies have evaluated the use of topical fluoride products and mouth-rinses" (EPA, 2010b, p. 78). Although mouthwashes are generally not recommended for children younger than 5 years, there is evidence that even this young age group is using—and likely ingesting—this fluoridated product. The 1983 National Health Interview Survey found that 5% of children under 5, and 17% of children ages 5-17, used mouthwashes (see Wagener & Nourjah, 1992). The U.S. Oral Care Market Research Report for 2000 indicates that nearly three-fifths of all U.S. adults use mouthwash (Packaged Facts, 2001).

Zuanon and Aranha (2005) found that children ages 3-6 years ingested 0.4-1.6 ml (8-32%) of mouthwash per use. This would translate to 0.09-0.37 mg F ingested per use of mouthwash containing 230 mg F/L. Other studies have found similar fluoride retention rates of 15-30% for fluoride mouth rinsing (Hellstrom, 1960; Ericsson and Forsman, 1969; Birkeland, 1973; Wei and Yiu, 1993). Taking into consideration the amount of mouthwash swallowed and the range of fluoride concentrations found in various mouthwashes, the Office of Environmental Health Hazard Assessment of the State of California (OEHHA, 1997) estimates that the fluoride intake for mouthwash alone would be 0.1-0.5 mg for children, and 0.2-1.0 mg for adults. This value is 5-33% of OW's estimated total intake from other sources (~2-3 mg F/day for children ≥4 years and adults; EPA, 2010b, p. 104)—hardly an insignificant amount that allows for exclusion from exposure estimates.

OW acknowledges that "Fluoride is released from a number of dental devices, including composite resins, resin-based cements, resin-bonding agents, orthodontic bracket adhesives, pit and fissure sealants, glass ionomer cements, and cavity varnishes" but then declares that, according to HHS (2010), "the exposure dose is probably small" (EPA, 2010b, p. 80). It is disheartening that OW has failed to do its own research on this matter, instead relying on HHS to provide not only a vague and unsubstantiated claim, but also one that is incorrect. A recent literature review of slow-release fluoride devices found that such devices release between 0.04-0.5 mg F/day (Pessan et al., 2009). A study of glass ionomers found that 15-15 mg F/L was released on the first day, with a cumulative fluoride release of 1.3-2.2 mg F/day over the course of 70 days (Hicks et al, 2003).

While OW accounts for fluoride ingested via toothpaste, the estimates used are flawed, as the exposure estimates for all age groups is based on only one brushing per day (EPA, 2010b, Table 6-4, p. 94). The American Dental Association (ADA) and most oral health providers recommend brushing twice daily (ADA, 2011; Bray, 2010), a practice that has found to be followed by most study participants (Ganss et al., 2009; Attin and Hornecker, 2005). OW acknowledges findings that perhaps 20-30% of 1-3 year olds brush more than once per day, and that a "substantial portion" of school-aged children and adults is likely to brush more than once per day (EPA, 2010b, p. 101). Additional studies have found that 60-70% of children 6 months to 5 years brush 2 to 3 times per day. However, OW refers to the changes in RSC values resulting from re-analysis of the data to account for brushing twice a day (for all age groups ≥7 years of age) as not substantial—despite up to a 4% decrease (EPA, 2010b, p. 101).

It is not understood why OW chose to use the term "substantial" instead of "significant." The latter carries statistical meaning, while the previous generally does not. If OW was indeed indicating lack of statistical significance, it should have at the very least provided the p-value at which the statistical tests were conducted. Although OW misstated the age categories it considered for re-analysis (i.e. actually calculated for all age groups ≥4 years), it is not understood why OW did not also consider children younger than 4 years. When re-analyzed for these age groups, the RSC values for drinking water decreased from 70 and 40% (for 0.5 - <1 year and 1 - <4 years) to 66 and 33%, a decrease in RSC for drinking water of 3 and 7%, respectively. While a 4% decrease in RSC may not be "substantial" according to OW, a 7% decrease certainly may be. OW should seriously reconsider its decision to include only one brushing per day in its exposure analysis.

2.4.2. OW has failed to consider fluoride exposure from dietary fluoride supplements in its analysis.

The American Dental Association (ADA) now offers the clinical recommendation that only children at high risk for developing dental caries, and whose primary drinking water contains less than "optimum" levels of fluoride (<0.6 mg/L) receive fluoride supplements (Rozier et al., 2010). Also recommended is that practitioners conduct a comprehensive survey of all sources of a patient's fluoride intake before prescribing supplements to children.

However, it is well known that physicians and dentists have "a lack of knowledge and inappropriate prescribing practices regarding fluoride supplements" (Horowitz, 1999). Kuthy and McTigue (1987) found that only 6.2 percent of physicians inquired about the fluoride status of the child's primary drinking water before prescribing supplements. An estimated 13 percent of fluorosis cases in fluoridated communities may result from the inappropriate use of fluoride supplements, with that proportion climbing to over 60 percent in nonfluoridated communities (Rozier et al., 2010). As noted by Horowitz (1999), "the inappropriate prescription of supplements to children drinking optimally fluoridated water has been shown to be a persistent problem."

If a 6 year-old child drinking water with "less than optimal" fluoride concentrations (e.g. 0.5 mg F/L) is prescribed daily fluoride supplements, that child would be ingesting 0.47 mg/day from drinking water, and perhaps an additional 1.00 mg F/day from supplements (Levy et al., 2001), resulting in a daily intake of 1.47 mg F. This is an 80% increase over the representative values for fluoride intakes for water (at 0.87 mg F/L) used in the RSC calculation, and would increase the total fluoride intake by 32% to 2.68 mg/day (0.127 mg/kg/day)—certainly not a trivial increase. OW should seriously reconsider its exclusion of dietary fluoride supplements for the Exposure and RSC Analysis.

2.4.3. OW has failed to consider pharmaceuticals and anesthetics that metabolize to the fluoride anion in its exposure analysis.

Fluorinated anesthetics are well known to metabolize to the fluoride anion in the human body. Lockwood et al. (2010) estimated brain elimination times of 33 hours, 52 hours, and 71 hours for desflurane, sevoflurane and isoflurane, respectively. They also estimated a whole-body retention rate of 4-13% of the absorbed dose.

While there is little in the published literature on the fluoride metabolites of pharmaceuticals, Chen et al. (2011) cited effects in five lung transplant patients on chronic voriconazole, a fluoride-containing compound, as "diffuse periostitis resembling hypertrophic osteoarthropathy and perostitis deformans."

Many of the top-selling drugs in 2009 were fluorine-containing pharmaceuticals, including Lipitor (42 million units sold), Lexapro (23.7 million units), Crestor (18.4 million units), Advair Diskus (17.4 million units), and Prevacid (14.5 million units) (Drugs.com, Undated). Considering the widespread, chronic use of such pharmaceuticals, OW should request from the Food and Drug Administration (FDA) a list pharmaceuticals that metabolize to the fluoride anion for use in its current review of fluoride exposure. This list should also be made to the public.

2.4.4. OW has failed to consider ambient air as a source of fluoride in its exposure analysis.

While OW states that "Exposure from ambient air are not included in the RSC equation because they are a minor contributor (<4 μg/day) to the total exposure estimate (EPA, 2010b, p. 97). However, OW does not consider above-average exposures in urban or industrialized areas. For ambient air, "The highest concentrations (of fluoride) correspond to urban locations or areas in the vicinity of industrial operations" (NRC, 2006, p. 43)—including oil refineries, incinerators, aluminum smelters, and coal plants. While the emissions from these industries are eventually dispersed, those living locally will be more heavily impacted, especially during times of precipitation.

One example of elevated levels of fluoride in ambient air is the emissions from the aluminum smelters in Massena, New York. At a site approximately seven miles from the smelters in Massena, the Ontario Ministry of Environment (MOE, 1999) performed an analysis of fluoride on 28 soil and 30 foliage samples in Cornwall, Ontario, Canada. All soil samples significantly exceeded the MOE's Guidelines for Use at Contaminated Sites in Ontario. Of the 30 foliage samles, 27 exceeded the MOE's

Upper Limits of Normal contaminant guidelines. While the soil levels represent deposition over decades, the foliage samples represent approximately six months of exposure to air-borne fluoride (MOE, 1999).

EPA's Toxic Release Inventory (TRI) for 2008 reports nearly 65 million pounds of hydrogen fluoride releases, with coal-fired electric utilities the major source, and 91,874 pounds of fluorine releases (FAN, 2011). However, not all sources or releases are included in TRI, and while EPA issues permits for pollutants such as hydrogen fluoride and fluorine, OW must take into account vulnerable populations living near fluoride emitting industries in this exposure assessment. It is also worth mentioning that coal-fired utilities are also the major source of mercury releases to the environment (Sierra Club, 1996), which is an established neurotoxicant. As fluoride is also known to affect the brain, the synergistic effects of the two could be devastating.

2.4.5. OW does not adequately consider exposure from cigarettes in its analysis.

Similar to the rationale given for other sources above, fluoride exposure from cigarettes is presumably not considered in the current analysis because cigarette smoking is not generally prevalent in the age range that is vulnerable to developing severe dental fluorosis. However, as explained previously, OW's endpoints of concern are severe dental fluorosis (for children up to 14 years) **and** stage II skeletal fluorosis **and** increased risk of bone fracture (for children over 14 years and for adults). By ignoring cigarette smokers, as well as those who are chronically exposed to second-hand smoke, OW has failed to acknowledge another important source of fluoride for a substantial proportion of the population.

In 2007, 7.2% of the population of the United States were considered high-intensity smokers ($\geq$20 cigarettes/day), and another 5.4% were considered moderate-intensity smokers (10-19 cigarettes/day) (Pierce et al., 2011). According to EPA (1988), "heavy cigarette smoking could contribute as much as 0.8 mg of fluoride per day to an individual (0.01 mg/kg/day for a 70 kg person). Thus, cigarettes "may be another significant source of fluoride intake by humans (Marier and Rose, 1977). Thus, more than 21 million Americans were possibly exposed to additional 0.8 mg F/day, and another 16 million were exposed to perhaps an additional 0.4 mg F/day, that were not accounted for in OW's exposure assessment. This additional exposure alone would increase the total fluoride intake for an adult from 2.91 mg/day to 3.71 mg/day, and would decrease the RSC for drinking water from 60% to 47%.

3. Conclusions

OW states that "the RfD represents an exposure that is estimated to provide the anticaries benefits from fluoride without causing severe dental fluorosis in 99.5% of the children who drink water with 0.87 mg/L F at a 90th percentile intake level and have average intakes from other media during the period of secondary tooth formation" (EPA, 2010b, p. 104). This means that, with current policies in place, *at least* 155,000 Americans will end up suffering for a lifetime with severe dental fluorosis.

Unfortunately, these policies ignore 1) the 10% of Americans (31 million people) drinking more than the 90th percentile for water consumption; 2) *at least* 3 million Americans drinking water with fluoride levels greater than 0.87 mg/L (likely many millions more, depending on the level of artificial fluoridation used; CDC, 1993; EPA, 2010b, p. 58); 3) *half* of the U.S. population (155 million people) weighing less than the average; 4) the majority of Americans who brush their teeth more than once each day; 5) the 5-60% (15.5-186.6 million people) who use a fluoridated mouthwash; 6) the 12% of Americans (37 million people) who are moderate- to high-intensity smokers; 7) the thousands of people who have naturally-occurring high levels of fluoride in their drinking water, but also consume sodas, beer, and fruit drinks made with fluoridated water; and 8) the thousands of people living near fluoride-emitting industries.

There is no way that many of these sources of fluoride or other factors can be controlled or even influenced by the EPA. However, there is one way that millions of Americans' exposure to fluoride can be dramatically reduced, and that is by removing the self-imposed constraint of protecting the water fluoridation program. This would free OW to determine an honest and science-based MCLG. If the EPA used the normal methodologies and assumptions used for other pollutants, an MCLG of no greater than 0.1 mg F/L—and more reasonably zero—would be the likely outcome.

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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	Hum Exp Toxicol. Mar 15. [Epub ahead of print] 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	Hum Exp Toxicol. Mar 15. [Epub ahead of print] Abstract

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	Environ Toxicol. 24(3):218-24. June.
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	World J Gastroenterol. 12(7):1144-8. Feb 21. Full
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	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**	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
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**	Exp Toxicol Pathol. Dec 10. [Epub ahead of print] 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	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 concentration of fluoride in drinking water**…"	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,	Fluoride 38(3):226. See Abstract Number 9
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 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.	Clinica Chimica Acta 411: 263–266. 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	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 endoplasmic reticulum stress in OS732 cells. "… **This study proved that PERK signaling play major roles in action of fluoride on osteoblast**, and suggested that bone response in skeletal fluorosis may be due in part to PERK signaling pathway."	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	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 intestinal failure** who are receiving home parenteral nutrition. • TABLE 3. Spinal bone status • TABLE 4. Femoral neck bone mineral density (BMD) • TABLE 5. Frequency of osteopenia and osteoporosis at the beginning and the end of	Am J Clin Nutr. 83(6):1429-37. June. Full Article

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	Biol Trace Elem Res. 133(1):71-82. Jan.
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	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	Experimental and Toxicologic Pathology [in press; available online
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: *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:	Wu N, et al. 2008. Behavioral Teratology in	Fluoride 41(2):129–133
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	Fluoride 38(4):284–92. 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 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*	Ding Y, et al. 2011. The **relationships between low levels of urine fluoride on children's**	Journal of Hazardous Materials 186:1942–1946.
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*	Trivedi MH, et al. 2007. Effect of High Fluoride Water on Intelligence of School Children in	Fluoride 40(3):178–83, Full Report
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**. *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, the whole body still retained between 4% and 13% of the absorbed dose**."	Br J Anaesth. 104(5):648-55. May. Abstract
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	Toxicology in Vitro 22(4):837–43. 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,

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 its content in bones of rats. "CONCLUSIONS: … longer exposure increased fluoride accumulation in the femur ($p < 0.001$). All groups exposed to NaF had significantly higher fluoride concentration in the femur as compared with control animals. Groups receiving NaF and AlCl3 showed lower fluoride concentration in serum and femur compared with those exposed to NaF only and higher in comparison with controls. Fluorine content in the femur of rats exposed to NaF and AlCl3 for four months was similar to the results obtained after one month of exposure."	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*	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,	Environmental Health Perspectives 115(4):643–47. 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 oxidative stress, **arsenic and fluoride levels in male mice**. “ Arsenic and fluoride concentration increased significantly on exposure. Interestingly, their concentration decreased significantly on concomitant exposure for 8 weeks. However, the group which was administered arsenic for 4 weeks followed by 4 weeks of fluoride administration showed no such protection suggesting that the antagonistic effect of fluoride on arsenic or vice versa is possible only during interaction at the gastro intestinal sites. These results are new and interesting and require further exploration.”	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	J Pub Health Dent 69(2):
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	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 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... There have been no randomized trials of water fluoridation… Although the prevalence of caries varies between countries, levels everywhere have fallen greatly in the past three decades, and national rates of caries are now universally low. **This trend has occurred regardless of the concentration of fluoride in water or the use of fluoridated salt**, and it probably reflects use of fluoridated toothpastes and other factors, including perhaps aspects of nutrition."	British Medical Journal 335(7622):699-702.
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	Clinical Oral Investigations 11(3):189-93.

2007 Dental Caries Pizzo G, et al. 2007. **Community water fluoridation and caries prevention: a critical review.** Clinical Oral Investigations 11(3):189-93.

"For the past 50 years, CWF (Community Water Fluoridation) has been considered the

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 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
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	NCHS data brief, no 53. Hyattsville, MD: National

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 dentifrice intake by participants when aged 16 to 36 months."	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	J Public Health Dent. 2069(4):267-75. Fall. 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	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 45% in the 1.1 ppm fluoride area and 21% in the 0.3 ppm fluoride area**."	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**.	Environ Res. 103(1):112-6. Jan. 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	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 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-**	Eur Rev Med Pharmacol Sci. 14(6):507-12. June. 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	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	Asian Pacific Journal of Tropical Medicine 3(2):136-140. Feb.

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**	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 hepatocytes**.	World J Gastroenterol. 12(7):1144-8. February 21. Full Report
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	J Am Diet Assoc. 111:285-289.

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	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, the whole body still retained between 4% and 13% of the absorbed dose**."	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.	J Dent Res. 88(2):142-5. Feb. 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-	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 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.	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	Caries Res. 40(6):494-500. Abstract
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	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. **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	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 commodities**."	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 calculations the new MCLG for fluoride in drinking water should be at most one tenth (0.4 mg/L) of the current MCLG of 4 mg/L, suggesting that the practice of fluoridation should be re-evaluated."**	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. 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. "… We found **statistically significant low T4 levels, hypocalcemia and hyponatremia**, increased QT and QTc interval in children with dental fluorosis. **Our results show that fluorosis might increase risk of arrhythmia indirectly**, due to its hypocalcemic, hypernatremic, and hypothyroidism effects… **Further studies concerning cardiovascular effect of fluorosis in both adults and children are needed**."	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 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 pollution with fluorine compounds**]	Gig Sanit. Nov-Dec;(6):53-5. Full Article - English Translation
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	Encyclopedia of Environmental Health (Editor-in-Chief: Jerome O. Nriagu, Elsevier B.V.), Pages 769-775.
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	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. "... Among the factors inducing intensified free radical processes, fluoride ions are listed, among others. **One of the organs most exposed to the toxic activity of fluorides is the kidney...** The studies carried out confirmed the disadvantageous effect of NaF upon the antioxidative system in rats (decrease in activity of antioxidative enzymes)."	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	J of Saudi Chemical Society. 14(4):413-416. Full Report
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	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, which may affect its functions**.”	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	Oncu M, et al. 2006. Effect of chronic fluorosis	Toxicol Ind Health.
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 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
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**	Free Radical Biology and Medicine 49(Suppl 1):S221. July.

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	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
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	J Appl Toxicol. 23(6):437-46. Nov-Dec. 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	J Appl Toxicol. 23(6):437-46. Nov-Dec. Abstract

2010	Muscle	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.
2011	Oxidative Stress	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	Oxidative Stress	Liu H, et al. 2010. Fluoride-Induced Oxidative Stress in Three-Dimensional Culture of **OS732 Cells and Rats.** "The study provided insight into the mechanism of skeletal fluorosis. Also, this study distinguished itself by identifying **oxidative stress as a potential modulator of osteogenesis in skeletal fluorosis."**	Biol Trace Elem Res. Oct 23. [Epub ahead of print] Abstract
2010	Oxidative Stress	Basha PM, et al. 2010. Evaluation of Fluoride-Induced Oxidative Stress in Rat Brain: A Multigeneration Study. "**Results of this study can be taken as an index of neurotoxicity in rats exposed to water fluoridation over several generations**."	Biol Trace Elem Res. Jul 24. [Epub ahead of print] Abstract
2010	Oxidative Stress	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).
2009	Oxidative Stress	García-Montalvo EA, et al. 2009. Fluoride exposure **impairs glucose tolerance** via decreased insulin expression and oxidative	Toxicology 263(2-3):75-83. Sept 19. Abstract
2009	Oxidative Stress	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	Oxidative Stress	Chouhan S, Flora SJ. 2008. Effects of fluoride on the **tissue oxidative stress and apoptosis in rats**: biochemical assays supported by IR spectroscopy data.	Toxicology 254(1-2):61-7. Dec 5. Abstract
2008	Oxidative Stress	Izquierdo-Vega JA, et al. 2008. Decreased in vitro **fertility in male rats** exposed to fluoride-induced oxidative stress damage and mitochondrial transmembrane potential loss.	Toxicol Appl Pharmacol. 230(3):352-7. Aug 1. Abstract
2008	Oxidative Stress	Gao Q, Liu Y-J, Guan Z-Z. 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**. Corrigendum: "the concentrations of fluoride should have been given as mM, instead of lM."	Toxicol In Vitro. 22(4):837-43. June. Abstract
2008	Oxidative Stress	Xu H, et al. 2008. Role of oxidative stress in **osteoblasts** exposed to sodium fluoride.	Biol Trace Elem Res. 123(1-3):109-15. Abstract
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
2007	Oxidative Stress	Jin XQ, et al. 2007. Fluoride-induced oxidative stress of **osteoblasts** and protective effects of baicalein against fluoride toxicity.	Biol Trace Elem Res. 116(1):81-9. April. Abstract
2007	Oxidative Stress	Jin XQ, et al. 2007. Fluoride-induced oxidative stress of **osteoblasts** and protective effects of baicalein against fluoride toxicity.	Biol Trace Elem Res. 116(1):81-90. April. Abstract
2007	Oxidative Stress	Bouaziz H, et al. 2007. Oxidative stress induced by fluoride in **adult mice and their suckling pups**.	Exp Toxicol Patho. 58(5):339-49. April 26. Abstract
2006	Oxidative Stress	Sarkar S, et al. 2006. Fluoride-induced immunotoxicity in **adult male albino rat**: a correlative approach to oxidative stress.	J Immunotoxicol. Jul 1;3(2):49-55. Abstract
2009	Pancreas	Ito M, Nakagawa H, Okada T, Miyazaki S, Matsuo S. 2009. ER-stress caused by accumulated intracistanal granules activates autophagy through a different signal pathway from unfolded protein response in **exocrine pancreas cells of rats** exposed to fluoride.	Arch Toxicol. 83(2):151- 9. February. Abstract
2011	Reproductive	Sun Z, et al. 2011. Fluoride-induced apoptosis	Arch Toxicol. 2011 Feb 22.
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2008	Reproductive	Izquierdo-Vega JA, et al. 2008. Decreased in vitro **fertility in male rats** exposed to fluoride-induced oxidative stress damage and mitochondrial transmembrane potential loss.	Toxicol Appl Pharmacol. 230(3):352-7. Aug 1. Abstract
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2008	Reproductive	Dvorakova-Hortova K, et al. 2008. The influence of fluorides on **mouse sperm** capacitation.	Anim Reprod Sci. 108(1-2):157-70. Oct. Abstract
2008	Reproductive	Huang C, et al. 2008. Effects of sodium fluoride on androgen receptor expression in **male mice**.	Fluoride 41(1):10-7. Jan-March. Full Article
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2007	Reproductive	Gupta RS, et al. 2007. The toxic effects of sodium fluoride on the reproductive system of **male rats**.	Toxicol Ind Health. 23(9):507-13. Oct. Abstract
2007	Reproductive	Jiang Q, Song XK, Cui QH, Chen LJ. 2007. [Effect of fluoride on expression of telomerase reverse transcriptase expression and proliferating cell nuclear antigen in **germ cells of rats' testes**]	Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 25(2):96-9. Feb. [Article in Chinese] Abstract
2007	Reproductive	Reddy PS, et al. 2007. Suppression of **male reproduction in rats** after exposure to sodium fluoride during early stages of development.	Naturwissenschaften 94(7):607-11. July. Abstract
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2006	Reproductive	Sarkar S, et al. 2006. Management of fluoride induced **testicular disorders** by calcium and vitamin-E co-administration in the albino **rat**.	Reprod Toxicol. 22(4):606-12. Nov. Abstract
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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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2010	Skeletal fluorosis	Choubisa SL, et al. 2010. Osteo-dental fluorosis in relation to age and sex in tribal districts of Rajasthan, India. “… Out of 11205 individuals of Dungarpur and 7416 of Udaipur districts, 8090 (72.1%) and	J Environ Sci Eng. 52(3):199-204. July. Abstract

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2007	Skeletal Fluorosis	Gupta RC, et al. 2007. Skeletal fluorosis **mimicking seronegative arthritis**.	Scandinavian Journal of Rheumatology, 36:2:154-5.
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2008	Teratogen	Wu N, et al. 2008. **Behavioral teratology** in rats exposed to fluoride. "...differences in motor coordination, auditory reaction, pain sensitivity, and other cognitive responses, some statistically significant, varying with time and F exposure, were noted, especially among the pups in the 25 mg/L group. 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):129-33. April-June. Full Article
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 T4 levels, hypocalcemia and hyponatremia**, increased QT and QTc interval in children with dental fluorosis. Our results show that fluorosis might increase risk of arrhythmia indirectly, due to its hypocalcemic, hypernatremic, and hypothyroidism effects... Further studies concerning cardiovascular effect of fluorosis in both adults and children are needed."	Anadolu Kardiyol Derg. 11(2):150-5. Full Report
2010	Thyroid / Parathyroid	Koroglu BK, et al. 2010. Serum Parathyroid Hormone Levels in Chronic Endemic Fluorosis.	Biol Trace Elem Res. Sep 14. [Epub ahead of print] Abstract

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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
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