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

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: 7 January 2011

SUBJECT: Sulfuryl Fluoride –Revised Human Health Risk Assessment for Fluoride to Incorporate New Hazard and Exposure Information

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1. Background

Sulfuryl fluoride (SF) is an insecticide registered for fumigation of structures and food commodities, and has been deemed by both the Office of Pesticide Programs (OPP) and the Office of Air and Radiation (OAR) to be a methyl bromide alternative. Following application, SF rapidly breaks down to form sulfate and fluoride (F). Analytical techniques used to analyze F following application of SF indicate that the F is generally bioavailable.

In 2004, the Health Effects Division (HED) of the OPP assessed the human health risks associated with SF fumigation of cereal grains, dried fruits and tree nuts (EPA, 2004). In 2005 and 2006, another assessment was completed in order to examine proposed uses of SF in food processing facilities (EPA, 2006). In both cases, the HED evaluated risks associated with exposure to SF and F, separately, and recommended for the proposed uses. Separate tolerances were established for residues of SF (40 CFR 180.575) as well as F (40 CFR 180.145) in/on a number of commodities. In assessing potential risks associated with fluoride exposure, the OPP used the Agency's maximum contaminant level goal (MCLG) for fluoride of 4 mg/L along with estimates of water consumption and body weight to calculate a reference dose in units of either mg/day or mg/kg/day. At the time those assessments were completed, the OPP was aware that the National Research Council (NRC) of the National Academies of Sciences (NAS) was reviewing, at the Agency's request, the toxicological data for fluoride, and the OPP stated that when the NRC review was completed, the F tolerances and risk assessment would be reevaluated.

The NRC review (*Fluoride in Drinking Water: A Scientific Review of EPA's Standards*, released March 2006) concluded, "In light of the collective evidence on various health end points and total exposure to fluoride, the committee concludes that EPA's MCLG[maximum contaminant level goal] of 4 mg/L [in drinking water] should be lowered. Lowering the MCLG will prevent children from developing severe enamel fluorosis and will reduce the lifetime accumulation of fluoride into bone that the majority of the committee concludes is likely to put individuals at increased risk of bone fracture and possibly skeletal fluorosis, which are particular concerns for subpopulations that are prone to accumulating fluoride in their bones." [Page 10] Although the NRC report recommends that the Agency "develop an MCLG that is protective against severe enamel fluorosis, clinical stage II skeletal fluorosis, and bone fractures…" [Page 10], the NRC report did not provide dose-response analyses to determine points of departure for assessing these effects. Since release of the NRC report, the Agency's Office of Water (OW) has been evaluating the NRC's findings and has performed a technical examination of the available data on dental fluorosis, skeletal fluorosis (the adverse effect that serves as the basis for the current MCLG), and skeletal fractures (EPA, 2010a).

In addition, the OW has produced a relative source contribution analysis (RSCA; EPA, 2010b) in order to examine the role of drinking water in overall fluoride exposure. The RSCA is an examination of fluoride exposure from a number of sources, including drinking water and other beverages, background levels in food, toothpaste ingestion, air, soil ingestion, and residues in food from the use of pesticides. The OW analysis is based on a comprehensive, in-depth review of the available literature (the previous OPP assessments associated with SF are based on exposure modeling where possible).

This assessment updates and revises OPP's risk estimates for fluoride conducted in 2004, 2005, and 2006, taking into account the OW hazard and exposure analyses. The Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (FQPA) of 1996, places certain legal requirements on the OPP with regard to risk assessment and making a safety finding. Of particular importance is the requirement that the OPP take into consideration the "... special susceptibility of infants and children to the pesticide chemical residues..." as well as the "...dietary consumption patterns of consumers (and major identifiable subgroups of consumers); ... [and] available information concerning the aggregate exposure levels of consumers (and major identifiable subgroups of consumers)..." The differences in the focus of the OPP and OW exposure assessments reflect the differences in requirements between FFDCA as amended by FQPA, and the Safe Drinking Water Act, which applies to the OW.

It should be noted that this assessment focuses, primarily, on the adverse effects of exposure to fluoride. There are, however, oral health benefits associated with fluoride exposure at lower levels. The National Academies of Sciences Institute of Medicine has established an adequate intake level of 0.05 mg/kg/day (IOM, 1997). At beneficial levels, fluoride reduces the incidence of dental caries by inhibiting the demineralization of enamel associated with the activity of cariogenic bacteria and by promoting rebuilding of demineralized enamel.

2. Hazard Assessment

2.1 Critical Effect

In its review of the effects of fluoride, the NRC included "the effects of fluoride on teeth, the musculoskeletal, reproductive, endocrine, gastrointestinal, renal, hepatic, and immune systems; and on the endpoints of developmental toxicity, neurotoxicity (including behavioral effects), genotoxicity, and carcinogenicity." (NRC, 2006, p. 2). Following their review, the NRC concluded that "...the tissues of most concern to fluoride exposures...were the teeth and bones." (NRC, 2006, p. 2) and that "Severe enamel fluorosis compromises this health-protective function by causing structural damage to the tooth. The damage to teeth caused by severe enamel fluorosis is a toxic effect that the majority of the committee judged to be consistent with prevailing risk assessment definitions of adverse health effects." (NRC, 2006, p. 127).

A detailed discussion of dental enamel fluorosis, including its biological basis and various measurement scales, can be found in the OW's Dose-Response Analysis for Non-Cancer Effects (DRA; EPA, 2010a). Briefly, dental fluorosis can range from the occurrence of a few white flecks or occasional white spots being present within the enamel to pitting of the enamel with brown staining and a corroded appearance. As discussed in the DRA, the EPA has determined that (1) the pitting associated with severe dental fluorosis is an adverse health effect and the assessment of the risks from fluoride exposure should be based on this endpoint, and that (2) an assessment based on severe dental fluorosis would be protective of other adverse dental and bone effects associated with fluoride exposure (*e.g.*, caries, skeletal fluorosis, increased risk of bone fractures). The NRC recommended that the EPA "develop an MCLG that is protective of severe enamel fluorosis, clinical stage II skeletal fluorosis, and bone fractures…" (NRC, 2006, p. 352). Although the purpose of this assessment is not to establish a new MCLG, focusing this FFDCA assessment on being protective of severe enamel fluorosis is in keeping with the NRC's recommendation.

While numerous non-dental and non-bone effects following fluoride exposure have been described in the literature, neither the cause-effect nor dose-response relationships of those effects are well documented resulting in significant limitations associated with using results from those studies for regulatory purposes.

2.2. Dose-Response Analysis and the Reference Dose

The OW has reviewed the available literature associated with fluoride exposure through drinking water and the prevalence of dental fluorosis, and has selected a study published in 1942 by Dean as the most appropriate for deriving a reference dose (RfD). A complete description of the hazard evaluation can be found in the DRA.

The OW notes in the DRA that there are a large number of epidemiological studies that are available and have the potential to serve as the critical study for establishing an RfD for severe dental fluorosis. Based on confounding factors regarding sources of fluoride exposure, sample sizes from individual studies, and the variability inherent in the evaluation of dental fluorosis across studies, the 1942 Dean study is the most appropriate for deriving the RfD. The OW conducted a benchmark dose (BMD) analysis with the data from Dean (1942) using the endpoint of severe dental fluorosis. The BMD for 0.5% severe dental fluorosis was determined to correspond to a fluoride concentration in drinking water of 2.14 mg/L. This BMD has a lower 95% confidence limit (BMDL) at 1.87 mg/L. The BMDL is derived in terms of F concentration in water. In order to determine a chronic RfD for severe dental fluorosis, age-group specific estimates of water intake (L/day) and body weight (kg) at the time of the Dean (1942) study were used to convert the BMDL into a point of departure (POD) with units of mg/kg/day. The resulting values range from 0.04 mg/kg/day to 0.09 mg/kg/day, depending on body weight and assuming mean water intake.

In examining the range of point-of-departure values, the OW selected 0.07 mg/kg/day as an appropriate POD for the drinking water component of the risk assessment because it provides a margin of 0.02 mg/kg/day between the Adequate Intake (AI, 0.05 mg/kg/day) and the upper end of the POD range, and is supported by the Hong et al (2006) report that all cases of severe dental fluorosis in their study had exposures > 0.06 mg/kg/day. Accounting for fluoride exposure from other sources (0.01 mg/kg/day) at the time of the 1942 Dean study results in a chronic RfD for severe dental fluorosis of 0.08 mg/kg/day. The OW has determined that the typical uncertainty factors of 10X to account for interspecies (UF_A) and intraspecies (UF_H) variability should be reduced to 1X. The DRA uncertainty factor analysis follows:

> *In establishing an oral RfD for fluoride, data on nutritional benefit were assessed in combination with the data on severe dental fluorosis to define a level that provides anticaries protection without causing severe dental fluorosis when consumed daily for a*

lifetime. Conventional application of uncertainty factors is not always appropriate when carrying out a risk assessment for nutrients and other beneficial substances, especially when there is a relatively small difference between the levels that satisfy need and those that cause adverse effects. For this reason the total uncertainty factor applied was 1. The widely recognized variability in epidemiological data on the prevalence of severe dental fluorosis combined with the data demonstrating the anticaries benefit of exposures to fluoride at concentrations at or below the BMDL do not support any other approach. The margin of difference between the AI and RfD is 0.03 mg/kg/day.

The point of departure for the drinking-water, oral RfD analysis is the lower bound for 0.5 % severe dental fluorosis in children. The sample size was large (138 to 404 individuals per data point in the critical area around the BMD (1.9–2.6 mg/L) and the participants were randomly selected. Geographic and climate differences related to the places of residence of the children examined were unlikely to contribute to sensitivity. The population studied is the group vulnerable to dental fluorosis of the secondary teeth (children ages 6 months to 14 years). In addition, human data provide the basis of the drinking-water, oral RfD. Therefore an adjustment for the use of animal data is not necessary. The duration of exposure covered the full period of sensitivity to severe dental fluorosis of the secondary teeth. A drinking-water, oral RfD of 0.08 mg/kg/day appears to be protective for possible impacts on bone fractures and skeletal fluorosis in adults, and should be protective of severe dental fluorosis of the primary teeth as well.

The standard toxicity database for fluoride is complete. It includes chronic, reproductive, and developmental studies in animals as well as a variety of epidemiology studies in humans (NRC, 2006). Although NRC (2006) did identify research needs for the endocrine, neurological and other effects of fluoride, they generally concluded that available studies on other effects were not sufficient to assess public health relevance to the U.S. population. To date, the best documented and established public health consequence of fluoride exposure is severe dental fluorosis, skeletal fluorosis and increased risk of bone fractures.

As a consequence, 1 is the chosen value for each of the following uncertainty factors used in this estimate of the fluoride drinking-water, oral RfD: UF_H, UF_A, UF_S, UF_L. *The composite UF is also equal to 1.* (EPA, 2010a, p. 106; UF_H = human-to-human intraspecies uncertainty factor, UF_A = animal-to-human uncertainty factor, UF_S = subchronic-to-chronic uncertainty factor, UF_L = LOAEL-to-NOAEL uncertainty factor)

As noted above, the DRA also includes evaluation of dietary fluoride exposure that was likely to have occurred at the time of the Dean study. Data from 1943 indicate that an additional 0.01 mg/kg/day is a reasonable estimate of the contribution of F from food at the time of the Dean study. Combining the point of departure from the Dean study with the exposure estimate from food and the total uncertainty factor of 1 results in a **chronic RfD of 0.08 mg/kg/day**, as noted in the above quotation. The above quotation also identifies children between the ages 6 months and 14 years as the age groups susceptible to the pitted enamel of severe dental fluorosis. Previous assessments of dental fluorosis have viewed the condition as a cosmetic effect and, therefore, focused on the visible teeth, whose enamel has generally been formed by the age of 6 years. In assessing severe dental fluorosis as an adverse effect, EPA has expanded the age range to 14 years in order to be protective of enamel formation in the third molars (wisdom teeth).

2.3 Children's Safety Factor (FQPA Factor)

For establishing tolerances for residues of pesticides, the OPP is bound by the Federal Food, Drug, and Cosmetic Act (FFDCA). Section 408(b)(2)(C) of FFDCA provides that EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the FQPA Safety Factor. In applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor. In making the determination for the FQPA Safety Factor, the OPP typically examines the completeness of the toxicity data as well as the toxicological effects associated with various life stages. In addition, the completeness of the exposure data and the potential for exposure estimates to underestimate exposures is considered.

2.3.1. Toxicology

2.3.1.1. Completeness of Data

The OPP has not received any guideline studies conducted with fluoride, *per se*. However, the toxicological database for the parent compound, sulfuryl fluoride, is complete with the exception of immunotoxicity and developmental neurotoxicity studies, which have been requested as part of registration review. To the extent that sulfuryl fluoride breaks down to the fluoride anion during testing, the studies that have been submitted for sulfuryl fluoride capture the effects of fluoride (dental fluorosis was observed in a number of studies). In addition to the guideline studies on sulfuryl fluoride, there is a large body of published literature regarding fluoride toxicology (see the uncertainty discussion in Section 2.2). Among these studies, the dental and skeletal effects for fluoride are well documented in humans and severe dental fluorosis is the effect in children recommended for quantification by NRC (2006).

2.3.1.2. Potential Pre- and Post-Natal Toxicity

The susceptible population for the critical effect, severe dental fluorosis, is children. Since the RfD was derived based on data collected from the susceptible population and the assessment is evaluating this population group, the susceptibility of infants and children is being accounted for directly.

2.3.2. Exposure

An important consideration for determining the children's safety factor is the protectiveness of the exposure assessment. As noted above, there are a number of sources that can contribute to overall fluoride exposure. There is a high degree of variability associated with some of these sources; therefore, there is the potential for wide-ranging exposure estimates depending on the assumptions that are made when considering each source. This variability, as well as the absolute magnitude of the exposure estimate for a particular source will affect the overall characteristics of the aggregate exposure estimates which result from combining the individual sources of exposure. A brief characterization of the various source estimates of fluoride follows, with the point of focus being their use in an FFDCA risk assessment. Note that a full discussion on exposure estimates is provided in Section 3.

Pesticidal Sources. Estimates of fluoride exposure from uses of sulfuryl fluoride are highly refined. There is little conservatism in the exposure estimates. On a relative basis, pesticides are not a significant contributor to fluoride exposure and the lack of conservatism in these estimates has little impact on the level of conservatism in the overall exposure assessment.

Soil and Air. As with pesticides, soil and air are not major contributors to overall fluoride exposure. The exposure estimates from soil and air can be characterized as relatively high-end, though the conservatisms in these estimates have little impact on the overall estimates. Note that for children with pica, a medical disorder resulting in an appetite for non-food materials including soil, this assessment may significantly underestimate exposure to fluoride from soil ingestion for children exhibiting this disorder who live in areas where soil has average-to-high fluoride content.

Foods and Commercial Beverages. This risk assessment is based on central-tendency estimate for fluoride in foods and commercial beverages developed by the OW in their RSCA (EPA 2010b). Monitoring studies indicate fluoride is ubiquitous in the food supply (e.g., World Health Organization. 2002; Rao, G. S. 1984; Sherlock, JC. 1984). To the extent that foods are broadly distributed, the use of average values for fluoride levels is likely to be an accurate reflection of dietary fluoride over longer-term exposure periods. Locally grown foods may consistently have higher or lower levels of fluoride than assumed for this assessment.

Drinking Water. The drinking water exposure estimates are based on high-quality monitoring data depicting fluoride levels in the drinking water supply for the majority of the population. The FFDCA exposure estimates are derived by coupling the fluoride concentration estimates with consumption data. While this assessment focuses on above-average fluoride concentrations, the OPP is aware that there are documented populations who consume water with a fluoride concentration greater than the highest value used to make the FFDCA exposure estimates. The OPP is also aware that there are groups of people who may chronically consume water at a rate greater than the U.S. average (*e.g.*, athletes, outdoor workers, diabetics, etc.). The exposure estimates for drinking water include community water used to prepare foods and beverages in the home.

Toothpaste. Ingestion of toothpaste may be a significant contributor to overall fluoride exposure. Estimates of toothpaste (and associated fluoride) ingestion vary greatly. Estimates of exposure from toothpaste described in the RSCA (EPA, 2010b) are middle to high-end estimates on a per-brushing basis. The FFDCA assessment assumes two brushings per day which results in some conservatism based on the frequency of brushing reported in the literature (weighted average = 1.13 brushings per day). In light of the recommendations of the American Dental Association and the American Academy of Pediatrics for two brushings per day, the variability noted in the data regarding number of brushings per day, and the variability in the data for the amount of toothpaste ingested per brushing, the assumption of two brushings per day overestimates exposure for many children, but is unlikely to provide a large margin for safety.

2.3.2.1. Potential to Underestimate Exposure

Although the exposure estimates in this FFDCA assessment may underestimate exposures for some population groups (e.g., people whose drinking water fluoride levels exceed 2.59 mg/L, people who chronically consume large amounts of water), exposure estimates for these groups can be adequately addressed by using different assumptions regarding fluoride concentrations and/or drinking water consumption. There are no data gaps that result in a systematic underestimate of fluoride exposure.

2.3.3. Information on the Dose-Response Curve for Fluoride

Fluoride can be an important tool for prevention of dental caries, especially for populations who do not receive regular dental care. The National Academy of Sciences' Institute of Medicine (IOM) has determined that the AI for fluoride is 0.05 mg/kg/day (IOM, 1997).

From the standpoint of overall oral health, fluoride can be said to have a "U" shaped dose-response curve, wherein too little fluoride can result in reduced oral health due to increased risk of dental caries and too much fluoride can result in reduced oral health due to increased risk of severe dental fluorosis. A benefit to oral health, in the form of reduced potential for dental caries, is associated with exposures between these two levels. This dose-response phenomenon is not a characteristic that is typical of pesticide chemicals, which are the focus of the FQPA Safety Factor. When evaluating chemicals that exhibit this type of dose-response curve, consideration should be given to the magnitude of the FQPA Safety Factor and its potential to produce an RfD at a level inconsistent with the scientific data.

2.3.4. Conclusions

Given the relative completeness of the fluoride toxicology database, the use of a children-specific endpoint that is the most sensitive effect and well-documented outcome in the literature, the data indicating that there is a U-shaped dose-response curve for oral health, and our understanding of the potential exposures to fluoride, the OPP is reducing the FQPA Safety Factor for fluoride to 1X. The chronic population-adjusted dose (PAD, equal to the RfD ÷ FQPA Safety Factor) for fluoride is, therefore, equivalent to the RfD (0.08 mg/kg/day).

3. Exposure Assessment

Previous FFDCA risk assessments by the OPP have considered fluoride exposures resulting from the use of sulfuryl fluoride as well as from cryolite (another pesticide), drinking water, background levels in foods (including beverages), toothpaste, and air. The RSCA (EPA, 2010b) presents exposure estimates from these sources as well as for soil (to address exposure via soil ingestion).

3.1. Pesticidal Sources

The OPP provided the OW with estimates of exposure to F due to use of SF and cryolite (EPA, 2010c) to be used in the RSCA. The exposure estimates are derived using food consumption data from the USDA Continuing Survey of Food Intake by Individuals (CSFII, 1994-1996, 1998) and average residue values, accounting for usage of the chemicals (i.e., percent of crop treated with the pesticides; % CT). Table 1 summarizes the exposure estimates associated with the use of sulfuryl fluoride. The estimates include the residues resulting from structural fumigation, where food items remaining in the structure may be unintentionally fumigated, as well as residues resulting from the intentional fumigation of human food commodities.

The estimates of exposure to fluoride from the pesticidal use of cryolite and sulfuryl fluoride are highly refined and there remains relatively little conservatism left in these estimates. The RSCA concluded that the data reflective of background levels of F in foods (Section 3.3 of this document) includes the contribution from cryolite because of that chemical's "long history of use on a variety of crops" and that to include cryolite separately would be double-counting it as a source of F exposure. Cryolite was registered in the U.S. in 1957. The OPP has data regarding the extent of cryolite use and has factored that information into its exposure estimates[1]. Although the food monitoring studies cited in the RSCA were not designed to specifically factor in % CT, the data do include some high values, particularly for grapes and raisins, which would indicate that use of cryolite is reflected in the data. Given the fluoride level profiles from the monitoring studies and the fact that cryolite plays a small role in overall fluoride exposure (similar to the values for sulfuryl fluoride presented in Table 1), the OPP concurs with the RSCA that cryolite's contribution to F exposure is adequately addressed by the estimates associated with background levels of F in foods. Unlike cryolite, sulfuryl fluoride did not have registered food uses at the time the data being used to estimate fluoride exposures from food were collected.

Table 1. Summary of Sulfuryl Fluoride Contributions to Dietary Fluoride Exposure.

Age Range, years	Average Estimated Exposure, mg/day			Average Estimated Exposure, mg/kg/day		
	SF Structural [a]	SF Food [b]	Total	SF Structural [a]	SF Food [b]	Total
0.5 - <1	0.0087	0.021	0.030	0.0008	0.0019	0.0027
1 - <4	0.012	0.033	0.045	0.0008	0.0022	0.0030
4 - <7	0.015	0.047	0.062	0.0007	0.0022	0.0029
7 - <11	0.017	0.054	0.071	0.0005	0.0017	0.0022
11 - <14	0.018	0.068	0.086	0.0004	0.0014	0.0018
14+	0.019	0.058	0.076	0.0003	0.0008	0.0011

[a] Reflecting residues resulting from fumigation of structures that may contain human food products.
[b] Reflecting residues resulting from intentional fumigation of human foods.

3.2. Drinking Water

As part of its second six-year review of the National Primary Drinking Water Regulations, the OW received the largest and most comprehensive set of drinking water compliance monitoring

[1] For different crops, estimates for % CT range from 1% to 33%, with most values falling below 5%. For crops without specific information regarding percent of crop treated, the OPP's analysis assumed 100%.

data ever compiled and analyzed by the Agency. The data include records from ca. 136,000 public drinking water systems with about 6500 to 9600 samples per year depicting detectable fluoride concentrations. There was an increase in the number of states reporting for the subset of data from 2002-2005; therefore, the RSCA focused on those data when estimating exposure to F from drinking water. For that time period, the average of the quarterly means across all samples is 0.87 ppm and the average for the quarterly 90th percentile values is 1.43 ppm. Below (Table 2) is a summary of the monitoring data from 2002-2005.

Table 2. Public Water System Fluoride Monitoring Data (2002-2005). Ranges are across quarterly data in each year. Data are from EPA 2010b.

Statistic	2002	2003	2004	2005
Number of Samples	6,126-8,295	6,910-8,562	8,231-9,580	7,051-9,635
% of Samples ≥ 2 ppm	4.0-5.1	5.2-6.2	4.9-6.4	5.4-6.8
Number of Systems	3,541-4,563	4,054-4,981	5.007-5,700	3,869-5,472
% of Systems ≥ 2 ppm	4.6-5.8	6.1-7.2	5.6-7.7	6.9-8.3
Mean*, ppm	0.78-0.89	0.86-0.93	0.80-0.90	0.84-0.95
Median*, ppm	0.70-0.85	0.80-0.85	0.69-0.80	0.75-0.86
90th Percentile*, ppm	1.40-1.44	1.40-1.47	1.40-1.50	1.40-1.50
Population, millions	50.3-82.6	44.4-87.1	47.7-86.7	58.8-102.5

* Non-detect values (<0.1 ppm) are not included in computation of the mean, median, and 90th percentile statistics.

The OW's RSCA is based on the average concentration of fluoride in water and 90th percentile consumption (consumers only) of municipal water ("direct" and "indirect" water)[2] to estimate exposure to fluoride from water. These estimates are summarized in Table 3.

Table 3. Fluoride Intake from Municipal Water (Estimates taken from EPA, 2010b).

Age Range, years	Water Consumption, L/day*	Fluoride Intake, mg/day†	Fluoride Intake, mg/kg/day§
0.5 - <1	0.97	0.84	0.093
1 - <4	0.72	0.63	0.045
4 - <7	0.94	0.82	0.039
7 - <11	0.99	0.86	0.027
11 - <14	1.42	1.23	0.024
14+	2.0 (EPA policy for adults)	1.74	0.025

* 90th percentile, consumers only.
† Assuming an average concentration of 0.87 mg/L
§ Calculated by OPP using the body weight estimates from Table 5.

The OW's approach to estimating exposure from drinking water is based on longstanding OW policy, which takes into account that, under the Safe Drinking Water Act, the OW is setting *nation-wide* standards for drinking water in circumstances where drinking water is the exposure route of concern. Due to the specific requirements of FFDCA section 408 and factors related to the distribution of pesticide residues and the manner of the distribution of drinking water, the OPP has traditionally followed a slightly different approach to estimating exposure from drinking water in evaluating the safety of pesticide tolerances. Section 408 requires EPA to assess "aggregate exposure" to a pesticide and "other related substances." Importantly, section

[2] "Direct" water is consumption of water as drinking water. "Indirect" water is the water used to prepare foods and beverages in the home. Water used in commercial food and beverage production is referred to as "commercial" water. Fluoride exposure from "commercial" water is assessed based on monitoring data of food and beverages. See Section 3.3, below.

408 explicitly mandates that this aggregate exposure determination must take into account the exposure of "major identifiable subgroups of consumers." In evaluating the exposure of such subgroups to pesticide residues in drinking water, the OPP has not typically focused on average residue values nationally because pesticide residues in drinking water often vary quite considerably based on where pesticides are used and on environmental factors (soil types, rainfall amounts, etc.) and because drinking water is generally consumed locally rather than being distributed nationally. Using average national residue values in drinking water in assessing aggregate exposure to a pesticide may not reflect relatively high exposures of major identifiable subgroups of consumers.

Due to the unique aspects of the fluoride assessment (the multiple sources of exposure including artificial fluoridation of water supplies), the OPP believes it is appropriate to present both the OW's approach to assessing exposure in drinking water as well as the OPP's approach in evaluating the safety of fluoride under FFDCA section 408. The OW's approach provides valuable information on the exposure of those consumers nationwide who have higher exposure levels due to their high consumption of water. The OPP's approach focuses on areas of the country where exposures generally will be higher within the exposed population due in part to the concentration of F in their water.

At the OPP's request, the OW has subsampled the monitoring data to focus on systems that had at least one detection equal to or greater than 2 ppm, 3 ppm, or 4 ppm fluoride (Khera, R., 2010). Data from those systems are summarized in Table 4. Given that the populations in these communities range from over 1 million to approximately 10 million, people consuming water from these water systems constitute a major identifiable population and, therefore, the fluoride levels associated with these systems are appropriate for use in this FFDCA risk assessment.

Table 4. Public Water System Fluoride Monitoring Data (2002-2005). Summary Statistics for Systems Reporting at Least One Sample ≥ 2, 3, or 4 mg F/L.			
Item	Surface Water Systems [1]	Ground Water Systems	All Systems
Number of people served by systems reporting at least one sample equal to or greater than:			
2 mg F/L	3,903,827	6,003,480	9,907,307
3 mg F/L	1,824,692	2,178,857	4,003,549
4 mg F/L	546,490	1,101,347	1,647,837
Number of systems reporting at least one sample equal to or greater than:			
2 mg F/L	134	2,275	2,409
3 mg F/L	40	980	1,020
4 mg F/L	18	499	517
Percent of reported monitoring periods with an average reported concentration equal to or greater than:[2]			
2 mg F/L	18.7%	56.0%	54.0%
3 mg F/L	18.8%	52.4%	51.1%
4 mg F/L	15.4%	45.9%	44.8%
Percent of reported monitoring periods with a maximum reported concentrations equal to or greater than:[3]			
2 mg F/L	26.9%	60.5%	58.7%
3 mg F/L	26.3%	58.0%	56.7%
4 mg F/L	23.4%	51.5%	50.5%
Average concentration (2002-2005) for systems reporting at least one sample equal to or greater than:[4]			
2 mg F/L	1.11 mg/L	1.86 mg/L	1.76 mg/L
3 mg F/L	1.26 mg/L	2.36 mg/L	2.28 mg/L
4 mg F/L	1.43 mg/L	2.64 mg/L	2.59 mg/L
90th percentile concentration (2002-2005) for systems reporting at least one sample equal to or greater than:			
2 mg F/L	1.79 mg/L	4.09 mg/L	3.84 mg/L
3 mg F/L	1.79 mg/L	4.92 mg/L	4.86 mg/L
4 mg F/L	2.00 mg/L	5.27 mg/L	5.22 mg/L

1. Includes surface water systems and systems classified as ground water under the influence of surface water.
2. Percent equals average percent across systems. The percent for each system equals the total number of monitoring quarters in which the system average concentration exceeds the threshold divided by the total number of monitoring quarters for that system.
3. Percent equals average percent across systems. The percent for each system equals the total number of monitoring quarters in which the system maximum concentration exceeds the threshold divided by the total number of monitoring quarters for that system.
4. Average of all samples reported in years 2002-2005 for systems in each threshold subset.

The OPP's estimates of exposure from drinking water (Table 5) assume average consumption (EPA 2004b) and average fluoride concentrations for systems reporting at least one sample greater than or equal to 2 mg F/L, systems reporting at least one sample greater than or equal to 3 mg F/L, and systems reporting at least one sample greater than or equal to 4 mg F/L (Table 4).

For comparison purposes, Table 5 also includes estimates from low-fluoride systems (represented by 0.1 mg F/L) and the national average (0.87 mg F/L).

Table 5. Estimates of Fluoride Exposure (mg/kg/day) from Drinking Water Based on Average Consumption.							
Age Range, years	Body Weight, kg *	Consumption, L/day *	Fluoride Concentration in Drinking Water, mg/L †				
			0.1	0.87	1.76	2.28	2.59
0.5 - <1	9	0.394	0.0044	0.038	0.077	0.10	0.11
1 - <4	14	0.316	0.0023	0.020	0.040	0.052	0.059
4 - <7	21	0.394	0.0019	0.016	0.033	0.043	0.049
7 - <11	32	0.430	0.0013	0.012	0.024	0.031	0.035
11 - <14	51	0.525	0.0010	0.0090	0.018	0.024	0.027
14+	70§	1.016	0.0015	0.013	0.026	0.033	0.038

* From EPA 2004b. Values reflect per-capita consumption. For the 14+ age group, the weighted average for consumption is presented.

† Exposure = Concentration (mg/L) × Consumption (L/day) ÷ Body Weight (kg).

§ EPA policy for adult body weight. EPA 2004b lists the average body weight for ages 15+ years as 75 kg.

The OPP notes that the data collected by the OW do not address fluoride levels in private wells. Studies by the U.S. Geological Survey (*Quality of Water from Domestic Wells in the United States*, http://water.usgs.gov/nawqa/studies/domestic_wells/) indicate that 1.2% of private wells contain fluoride at concentrations of at least 4 mg/L (the current MCL) and that approximately 4% of wells in the western and south-central U.S. exceed the 4 mg/L standard. A review of other fluoride monitoring data compiled by the USGS indicates that the range of concentrations of fluoride in private wells is adequately represented by the monitoring data from the public water systems summarized in Tables 2 and 4. The OPP also notes that the exclusion of the non-detect samples in the analysis of the monitoring data will have little, if any, impact on the values being used in the FFDCA assessments since those assessments focus on population subgroups being served by systems reporting higher levels of fluoride and reporting of non-detectable concentrations of fluoride are unlikely for these systems.

3.3. Background Exposure from Foods and Commercial Beverages

The RSCA includes a critical review of a large number of studies, including monitoring studies, wherein fluoride levels in various foods and commercial beverages were reported, as well as diet studies, where actual intake of dietary fluoride was estimated. The RSCA considered commercial beverages (i.e. not municipal drinking water consumed as drinking water or drinking water used to prepare beverages in the home) separately from solid foods. A summary of the RSCA food and beverage fluoride exposure estimates is presented in Table 6.[3]

[3] This approach to assessing fluoride in commercial beverages is necessary because the Agency does not have estimates for the consumption of "commercial water;" therefore, this source of fluoride exposure cannot be accounted for using the "consumption × concentration" approach used for assessing fluoride from "direct" and "indirect" drinking water.

Table 6. Summary of Estimated Fluoride Exposures Attributable to Background Levels in Food and Commercial Beverages. Data are from EPA, 2010b.							
Age Range, years	Body Weight, kg†	Estimated Fluoride Exposure, mg/day			Estimated Fluoride Exposure, (mg/kg/day)		
		Solid Food*	Commercial Beverages	Total	Solid Food*	Commercial Beverages	Total
0.5 - <1	9	0.26	--*	0.26	0.029	--*	0.029
1 - <4	14	0.16	0.36	0.52	0.011	0.026	0.037
4 - <7	21	0.35	0.54	0.89	0.017	0.026	0.042
7 - <11	32	0.41	0.60	1.01	0.013	0.019	0.032
11 - <14	51	0.47	0.38	0.85	0.0092	0.0075	0.017
14+	70	0.38	0.59	0.97	0.0054	0.0084	0.014

† From Table 5.

* Solid food includes milk as well as fruit and vegetable juices not made from concentrate. These are not categorized as beverages in the FDA Total Diet Study (Egan et al., 2007). For the age range 0.5-<1 year, all fluoride was considered to be from powdered formula and falls into the food category.

3.4. Toothpaste

A large number of studies have investigated the exposure to fluoride through use of fluoridated toothpaste. Ingestion of toothpaste is an important component in overall fluoride exposure estimates, and assumptions regarding the number of brushings per day greatly affect the aggregate exposure estimate. A summary of the RSCA regarding these studies follows.

> *There are a number of studies that report on toothpaste use and resultant potential total exposure from fluoridated dentifrice. A more limited set of data are available from studies where the ingestion of toothpaste during tooth brushing was measured. In the toothpaste ingestion studies, the toothpaste placed on the toothbrush was measured and corrected for that left on the toothbrush after brushing and that expectorated during post-brushing rinsing of the mouth. The difference was assumed to be swallowed. The data from these studies are summarized in Table 6-4. Each estimate is highly uncertain since the confidence bounds around the mean values are indicative of high inter-individual variability (See Table 4-9). Estimates may be high because the studies were conducted before the recommendation became widely publicized for children to use only a pea-sized amount of fluoride when brushing.*
>
> *Fluoride intakes represent one brushing per day, a value that is applicable to about half the population for children < 3 years old according to the data collected by Franzman et al. (2006), Levy et al. (1997), and Simard et al. (1991). The number of brushings appears to increase to twice a day for older children (Simard et al., 1989) but this estimate lacks confirmation from other studies.* (EPA, 2010b, p. 97)

Table 7. Summary of Estimated Fluoride Exposures from Incidental Ingestion of Fluoridated Toothpaste. Data are from EPA, 2010b.				
Age Range, years	Estimated Fluoride Exposure, mg/day		Estimated Fluoride Exposure, mg/kg/day*	
	1 brushing per day	2 brushings per day	1 brushing per day	2 brushings per day
0.5 - <1	0.07	0.14	0.0078	0.016
1 - <4	0.34	0.68	0.024	0.049
4 - <7	0.22	0.44	0.010	0.021
7 - <11	0.18	0.36	0.0056	0.011
11 - <14	0.2	0.4	0.0039	0.0078
14+†	0.1	0.2	0.0014	0.0029

*Calculated by the OPP using body weight estimates from Table 5.

†No data were available for this age group. The exposure estimate is one half that of the 11-14 year group.

3.5. Other Sources

The RSCA includes consideration of a number of other sources of fluoride exposure. Of these, only exposure from ingestion of soil was quantified. The RSCA summarized these other sources as follows:

> *There are other sources of fluoride exposure such as ambient air, dietary supplements, professional dental treatment products, and some pharmaceuticals. These sources make minimal contributions to daily exposures during the period of dental fluorosis vulnerability. NRC (2006) estimated that average exposures from ambient air would be 2 micrograms per day for children and 4 micrograms per day for adults. Supplements are not recommended for use in cases where water is fluoridated and thus would not be appropriate at the 0.87 mg/L concentration that represents the national average fluoride concentration for public water systems (Section 3.3) because it falls within the recommended fluoridation range. Professional dental fluoride treatments are episodic and do not contribute greatly to the average daily intake when normalized across time. The major chronic-use, fluoride containing pharmaceuticals (i.e. Zocor and Prozac) do not include young children among their target population. Intakes of the antibiotic Ciptoflaxozin (Cipro) by children would be episodic rather than chronic. In addition, the covalently-bound fluorine in pharmaceuticals does not appear to be bioavailable (NRC, 2006).* (EPA, 2010b, p. 91 ff)
>
> *Fluoride ranks 13th or 14th in terms of its elemental abundance in the earth's crust. Thus, fluoride in soil could be a source of inadvertent exposure, primarily for children. Typical fluoride concentrations in soil in the United States range from very low (<10 ppm) to as high as 7% (70,000 ppm) in some areas with high concentrations of fluorine-containing minerals (ATSDR, 2003). Mean or typical concentrations in the United States are on the order of 300-430 ppm. Soil fluoride content may be higher in some areas due to use of fluoride-containing phosphate fertilizers or to deposition of airborne fluoride released from industry.*
>
> *The EPA (2008) Child-Specific Exposure Factor's Handbook recommends use of a combined soil and outdoor dust ingestion rate of 60 mg/day for children < 1 year old and 100 mg/day for children 1 to < 21 years of age. Using an average fluoride concentration of 400 ppm, the exposure from soils for an infant (<1 year) would be 0.02 mg/day and that for older children and adolescents would be 0.04 mg/day. The estimated intake for*

adults in the EPA (1997) Exposure Factors Handbook is 50 mg/day and equivalent to a 0.02 mg/day exposure from soils with an average concentration of 400 ppm. Erdal and Buchanan (2005) estimated intakes of 0.0025 and 0.01 mg/kg/day for children (3–5 years), for mean and reasonable maximum exposures, respectively, based on a fluoride concentration in soil of 430 ppm. In their estimates, fluoride intake from soil was 5–9 times lower than that from fluoridated drinking water.

For children with pica (a condition characterized by consumption of nonfood items such as dirt or clay), an estimated value for soil ingestion is 10 g/day (U.S. EPA, 1997). For a 20-kg child with pica, the fluoride intake from soil containing fluoride at 400 ppm would be 4 mg/day or 0.2 mg/kg/day. Although pica in general is not uncommon among children, the prevalence is not known (U.S. EPA, 1997). Pica behavior specifically with respect to soil or dirt appears to be relatively rare but is known to occur (U.S. EPA, 1997). Fluoride intake from soil for a child with pica could be a significant contributor to total fluoride intake. For most children and for adults, fluoride intake from soil probably would be important only in situations in which the soil fluoride content is high, whether naturally or due to industrial pollution. (EPA, 2010b, p. 89 ff)

Table 8. Summary of Estimated Fluoride Exposures from Incidental Ingestion of Soil and Outdoor Dust. Data are from EPA, 2010b.

Age Range, years	Estimated Fluoride Exposure*, mg/day	Estimated Fluoride Exposure, mg/kg/day†
0.5 - <1	0.02	0.0022
1 - <4	0.04	0.0029
4 - <7	0.04	0.0019
7 - <11	0.04	0.0013
11 - <14	0.04	0.00078
14+	0.02	0.00029

*Assumes soil and dust contains 400 ppm fluoride.
† Calculated by the OPP using body weight estimates from Table 5.

The fluoride concentration estimate is from the upper end of the range of average values, and the soil/dust ingestion estimate from the Child-Specific Exposure Factor's Handbook is an upper-end estimate, resulting in a conservative estimate for most people. Generally, soil is not a major contributor to overall fluoride exposure and inclusion of higher-end exposure estimates will not have a significant impact on aggregate risk estimates relative to the variability in estimates from other sources. The estimates in Table 8 are likely to underestimate exposure for children with pica who live in areas with soils that contain average or higher F levels. For these children, the NRC estimates fluoride exposure from soil ingestion alone could be as high as 0.2 mg/kg/day (NRC, 2006, p. 46).

4. Aggregate Exposure and Risk

4.1. Exposure Analysis

Aggregate exposure to fluoride is dependent on its concentration in various media (foods, beverages, soils, toothpaste, etc.) as well as on various behaviors within the population. These behaviors include dietary patterns, water consumption, oral hygiene, pica behavior, etc; and may be influenced by socio-economic status and other parameters with environmental justice implications.

Estimates of exposure from foods, commercial beverages, drinking water ("direct" and "indirect"), toothpaste, soil, and from the use of sulfuryl fluoride have been combined to estimate aggregate fluoride exposure. Adding the contributions from each of these sources as point estimates in order to obtain average exposure estimates is appropriate since all of the point estimates being combined are central-tendency values. The range of exposure estimates depends, of course, on the assumptions regarding fluoride levels used in the analyses. Some discussion of the fluoride levels being used for the aggregate exposure analysis is presented below. A ranking of the exposure estimates discussed in Section 3 shows that for all population age groups, soil and sulfuryl fluoride contributes very little to overall exposure when looking at central-tendency estimates for all sources.

4.1.1. Fluoride in Foods

The OPP has selected the central-tendency exposure estimates from fluoride in foods as reported in the OW RSCA. The use of central-tendency values is in keeping with OPP policies regarding chronic exposure assessments, with the understanding that the nation-wide distribution of foods and the variability of food consumption patterns over a long-term period effectively result in central-tendency exposures over that period.

4.1.2. Fluoride in Commercial Beverages

As with the exposure from foods, the OPP has used the exposure estimates for commercial beverages reported in the OW RSCA. Those values are central-tendency estimates.

4.1.3. Fluoride in Drinking Water

The OPP has used different values for fluoride in drinking water to estimate the range of aggregate exposures. The lowest value, 0.1 mg/L, is the modal minimum reporting level from the public water system monitoring data. This represents a limit of quantitation for fluoride analysis. Although this is the lowest value being used, exposure estimates based on this value may overestimate exposure from drinking water for persons whose water supply has very low fluoride levels (*i.e.*, less than 0.1 mg F/L). The highest value being modeled is 2.59 mg/L, which is the average value from public water systems reporting at least one sample with a fluoride concentration of at least 4 mg/L. People being served by a private well may be exposed to fluoride concentrations in their water that are significantly greater than that depicted by results from the assessment based on 2.59 mg F/L. It is difficult to estimate how many people fall in this category. As a point of reference, exposures have also been estimated based on the overall average concentration of F in drinking water (0.87 mg/L).

The OPP has identified people being served by systems reporting at least one sample with a fluoride concentration of at least 2 mg/L as an identifiable population of consumers. In order to estimate exposures and risks associated with fluoride exposure for this population group, the OPP has modeled exposure based on fluoride concentrations of 1.76 mg/L in drinking water (the average fluoride concentration for these systems) as well as 2.28 mg/L (the average for systems reporting at least one sample ≥ 3 mg/L) and 2.59 mg/L (the average for systems reporting at least one sample ≥ 4 mg/L). The OPP typically uses high-end, worst-case estimates of pesticide residues in drinking water when assessing human health risk. Given that 2.59 mg/L is an average value from water systems reporting at least one sample ≥ 4 mg/L, there are likely to be populations of consumers whose drinking water fluoride level exceeds 2.59 mg/L; therefore, estimates derived from this level of fluoride in drinking water are likely to underestimate aggregate exposure for some people.

The OPP notes that it is possible to incorporate a distribution of values to represent the level of fluoride in drinking water rather than assess multiple point estimates. An examination of the fluoride data compiled by the U.S. Geological Survey (www.usgs.gov) shows that temporal variation in fluoride concentrations is, on average, less than 20%. This implies that fluoride concentrations are fairly consistent; therefore, assessing exposure for people being served by a particular water system by assuming a broad range of fluoride concentrations would not be appropriate.

4.1.4. Fluoride from Incidental Toothpaste Ingestion

The OPP has included a range of exposure estimates associated with ingestion of toothpaste. Unlike drinking water, the concentration of fluoride in toothpaste is quite consistent (1000 – 1100 ppm fluoride ion). Behavioral aspects of brushing teeth, including frequency and the amount of toothpaste that is swallowed, can be quite variable. In estimating aggregate exposure, the OPP has used central-tendency estimates for the amount of fluoride ingested (see Table 8) and assumed 0, 1, or 2 brushings per day. As described above (Section 2.3.2), the assumption of 1 brushing per day is near the weighted average (1.13 brushings per day) from the study data reported in the RSCA. Two brushings per day is in keeping with health care recommendations and appears to be representative of a significant portion of the study populations.

4.2. Aggregate Exposure Estimates

Table 9 presents modeled estimates, derived from the dietary model discussed above (Section 4.1), of fluoride exposure from foods (naturally occurring fluoride + cryolite-derived fluoride), commercial beverages, incidental soil and toothpaste ingestion, the use of sulfuryl fluoride, and drinking water. For drinking water, the fluoride concentration values of 1.76, 2.28, and 2.59 mg/L were selected to be representative of the systems discussed above. The two remaining scenarios depicted in Table 9 are intended to reflect fluoride exposures for consumers with very low fluoride levels in their drinking water (0.1 mg/L) and consumers being served by systems that actively fluoridate the water supply (0.87 mg F/L is the overall average from the monitoring data and falls within the range of recommended fluoridation levels, 0.7 – 1.2 mg F/L). Modeling this range of fluoride concentrations in drinking water provides estimates of the range of fluoride exposures from these sources for the U.S. age groups susceptible to severe dental fluorosis.

FFDCA Estimates. OPP has focused, specifically, on people who are served by systems reporting at least one monitoring sample with levels of fluoride ≥ 2 mg/L. The average value for these systems is 1.76 mg F/L (Table 4). The FFDCA estimates assume average consumption of foods, drinking water, and commercial beverages; ingestion of fluoride from brushing teeth twice per day (which is the frequency currently recommended by the American Dental Association and the American Academy of Pediatrics); average exposure from soil; and average exposure from use of sulfuryl fluoride. The estimates listed in Table 9 include fluoride concentrations in drinking water of 1.76 mg/L, 2.28 mg/L or 2.59 mg/L which are the average from systems reporting at least one sample ≥ 2 mg/L, ≥ 3 mg/L, or ≥ 4 mg/L, respectively. Other sets of assumptions may result in exposure estimates greater than those listed as FFDCA estimates (Table 9). The range of these estimates is reflected in Figure 1. There may be populations whose characteristics do not match the assumptions listed for the FFDCA estimates and whose exposure is greater than those estimates.

RSCA Estimates. The exposure estimates from the RSCA are included for comparative purposes. These estimates are based on average, literature-reported estimates of exposure from food and commercial beverages; a single brushing per day with fluoride toothpaste (Section 3.4); sulfuryl fluoride and soil as discussed in Sections 3.1 and 3.5, respectively; and 90th percentile estimates for consumers only of drinking water with fluoride at the average concentration (0.87 mg/L).

Comparing the FFDCA and RSCA exposure assessments indicates that the exposure levels are fairly similar. Although these assessments have different underlying assumptions, they are mutually supportive in that they identify major subgroups of people – whether those subgroups are defined nationally or locally – with similar exposure patterns.

Table 9. Estimates of Aggregate Fluoride Exposure.

Age Range, Years	Exposure Estimates, mg/kg/day					Aggregate Exposure Estimates, mg/kg/day				
							OW	FFDCA [g]		
	Dietary [a]	Toothpaste [b] (once/day)	Toothpaste [b] (twice/day)	Soil [c]	Sulfuryl Fluoride [d]	Average [e]	RSCA [f]	1.76 mg F/L	2.28 mg F/L	2.59 mg F/L
0.5 - <1	0.029	0.0078	0.016	0.0022	0.0027	0.080	0.13	0.13	0.15	0.16
1 - <4	0.037	0.024	0.049	0.0029	0.0030	0.087	0.11	0.13	0.14	0.15
4 - <7	0.042	0.010	0.021	0.0019	0.0029	0.074	0.097	0.10	0.11	0.12
7 - <11	0.032	0.0056	0.011	0.0013	0.0022	0.052	0.068	0.070	0.077	0.081
11 - <14	0.017	0.0039	0.0078	0.00078	0.0018	0.032	0.047	0.045	0.051	0.054
14+	0.014	0.0014	0.0029	0.00029	0.0011	0.029	0.042	0.044	0.051	0.056

[a] From Table 6; dietary = foods + commercial beverages.
[b] From Table 7.
[c] From Table 8.
[d] From Table 1.
[e] Assumes average dietary exposure + average water consumption of drinking water (0.87 mg F/L; Table 5) + 1 brushings/day with fluoride toothpaste + average exposure estimates from soil + average exposure estimates from sulfuryl fluoride.
[f] Values are from the OW Relative Source Contribution Analysis, adjusted for body weight. Estimates assume 90th percentile consumption of drinking water (consumers only) containing 0.87 mg F/L (Table 3) + average exposure from food and commercial beverages + 1 brushing/day with fluoride toothpaste + average exposure estimates from soil + average exposure estimates from sulfuryl fluoride.
[g] The FFDCA estimates assume average dietary exposure at various fluoride concentrations in drinking water + 2 brushings/day with fluoride toothpaste + average exposure estimates from soil + average exposure estimates from sulfuryl fluoride. These estimates are applicable to a relatively small, but fairly highly exposed subpopulation. The contribution from water at the various fluoride concentrations comes from Table 5.

4.3. Aggregate Risk Estimates

In estimating aggregate risks, the OPP compares the population-adjusted dose (PAD; 0.08 mg/kg/day) with exposure estimates for the populations being assessed. Risk estimates are generally of concern when the exposure estimates exceed the PAD.

In the case of fluoride, the variety of exposure sources and variability in human hygiene and dietary behaviors result in a broad range of exposure estimates. These estimates, as shown in Figure 1, indicate that for some populations the fluoride exposures are below levels that are beneficial for oral health (*i.e.*, less than the IOM's adequate intake level of 0.05 mg/kg/day). The estimates also show that for other populations, the fluoride exposures are well above the level deemed to be protective against adverse effects (0.08 mg/kg/day). The OPP stresses that this assessment does NOT indicate that the majority of the U.S. population is receiving excessive exposure to fluoride. Furthermore, the fluoride exposure for a particular individual can only be determined based on that individual's particular set of circumstances. As noted above, however, there are major identifiable subgroups of consumers within the U.S., for whom there is a high degree of certainty that their exposure to fluoride is greater than the PAD. These populations are likely to have one or more of the following characteristics: higher-than-average fluoride levels in their drinking water; higher-than-average rates of water consumption; and/or poor control of their swallow reflex, resulting in toothpaste ingestion. Other factors, such as dietary patterns (*e.g.*, high tea consumption), may lead to fluoride exposure that falls within the range of being a concern.

Currently, the FDA regulation regarding fluoridated toothpaste (fluoride concentration ranging from 850 to 1,150 ppm) requires that labeling of the product contains directions stating, "Children under 2 years of age: Consult a dentist or doctor." Given the uncertainty about how the statement impacts the use of fluoridated toothpaste for this age group and the published survey data indicating that fluoridated toothpaste is being used by children less than 2 years old, the OPP has not attempted to separately assess aggregate exposure without toothpaste for children <2 years old. The OPP notes that the FFDCA exposure estimates for these two age groups remain above the RfD even after subtracting the contribution from toothpaste.

Within the framework of the FFDCA, and based on the most recent findings regarding severe dental fluorosis as an adverse effects and the levels of fluoride exposure at which it occurs, the HED concludes that the required reasonable-certainty-of-no-harm finding cannot be made for aggregate exposure to fluoride consistent with its understanding and prior application of that standard.

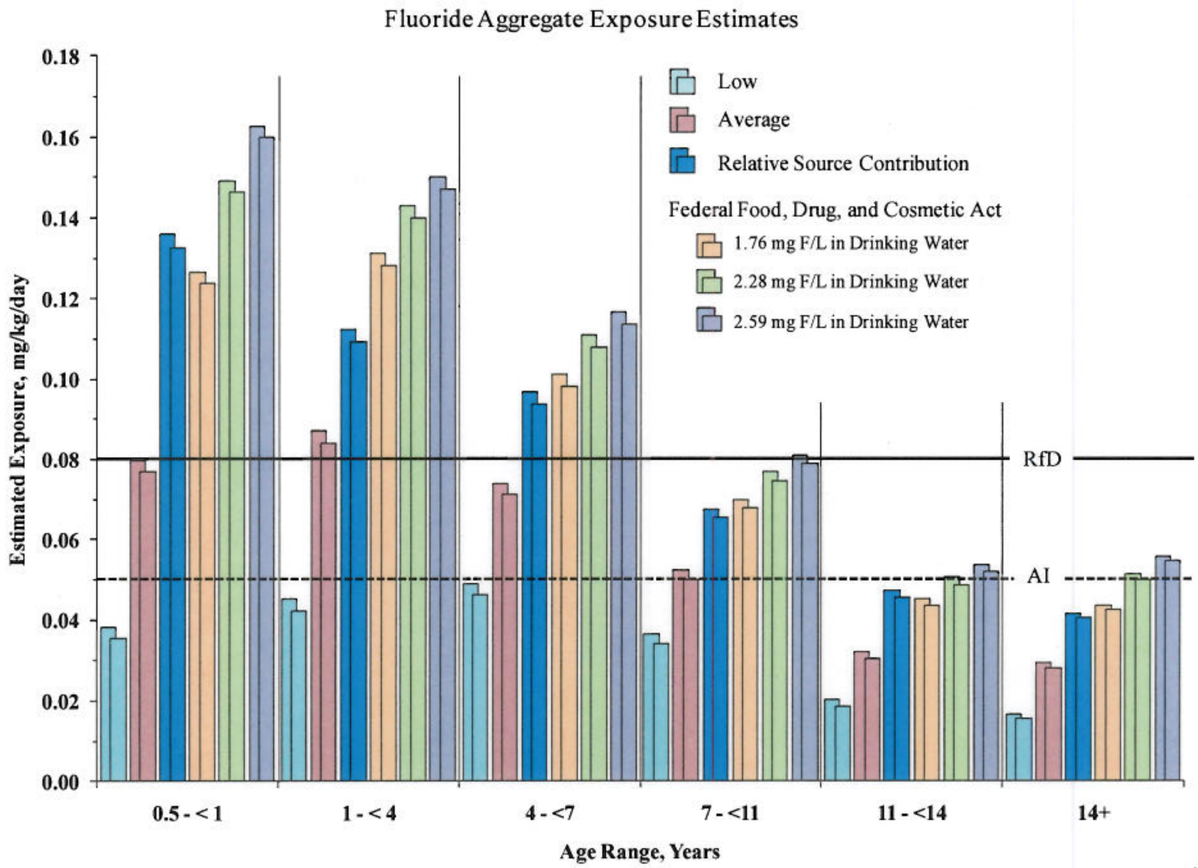

Figure 1. Range of fluoride exposure estimates. Estimates include fluoride from foods, commercial beverages, drinking water, incidental ingestion of fluoride toothpaste, and average incidental ingestion of soil. Within each grouping of paired columns, the higher column reflects the aggregate estimate including the average contribution from the use of sulfuryl fluoride whereas the lower column does not include the contribution from sulfuryl fluoride.

Legend: **Low** = Average consumption of food, commercial beverages and drinking water containing 0.1 mg F/L and no contribution from toothpaste.

Average = Average consumption of food, commercial beverages and drinking water containing 0.87 mg F/L and one brushing per day with fluoride toothpaste.

OW RSCA = 90th percentile consumption of drinking water (consumers only) containing 0.87 mg F/L + average exposure from food and commercial beverages (literature-reported values) + 1 brushing/day with fluoride toothpaste + average exposure estimates from soil + average exposure estimates from sulfuryl fluoride.

Federal Food, Drug, and Cosmetic Act = Three sets of estimates are provided. All assume average consumption of food, commercial beverages and drinking water, and two brushings per day with fluoride toothpaste. The concentrations of fluoride in drinking water are 1.76 mg/L, 2.28 mg/L or 2.59 mg/L which are the average from systems reporting at least one sample ≥ 2 mg/L, ≥ 3 mg/L, or ≥ 4 mg/L, respectively.

RfD = Reference dose protective for development of severe dental fluorosis = 0.08 mg/kg/day.

AI = Adequate intake established by the Institute of Medicine = 0.05 mg/kg/day.

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