UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: October 12, 2004

MEMORANDUM

Subject: Corrected Human Health Risk Assessment for Sulfuryl Fluoride and Fluoride Anion Addressing the Section 3 Registration of Sulfuryl Fluoride Post-Harvest Fumigation of Stored Cereal Grains, Dried Fruits and Tree Nuts and Pest Control in Grain Processing Facilities. PP# 1F6312.

DP Number: 309013
PC Code: 078003
40 CFR 180: 575 (sulfuryl fluoride)
145 (fluorine compounds)

Class: Fumigant

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NOTE: This assessment is being issued to correct errors present in the original assessment (D275199, M. Doherty, 1/20/2004). The original assessment included a dietary analysis that did not properly account for processing factors associated with fluoride residues on raisins produced from cryolite-treated grapes. Furthermore, the original assessment recommended a tolerance level for residues of sulfuryl fluoride in/on corn grits that is 1000-fold too high because residues were not converted from parts-per-billion to parts-per-million. As a result, *HED's recommended tolerance level for sulfuryl fluoride in/on corn, field, grits is now 0.02 ppm* rather than the 15-ppm value recommended previously. Other than the corrected tolerance value, the corrected fluoride-from-cryolite exposure estimate, and the corrected aggregate exposure estimate, the information presented in this assessment is identical to that contained in the original human health risk assessment cited above.

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1.0 EXECUTIVE SUMMARY

Dow AgroSciences has petitioned the Agency to register sulfuryl fluoride to control numerous pests in grain processing facilities and stored cereal grain, dried fruit, and tree nut commodities. In conjunction with that petition, Dow AgroSciences has requested the establishment of permanent tolerances for residues of sulfuryl fluoride and of fluoride anion on those commodities. Sulfuryl fluoride is a potential methyl bromide replacement for these uses. Under the proposed use, grain processing facilities and stored cereal grains, dried fruits, and tree nuts will be fumigated with sulfuryl fluoride formulated as the 99% a.i. ProFume. Fumigation may be carried out at ambient pressures or under vacuum conditions. Dow AgroSciences has developed software to tailor the application rate based on pressure, volume of the structure/chamber being fumigated, and pest species. Maximum fumigation rates are 1500 oz·hrs/1000 ft^3 (1500 mg·hrs/L) at ambient pressure and 200 mg·hrs/L under vacuum conditions. Sulfuryl fluoride is currently registered as Vikane for the fumigation of domestic structures and the Agency has granted an Experimental Use Permit to evaluate ProFume as a pest-control agent for walnuts and raisins (M. Doherty et al., D267729, 7/9/2001).

HED has reviewed the toxicology and residue chemistry data submitted to support the petition and has examined the potential for exposures via dietary (food and drinking water), non-dietary oral, inhalation, and dermal routes. Residues of concern for sulfuryl fluoride are sulfuryl fluoride, *per se*, and fluoride anion (also referred to as "fluoride" in this document). This assessment addresses the human health risk associated with sulfuryl fluoride and fluoride anion. Due to the different toxicological effects elicited by these two chemicals, their risks have been assessed separately.

Sulfuryl Fluoride. Based on the submitted toxicology data, taken in conjunction with the proposed uses, and the physical-chemical properties of sulfuryl fluoride, HED has determined that acute, short-term, and intermediate-term assessments are not appropriate for addressing risks to persons who are not working directly with sulfuryl fluoride. Chronic exposure to sulfuryl fluoride may occur through dietary exposure. Because of its chemical properties, sulfuryl fluoride is extremely unlikely to occur in water; therefore, chronic dietary exposure would occur only through residues in/on food. In conducting the chronic dietary assessment, HED has assumed average residue levels based on residue trials conducted at the maximum fumigation rate and has incorporated conservative market share estimates. The population-adjusted dose (PAD) that HED has determined is appropriate for evaluating chronic exposures is 0.003 mg/kg/day. The estimated dietary exposures for the general U.S. population and all population subgroups, including those of infants and children, are less than 1% of the chronic PAD. Generally, HED is concerned about estimated risk levels when they exceed 100% of the PAD; therefore, these risk estimates are well below HED's level of concern. As noted above, chronic dietary (food only) exposure is the only relevant exposure pathway for inclusion in aggregate risk estimates. Aggregate risk estimates from exposure to sulfuryl fluoride, therefore, are below HED's level of concern for all population subgroups.

HED has also evaluated the potential risks to workers conducting fumigations with sulfuryl fluoride and to personnel engaged in post-fumigation activities. The most current proposed label

and use booklet mandates that all workers must wear approved self-contained breathing apparatus if they will be in an area where the concentration of sulfuryl fluoride exceeds 1 ppm or is unknown. Workers not wearing proper respiratory protection may enter a fumigated area only after the concentration of sulfuryl fluoride has been shown to be below 1 ppm. Based on information available to HED, short-term, intermediate-term and chronic exposure to sulfuryl fluoride may occur for professionals working with sulfuryl fluoride or sulfuryl fluoride fumigated commodities. HED has estimated exposures and risks for fumigators and tent workers based on sulfuryl fluoride data depicting exposure to workers following structural fumigation with Vikane. For the ProFume assessments, exposure estimates for Vikane were reduced by 5-fold to account for the fact that data were collected based on a 5-ppm reentry concentration and ProFume will have a 1-ppm reentry concentration. Occupational MOEs for ProFume range from 300 to 2100. Target MOEs are 100 for short- and intermediate-term exposures, and 300 for long-term exposures.

Fluoride Anion. In assessing the risks associated with exposure to fluoride, HED has relied on the toxicological assessment and Maximum Contaminant Levels (MCLs) established by the Agency's Office of Water. A MCL is an enforceable level that is set as closely as feasible to the Maximum Contaminant Level Goal (MCLG) of a contaminant. The MCLG is the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, and which allows an adequate margin of safety. Maximum contaminant level goals are non-enforceable health goals. For fluoride, both the MCL and the MCLG have been set at 4.0 ppm in order to protect against crippling skeletal fluorosis. The Office of Water has also established a secondary MCL (SMCL) for fluoride at 2.0 ppm. The SMCL is a non-enforceable level established to be protective against the cosmetic and aesthetic effects of objectionable dental fluorosis. At this time, based on the information available to the Agency, EPA is not concluding that dental fluorosis associated with fluoride exposure is an adverse health effect under the Federal Food, Drug, and Cosmetic Act (FFDCA). The current arguments that dental fluorosis is more than a cosmetic effect are not sufficiently persuasive to warrant regulation as an adverse health effect under the FFDCA. Accordingly, consistent with the action taken by the Office of Water under the Safe Drinking Water Act, 40 FR 47142 (November 14, 1985) (WH-FRL-2913-8(b)), the Agency believes that the appropriate endpoint for regulation under the FFDCA is skeletal fluorosis. While the tolerance safety determination under the FFDCA is a health based standard, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires the balancing of all costs, taking into account the economic, social, and environmental effects as well as health based risks, against the benefits associated with the pesticide use. Therefore, the Agency has consider dental fluorosis in determining whether sulfuryl fluoride meets the requisite standard under FIFRA (see Appendix I).

Using body weight and water consumption estimates, the MCL has been converted from a concentration basis (mg/L) to an exposure basis (mg/kg/day). The resulting values for the population groups addressed in the fluoride risk assessments are as follows:

U.S. Population . . . . . 0.114 mg/kg/day
Infants (< 1 year old) . . . . . 0.571 mg/kg/day
Children 1-2 years old . . . . . 0.308 mg/kg/day

Children 3-5 years old ..... 0.182 mg/kg/day
Children 6-12 years old ..... 0.100 mg/kg/day
Youth 13-19 years old ..... 0.133 mg/kg/day
Adults 20+ years old ..... 0.114 mg/kg/day
Females 13-49 years old ..... 0.131 mg/kg/day

For fluoride risk assessments addressed in this document, these MCL values have been used in a manner analogous to a reference dose (RfD).

This assessment includes quantitative estimates of dietary exposure from background levels of fluoride in food, fluoride in water, and fluoride from the pesticidal food uses of cryolite and sulfuryl fluoride; non-dietary exposure from the use of fluoridated toothpaste, and non-dietary exposure from fluoride residues in air. For each of these pathways of exposure, residue estimates are conservative to moderately conservative in nature. Other potential sources of fluoride exposure have not been included in this assessment in a quantitative manner, primarily due to lack of demographic and/or exposure information. Non-quantified pathways of exposure are not expected to significantly increase exposure estimates for the various population subgroups at large.

Risk estimates for individual fluoride exposure pathways are below 100% of the MCLs for the general U.S. population and all population subgroups, including those of infants and children. When all quantified dietary and non-dietary exposure pathways are combined, risk estimates range from 37 to 42% of the MCL. These aggregate risk estimates are below HED's level of concern for all population subgroups. HED believes that the assessment is sufficiently conservative to ensure that it does not underestimate actual fluoride exposures experienced by members of the U.S. population. HED further notes that the fluoride exposures due to the uses of sulfuryl fluoride, the primary subject of this petition, are minuscule in comparison to exposures from water, toothpaste, and background residues already occurring in foods.

Deficiencies in the sulfuryl fluoride data are noted in Section 8. HED is recommending that any food-use registrations for sulfuryl fluoride be made conditional upon resolution of these deficiencies. The tolerances proposed by Dow AgroSciences and HED's recommended tolerance levels are summarized in Table 8.1. HED notes that the Office of Water, via the National Academy of Sciences, is reevaluating the available information regarding fluoride. Therefore, HED is recommending that these tolerances be time-limited and that OPP reexamine this risk assessment once the Office of Water has completed its review.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Sulfuryl fluoride (SO_2F_2) is a fumigant that is being proposed as a methyl bromide replacement for the post-harvest control of pests in stored commodities and grain processing facilities. Sulfuryl fluoride is a gas at standard temperature and pressure. It has a melting point of -136°C, a boiling point of -55°C, and a vapor pressure of 9150 mm Hg (Torr) at 10°C. Sulfuryl fluoride rapidly breaks down to form sulfate and fluoride anion. As Profume® and

Vikane®, sulfuryl fluoride constitutes 99% of the product and there are no known impurities of toxicological concern.

Fluorine has an atomic mass of 18.99, is extremely electronegative and reactive, and occurs as the diatomic F_2 in its elemental form. Due to its high reactivity, fluorine does not typically exist outside of the laboratory. In the environment, fluorine readily reacts with all other elements except nitrogen, oxygen, and the lighter noble gases to form various fluoride complexes. It is these fluoride complexes that govern the behavior and bioavailability of fluoride. Due to its ability to readily react with other elements and molecules, fluoride has the potential to occur in food, water, and air, and exposure to humans may occur through any of these media.

3.0 HAZARD CHARACTERIZATION

3.1 Sulfuryl Fluoride

3.1.1 Hazard Profile

Table 3.1.1. Acute Toxicity of Technical Grade Sulfuryl Fluoride (99.8% active ingredient)

Guideline No.	Study Type	MRID	Results	Tox Category
870.11	Acute Oral Rats	43314	M: LD_{50} = 100 mg/kg F: LD_{50} = 100 mg/kg	II*
870.12	Acute Dermal	-----	Study Waived *	IV**
870.13	Acute Inhalation Mice (4 hour exposure)	41769101	M: LC_{50} = 660 ppm (2.56 mg/L) F: LC_{50} = 642 ppm (2.49 mg/L)	I*
870.13	Acute Inhalation Rats (1 hour exposure)	238663	LC_{50} = 4512 ppm (17.5 mg/L)	I*
870.24	Primary Eye Irritation	-----	Study Waived *	I**
870.25	Primary Skin Irritation	-----	Study Waived *	IV**
870.26	Dermal Sensitization	-----	Study Waived *	Non-Sensitizer **
--------	Dermal Vapor Rats (4 hour dermal exposure)	41712001	No adverse effects at 9600 ppm (40.3 mg/L)	N/A

* Memorandum by M. Lewis (SRRD) to V. Dutch (SRRD), 11/17/99, HED Doc. No. 078003.
** Assumed Toxicity Category. See memorandum by M. Lewis (above).
N/A Not applicable

Table 3.1.2. Toxicity Profile of Technical Grade Sulfuryl Fluoride (99.8% active ingredient)		
Guideline No.	Study Type	Results
-------- (inhalation study)	2-Week inhalation toxicity, rats 0, 100, 300, 600 ppm (0/0, 83/89, 249/267, 498/534 mg/kg/day) (M/F)	**NOAEL**: 83/89 mg/kg/day (M/F) **LOAEL**: 249/267 mg/kg/day (M/F): M&F = slightly increased kidney weights, minimal histopathology in kidney. At 498/534 mg/kg/day (M/F): M&F = high mortality, decreased body weights, severe histopathology in kidney, gross and histopathology in many tissues/organs (secondary to kidney effects); severe inflammation of respiratory tissues in 1 survivor. No treatment-related neurotoxicity.
-------- (inhalation study)	2-Week inhalation toxicity, dogs 0, 30, 100, 300 ppm (0/0, 7.9/8.0, 26/27, 79/80 mg/kg/day) (M/F)	**NOAEL**: 26/27 mg/kg/day (M/F) **LOAEL**: 79/80 mg/kg/day (M/F): M&F = intermittant tremors and tetany during exposures, minimal inflammatory changes in upper respiratory tract, decreased body weight (F only). Note–increased serum fluoride at ≥26/27 mg/kg/day.
-------- (inhalation study)	2-Week inhalation toxicity, rabbits 0, 100, 300, 600 ppm (0/0, 30/30, 90/90, 180/180 mg/kg/day) (M/F)	**NOAEL**: 30/30 mg/kg/day (M/F) **LOAEL**: 90/90 mg/kg/day (M/F): M&F = malacia (necrosis) in cerebrum, vacuolation of cerebrum, moderate inflammation of respiratory tissues. At 180/180 mg/kg/day (M/F): M&F = convulsions, hyperactivity, malacia (necrosis) in cerebrum, vacuolation of cerebrum, moderate inflammation of respiratory tissues.
(870.3100) (inhalation study)	90-Day inhalation toxicity, rats 0, 30, 100, 300 ppm (0/0, 24/25, 80/83, 240/250 mg/kg/day) (M/F)	**NOAEL**: 24/25 mg/kg/day (M/F) **LOAEL**: 80/83 mg/kg/day (M/F): M&F = dental fluorosis. At 240/250 mg/kg/day (M/F): M&F = vacuolation of caudate-putamen nucleus and white fiber tracts of the internal capsule of the brain, decreased body weight, inflammation of nasal passages, alveolar histiocytosis; slight hyperplasia of renal collecting ducts (F only).
(870.3100) (inhalation study)	90-Day inhalation toxicity, mice 0, 10, 30, 100 ppm (0/0, 12.5/12.1, 38/36, 125/121 mg/kg/day) (M/F)	**NOAEL**: 38/36 mg/kg/day (M/F) **LOAEL**: 125/121 mg/kg/day (M/F): M&F = microscoic lesions in caudate-putamen nucleus and external capsule, decreased body weight, decreased body weight gain, follicular cell hypertrophy in thyroid. Note–increased serum fluoride at ≥38/36 mg/kg/day.
(870.3150) (inhalation study)	90-Day inhalation toxicity, dogs 0, 30, 100, 200 ppm (0/0, 7.5/7.6, 25/26, 50/51 mg/kg/day) (M/F)	**NOAEL**: 25/26 mg/kg/day (M/F) **LOAEL**: 50/51 mg/kg/day (M/F): M&F = slight histopathology of the caudate nucleus of the basal ganglia, decreaed bodyweight, decreased body weight gain, transient neurological signs (lateral recumbancy, tremors, incoordination, salivation, tetany, inactivity) starting at day 19 in 1 M.
(870.3150) (inhalation study)	90-Day inhalation toxicity, rabbits 0, 30, 100, 600/300* ppm (0/0, 8.6/8.5, 29/28, 86/85 mg/kg/day) (M/F) * 600 ppm reduced to 300 ppm after 9	**NOAEL**: 8.6/8.5 mg/kg/day (M/F) **LOAEL**: 29/28 mg/kg/day (M/F): M&F = decreased body weight, decreased liver weight, dental fluorosis, vaculoation of white matter of the brain (F only). At 86/85 mg/kg/day (M/F): M&F = malacia (necrosis) and vacuolation of putamen, globus pallidus and internal & external capsules in brain, decreased body weight gain, alveolar histiocytosis, histopathology in nasal epithelium. Note–increased serum fluoride at all dose levels (≥8.6/8.5 mg/kg/day).

Table 3.1.2. Toxicity Profile of Technical Grade Sulfuryl Fluoride (99.8% active ingredient)		
Guideline No.	Study Type	Results
	exposures due to convulsions and hind leg paralysis .	
(870.3700) (inhalation study)	Developmental toxicity inhalation study, rats 0, 25, 75, 225 ppm (0, 27, 81, 243 mg/kg/day)(F)	**Maternal NOAEL**: 243 mg/kg/day (F): highest dose tested. **Maternal LOAEL**: >243 mg/kg/day (F). Note-significant maternal toxicity observed in range-finding study at 300 ppm. **Developmental NOAEL**: 243 mg/kg/day (F): highest dose tested. **Developmental LOAEL**: >243 mg/kg/day (F)
(870.3700) (inhalation study)	Developmental toxicity inhalation study , rabbits 0, 25, 75, 225 ppm (0, 9.5, 29, 86 mg/kg/day)(F)	**Maternal NOAEL**: 29 mg/kg/day (F) **Maternal LOAEL**: 86 mg/kg/day (F): F = decreased body weight and decreased body weight gain during treatment. Note-significant maternal toxicity observed in range-finding study at 300 ppm. **Developmental NOAEL**: 29 mg/kg/day (F) **Developmental LOAEL**: 86 mg/kg/day (F): F = decreased fetal body weight, decreased crown-rump length, possibly incresed fetal liver pathology (pale liver).
(870.3800) (inhalation study)	2-Generation reproduction inhalation study, rats 0, 5, 20, 150 ppm (0/0, 3.6/3.6, 14/14, 108/108 mg/kg/day) (M/F)	**Parental NOAEL**: 3.6/3.6 mg/kg/day (M/F) **Parental LOAEL**: 14/14 mg/kg/day (M/F): M&F = pale foci in lungs, increased alveolar macrophages in lungs. At 108/108 mg/kg/day (M/F): M&F = vacuolation of caudate putamen tracts in brain, decreased body weight, histopathology in lungs, dental fluorosis. **Offspring NOAEL**: 14/14 mg/kg/day (M/F) **Offspring LOAEL**: 108/108 (M/F): Decreased pup weights in F1 and F2 generations (probably secondary to maternal body weight loss).
870.41	Chronic toxicity, rats	See (870.4300)
(870.4100) (inhalation study)	1-Year chronic inhalation toxicity, dogs 0, 20, 80, 200 ppm (0/0, 5.0/5.1, 20/20, 50/51 mg/kg/day) (M/F)	**NOAEL**: 5.0/5.1 mg/kg/day (M/F) **LOAEL**: 20/20 mg/kg/day (M/F): M&F = decreased body weight gain, increased alveolar macrophages in lungs, dental fluorosis. At 50/51 mg/kg/day (M/F): M&F = increased mortality, malacia (necrosis) in caudate nucleus of brain, follicular cell hypertrophy in thyroid, histopathology in lung.
870.42	Carcinogenicity, rats	See (870.4300)
(870.4200) (inhalation study)	18-Month carcino-genicity inhalation study, mice 0, 5, 20, 80 ppm (0/0, 5.3/6.3, 25/25, 101/101 mg/kg/day) (M/F)	**NOAEL**: 25/25 mg/kg/day (M/F) **LOAEL**: 101/101 mg/kg/day (M/F): M&F = cerebral vacuolation in brain, decreased body weight gain; follicular cell hypertrophy in thyroid (M only); increased mortality (F only), heart thrombus (F only), lung congestion (F only). Negative for carcinogenicity in M and F.
(870.4300) (inhalation study)	2-Year combined chronic toxicity/ carcinogenicity inhalation study, rats 0, 5, 20, 80 ppm (0/0, 3.5/3.9, 14/16,	**NOAEL (M)**: 3.5 mg/kg/day **LOAEL (M)**: 14 mg/kg/day: M = dental fluorosis. At 56 mg/kg/day (M): M = effects similar to those in F at 62 mg/kg/day. **NOAEL (F)**: 16 mg/kg/day **LOAEL (F)**: 62 mg/kg/day: F = greatly increased mortality (due mostly to severe kidney toxicity which led to kidney failure); histopathology in brain (vacuolation in cerebrum and thalamus/hypothalamus), adrenal

Table 3.1.2. Toxicity Profile of Technical Grade Sulfuryl Fluoride (99.8% active ingredient)		
Guideline No.	Study Type	Results
	56/62 mg/kg/day) (M/F)	cortex, eyes, liver, nasal tissue, and respiratory tract; dental fluorosis. Negative for carcinogenicity in M and F.
870.5100	Mutagenicity - Reverse gene mutation (S. typhimurium)	Negative without and with S-9 activation.
870.5395	Mutagenicity - *in vivo* micronucleus assay, mice (bone marrow cells)	Negative.
870.5500	Mutagenicity - unscheduled DNA synthesis (primary rat hepatocytes)	Negative.
(870.6200) (inhalation study)	Acute inhalation neurotoxicity study, rats (special design) 0, 100, 300 ppm (0, 118, 354 mg/kg/day) (F only)	**Systemic NOAEL**: 354 mg/kg/day (F): highest dose tested. **Systemic LOAEL**: >354 mg/kg/day (F). **Neurotoxic NOAEL**: 354 mg/kg/day (F): highest dose tested. **Neurotoxic LOAEL**: >354 mg/kg/day (F). Note-study included electrophysiological parameters, but no microscopic pathology.
(870.6200) (inhalation study)	90-Day inhalation neurotoxicity study, rats (special design) 0, 30, 100, 300 ppm (0/0, 24/25, 80/83, 240/250 mg/kg/day) (M/F)	**Systemic NOAEL**: 24/25 mg/kg/day (M/F) **Systemic LOAEL**: 80/83 mg/kg/day (M/F): M&F = pale foci in pleura and macrophages in lungs, dental fluorosis At 240/250 mg/kg/day (M/F): M&F = decreased body weight, excessive salivation, poor grooming. **Neurotoxic NOAEL**: 24/25 mg/kg/day (M/F) **Neurotoxic LOAEL**: 80/83 mg/kg/day (M/F): M&F = disturbances in electrophysiologic parameters (slowing of VER and SER waveforms in F and ABR waveforms in M). At 240/250 mg/kg/day (M/F): M&F = slowing of all waveforms except CNAP, vacuolation of white matter in caudate putamen in cerebrum. Note-study included electrophysiological parameters.
(870.6200) (inhalation study)	1-Year inhalation neurotoxicity study, rats (special design) 0, 5, 20, 80 ppm (0/0, 3.5/3.9, 14/16, 56/62 mg/kg/day) (M/F)	**Systemic NOAEL**: 3.5/3.9 mg/kg/day (M/F) **Systemic LOAEL**: 14/16 mg/kg/day (M/F): M&F = dental fluorosis. At 56/62 mg/kg/day (M/F): M&F = increased kidney and liver weights, progressive kidney disease, histopathology in lung. **Neurotoxic NOAEL**: 56/62 mg/kg/day (M/F): highest dose tested. **Neurotoxic LOAEL**: >56/>62 mg/kg/day (M/F). Note-study did not include electrophysiological parameters.
870.6300	Developmental neurotoxicity, rats	No study available. Required to be performed and submitted by HIARC (April 11, 2001 and October 21, 2003).
870.7485	Metabolism and pharmacokinetics, rats	No study available. Study waived in Reregistration Eligibility Document (RED) published by EPA in 1993.
870.7600	Dermal Penetration, rats	No study available. Not required.

Technical grade sulfuryl fluoride (99.8% active ingredient) is marketed as a liquified gas in pressurized steel cylinders. The acute oral LD50 of sulfuryl fluoride has been estimated to be approximately 100 mg/kg in rats (Toxicity Category II). The acute inhalation LC50 in mice (4 hour exposure) is 660 ppm (2.56 mg/L) in males and 642 ppm (2.49 mg/L) in females. The acute inhalation LC50 in rats (1 hour exposure) is 4512 ppm (17.5 mg/L). Based on the use pattern for sulfuryl fluoride and several reported incidences of human poisonings in the general toxicologic literature, the Agency has classified sulfuryl fluoride as Toxicity Category I for acute inhalation toxicity. When released from pressurized steel cylinders, sulfuryl fluoride causes freezing of skin and eye tissues on contact. Therefore, no dermal studies or eye irritation studies have been required to be submitted. The acute dermal toxicity study (assumed Toxicity Category of IV), the primary skin irritation study (assumed Toxicity Category of IV), the primary eye irritation study (assumed Toxicity Category of I), and the dermal sensitization study (assumed to be a non-sensitizer) have been waived. In a non-guideline study in which rats were dermally exposed (with no inhalation exposure) to vapors of sulfuryl fluoride gas at an exposure concentration of 9600 ppm (40.3 mg/L) for 4 hours, no treatment-related adverse effects were observed.

In 2-week inhalation studies in rats, dogs and rabbits, different target organs were affected. In rats, the primary target organ was the kidney, in which severe histopathological lesions were observed. These lesions included papillary necrosis, hyperplasia of the epithelial cells of the papillae, and degeneration/regeneration of collecting tubules and proximal tubules. In dogs, the primary target organ was the upper respiratory tract, in which minimal inflammation was observed. Intermittant tremors and tetany were also noted in dogs. In rabbits, the primary target organ was the brain, in which malacia (necrosis) and vacuolation were observed in the cerebrum. Inflammation of the upper respiratory tract was also noted in rabbits.

In subchronic (90-day) inhalation studies in rats, mice, dogs and rabbits, the brain was the major target organ. Malacia and/or vacuolation were observed in the white matter of the brain in all four species. The portions of the brain most often affected were the caudate-putamen nucleus in the basal ganglia, the white fiber tracts in the internal and external capsules, and the globus pallidus of the cerebrum. In dogs and rabbits, clinical signs of neurotoxicity (including tremors, tetany, incoordination, convulsions and/or hind limb paralysis) were also observed. Inflammation of the nasal passages and histiocytosis of the lungs were observed in rats and rabbits, but not in dogs, in which species inflammation of the upper respiratory tract was more prominent in the 2-week study. In rats, kidney damage was also observed. In mice, follicular cell hypertrophy was noted in the thyroid gland. Decreased body weights and body weight gains were also observed in rats, dogs and mice.

In chronic (1-2 year) inhalation studies in rats, dogs and mice, target organs were the same as in the 90-day studies. In rats, severe kidney damage caused renal failure and mortality in many animals. Additional gross and histopathological lesions in numerous organs and tissues were considered to be secondary to the primary effect on the kidneys. Other treatment-related effects in rats included effects in the brain (vacuolation of the cerebrum and thalamus/ hypothalamus) and respiratory tract (reactive hyperplasia and inflammation of the respiratory epithelium of the nasal turbinates, lung congestion, aggregates of alveolar macrophages). In dogs and mice, increased mortality, malacia and/or vacuolation in the white matter in the brain,

histopathology in the lungs, and follicular cell hypertrophy in the thyroid gland were observed. Decreased body weights and body weight gains were also noted in all three species. No evidence of carcinogenicity was observed in either the combined chronic toxicity/carcinogenicity study in rats or in the 18-month carcinogenicity study in mice.

In many subchronic and chronic inhalation studies in rats, dogs, and rabbits, dental fluorosis was the most sensitive effect observed in the study. In two 90-day studies in mice and rabbits, in which serum fluoride levels were determined, an increased serum level of fluoride anions was observed at even lower dose levels. The increased serum fluoride levels were due to the conversion of sulfuryl fluoride to fluoride anions in the body.

In specially designed acute and subchronic inhalation neurotoxicity studies in rats, several electrophysiological parameters (electroencephalograms, EEGs) were recorded in addition to observations for clinical signs of neurotoxicity, functional observational battery (FOB) and motor activity testing, and/or neurohistopathologic examination. Following two exposures on consecutive days for 6 hours/day at 300 ppm of sulfuryl fluoride (354 mg/kg/day), no treatment-related neurotoxic effects were noted. In a 90-day study, changes in some EEG patterns were observed at 100 ppm (80 mg/kg/day) and in several additional patterns at 300 ppm (240 mg/kg/day). Vacuolation of the white matter in the cerebrum was also observed at 300 ppm in this study. In a specially designed 1-year chronic inhalation neurotoxicity study in rats, no treatment-related neurotoxic effects were observed at 80 ppm (56 mg/kg/day). EEGs were not recorded in this study.

In a developmental toxicity inhalation study in rats, no developmental toxicity was observed in the pups. Although no maternal toxicity was observed in this study at the highest dose tested (225 ppm), significant maternal toxicity (decreased body weight, body weight gain and food consumption; increased water consumption and kidney weights; and gross pathological changes in the kidneys and liver) was observed in a previously conducted range-finding study at a slightly higher dose level (300 ppm). In a developmental toxicity inhalation study in rabbits, decreased fetal body weights were observed in the pups. At the same dose level, decreased body weight and body weight gain were observed in the dams. In a 2-generation reproduction inhalation study in rats, vacuolation of the white matter in the brain, pathology in the lungs (pale, gray foci; increased alveolar macrophages) and decreased body weights were observed in the parental animals. Decreased pup body weights in the F1 and F2 generations were observed in the offspring. No effects on reproductive parameters were noted in this study. No quantitative or qualitative evidence of increased susceptibility of fetuses or pups was observed in the developmental toxicity or reproduction studies on sulfuryl fluoride.

A battery of mutagenicity studies was negative for genotoxic potential. The studies included a reverse gene mutation assay in *Salmonella typhimurium*, an unscheduled DNA synthesis assay in primary rat hepatocytes, and a micronucleus assay in mouse bone marrow cells.

In carcinogenicity studies in male and female rats and in male and female mice, sulfuryl fluoride did not demonstrate evidence of carcinogenic potential. Sulfuryl fluoride is classified as

"not likely to be carcinogenic to humans" according to the July 2, 1999 EPA *Draft Proposed Guidelines for Carcinogen Risk Assessment.*

Poisonings and fatalities have been reported in humans following inhalation exposure to sulfuryl fluoride. The severity of these effects has depended on the concentration of sulfuryl fluoride and the duration of exposure. Short-term inhalation exposure to high concentrations has caused respiratory irritation, pulmonary edema, nausea, abdominal pain, central nervous system depression, and numbness in the extremities[1]. In addition, there have been two reports of deaths of persons entering houses treated with sulfuryl fluoride. One person entered the house illegally and was found dead the next morning. A second person died of cardiac arrest after sleeping in a house overnight following fumigation. A plasma fluoride level of 0.5 mg/L (10 times normal) was found in this person following exposure[2]. These acute poisonings in humans, however, occurred only after label directions were grossly violated and persons were subsequently exposed to extremely high concentrations of sulfuryl fluoride. Prolonged chronic inhalation exposures to concentrations of sulfuryl fluoride gas significantly above the threshold limit value (TLV) of 5 ppm have caused fluorosis in humans because sulfuryl fluoride is converted to fluoride anion in the body[1]. Fluorosis is characterized by binding of fluoride anion to teeth (causing mottling of the teeth) and to bone. Sulfuryl fluoride and fluoride anion are the residues of concern associated with sulfuryl fluoride.

3.1.2 FQPA Considerations

On October 21, 2003, the HED Hazard Identification Assessment Review Committee (HIARC) met to re-evaluate the potential for increased susceptibility of infants and children from exposure to sulfuryl fluoride, as required by the Food Quality Protection Act (FQPA) of 1996, according to the 2002 OPP 10X Guidance Document. This re-evaluation was conducted to update the decision which was reached on April 11, 2001 using previous OPP policy.

Based on the available evidence, HIARC reiterated its earlier recommendation that an inhalation developmental neurotoxicity (DNT) study in rats (Guideline No. 870.6300) be required in order to more clearly and fully characterize the potential for neurotoxic effects in young animals.

HIARC determined that a 10X database uncertainty factor (UF_{DB}) is needed to account for the lack of the DNT study since the available data provide no basis to support reduction or removal of the default 10X factor. The following points were considered in this determination:

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[1]U.S.EPA, Structural fumigation using sulfuryl fluoride: DowElanco's Vikane ™ Gas Fumigant, Methyl bromide alternative case study, Part of EPA 430-R-021, 10 Case studies, volume 2, December 1996, p. 3. Available at http://www.epa.gov/spdpublc/mbr/sulfury2.html.

[2]U.S.EPA, Reregistration Eligibility Decision (RED); Sulfuryl fluoride, 1993, p. 9.

- The current regulatory dose for chronic dietary risk assessment is the NOAEL of 8.5 mg/kg/day (30 ppm; 0.13 mg/L) selected from a 90-day inhalation toxicity study in rabbits. This dose is also used for intermediate- and long-term inhalation exposure risk assessments. The current dose for the short-term inhalation exposure risk assessment is the NOAEL of 30 mg/kg/day (100 ppm; 0.42 mg/L) from a 2-week inhalation toxicity study in rabbits.

- After considering the dose levels used in the neurotoxicity studies and in the 2-generation reproduction study, it is assumed that the DNT study with sulfuryl fluoride will be conducted at dose levels similar to those used in the 2-generation reproduction study (0, 5, 20, 150 ppm; 0, 0.02, 0.08, 0.6 mg/L). It is considered possible that the results of the DNT study could impact the endpoint selection for risk assessments because the lowest dose that may be tested in the DNT (5 ppm or 0.02 mg/L), based on the HIARC's dose analysis, could become an effect level which would necessitate an additional factor resulting in doses which would then be lower than the current doses used for chronic dietary (8.5 mg/kg/day), intermediate and long-term inhalation (30 ppm or 0.13 mg/L) and short term inhalation (100 ppm or 0.42 mg/L) risk assessments. Given these circumstances, the HIARC does not have sufficient reliable data justifying selection of an additional safety factor for the protection of infants and children lower than the default value of 10X. Therefore, a UF_{DB} of 10X will be applied to repeated dose exposure scenarios (i.e. chronic RfD, and residential short, intermediate and long term inhalation) to account for the lack of the DNT study with sulfuryl fluoride.

The HIARC determined that there is no need for a special FQPA safety factor (i.e., 1X) since there are no residual uncertainties for pre- and/or post-natal toxicity based on the following:

- In the developmental toxicity study in rats, neither quantitative nor qualitative evidence of increased susceptibility of fetuses to *in utero* exposure to sulfuryl fluoride was observed.

- In the developmental toxicity study in rabbits, neither quantitative nor qualitative evidence of increased susceptibility of fetuses to *in utero* exposure to sulfuryl fluoride was observed.

- In the 2-generation reproduction toxicity study in rats, neither quantitative nor qualitative evidence of increased susceptibility of fetuses to sulfuryl fluoride was observed.

3.1.3 Dose-Response Assessment

The endpoint selection and rationale are provided, below and in Table 3.1.3, for the various exposure route and duration combinations.

Acute Reference Dose (RfD). None. No toxicological endpoint attributable to a single exposure was identified in the available toxicology studies on sulfuryl fluoride that would be appropriate for an acute risk assessment and would be applicable to females (13-50 years old) or to the general population (including infants and children).

Chronic Reference Dose (RfD). 0.003 mg/kg/day from the 90-Day subchronic inhalation toxicity study in rabbits. In that study, the LOAEL is 28 mg/kg/day based on vacuolation of white matter in the brain of females, and decreased body weights, decreased liver weights and dental fluorosis in males and females. The NOAEL is 8.5 mg/kg/day. The Uncertainty Factor associated with the chronic RfD is 3000 and is based on 10X for intraspecies variation, 10X for interspecies extrapolation, 3X Uncertainty Factor for using a subchronic (90-day) study for chronic risk assessment (UF_S), and 10X Database Uncertainty Factor (UF_{DB}) for lack of a DNT study. We note that a chronic dog study with an NOAEL of 5 mg/kg/day is available. In that study, the noted effects at the LOAEL of 20 mg/kg/day were decreased body weight gain, increased alveolar macrophages, and dental fluorosis. This study was not selected as the basis for the RfD because the effects from the rabbit study are considered to be more severe. Had this dog study been used, the resulting RfD (0.005 mg/kg/day) would have been nearly identical to that derived from the 90-day rabbit study. A chronic rat study with an NOAEL of 3.5 mg/kg/day is also available. In that study, the effect at the LOAEL of 14 mg/kg/day was dental fluorosis. The effects in the rabbit study are considered to be more severe than those in the rat study. If this rat study had been selected, the resulting RfD (0.0035 mg/kg/day) also would have been nearly identical to that derived from the 90-day rabbit study. The selected chronic RfD for sulfuryl fluoride is considered to be protective of all effects, including dental fluorosis.

For sulfuryl fluoride, the endpoint from an inhalation toxicity study was used to calculate the chronic RfD which is to be used to perform risk assessments for oral exposures. HIARC believes this is a very conservative methodology which is supported by the following considerations:

- A higher and more persistent level of parent test material in the body may occur following inhalation exposure as compared to an oral exposure because the parent test material is immediately distributed throughout the circulatory system following inhalation, rather than first being directly shunted to the liver (where most metabolism occurs) as in the case of oral exposure.

- In addition, for sulfuryl fluoride, the NOAEL on which the chronic RfD was calculated is from a study in rabbits (which is the most sensitive species for neurotoxic effects) and the LOAEL in this study was close to a threshold effect level (the effect was observed in only one female rabbit).

The LOAEL of 100 ppm (equivalent to 28 mg/kg/day) in the 90-day rabbit study, which was used to calculate the chronic RfD, was considered to be close to a threshold effect level because only one female rabbit at this concentration had vacuolation of the white matter in the brain. The HIARC considered applying an additional uncertainty factor to the NOAEL in this study due to the severity of the effect at the LOAEL, but concluded that application of an additional uncertainty factor would not be necessary since the LOAEL was an approximate threshold effect level.

For the purpose of determining a chronic oral RfD, the HIARC believes that an endpoint based on a well-defined morphological/pathological effect, such as the neurological effect

observed in the 90-day rabbit study, is preferable to one based on a more equivocal and/or dubious effect such as dental fluorosis (mottling of teeth). The HIARC also believes that it is not appropriate to utilize an effect on the respiratory system in an inhalation study as the basis for calculating an oral RfD. Therefore, the NOAEL of 5 ppm (equivalent to 3.5 mg/kg/day) for male rats in the combined 2-year chronic/carcinogenicity inhalation study in rats (MRID 43354902) was not used to calculate the chronic RfD because the effect observed at the LOAEL of 20 ppm (equivalent to 14 mg/kg/day) was dental fluorosis. Also, the parental NOAEL of 5 ppm (equivalent to 3.6 mg/kg/day) in the 2-generation reproduction inhalation study in rats (MRID 42179801) was not used because the effect observed at the parental LOAEL of 20 ppm (equivalent to 14 mg/kg/day) was pathological changes in the lungs. In addition, the NOAEL of 20 ppm (equivalent to 5.0 mg/kg/day) in the 1-year chronic inhalation toxicity study in dogs (MRID 43354901) was not used because the effect observed at the LOAEL of 80 ppm (equivalent to 20 mg/kg/day) was decreased body weight gain, dental fluorosis, and histopathological changes in the lungs.

Incidental Oral Exposure (All Durations). None. Sulfuryl fluoride is a gas at ordinary temperatures and pressures and because of its use pattern as a fumigant in enclosed structures and spaces only, it is not anticipated that toxicologically significant residues of sulfuryl fluoride or its degradates will remain in/on the contents of residential or other structures after the aeration period is completed. Consequently, there is no potential for incidental ingestion by toddlers. Therefore, HIARC did not select endpoints for this exposure scenario.

Dermal Exposure (All Durations). None. No hazard was identified and quantification of risk is not necessary.

Inhalation - Short-term (1-30 days). NOAEL = 30 mg/kg/day (100 ppm; 0.42 mg/L) from the 2-week inhalation toxicity study in rabbits. The NOAEL is based on malacia (necrosis) in the cerebrum in 1 male and 1 female, vacuolation in the cerebrum in all male and females, and moderate inflammation of nasal tissues in most animals and acute inflammation of the trachea in some animals at the LOAEL of 90 mg/kg/day (300 ppm; 1.25 mg/L). The results of this study provide the best information available pertaining to assessment of the potential short-term (1 - 30 days) risk via inhalation exposure.

The HIARC determined there is no need to quantify the inhalation risk resulting from a single residential or occupational inhalation exposure to sulfuryl fluoride. No treatment-related neurotoxic or other effects were observed in a specially designed acute neurotoxicity inhalation study (MRID 42772001) in which rats were exposed on two consecutive days for 6 hours/day to concentrations up to 300 ppm of sulfuryl fluoride (equivalent to 1.25 mg/L). Further, no appropriate endpoints resulting from a single inhalation exposure were identified in any of the available toxicity studies on sulfuryl fluoride. Therefore, no hazard attributable to a single inhalation exposure was identified and quantification of risk for single inhalation exposures was determined to be unnecessary. The HIARC noted that poisonings and fatalities have been reported in humans following inhalation exposure to sulfuryl fluoride. The severity of these effects has depended on the concentration of sulfuryl fluoride and the duration of exposure. Short-term inhalation exposure to high concentrations has caused respiratory irritation,

pulmonary edema, nausea, abdominal pain, central nervous system depression, and numbness in the extremities[3]. In addition, there have been two reports of deaths of persons entering houses treated with sulfuryl fluoride (see end of section 3.1.1). As previously stated, these acute poisonings in humans, however, occurred only after label directions were grossly violated and persons were subsequently exposed to extremely high concentrations of sulfuryl fluoride.

Inhalation - Intermediate-term (1-6 months). NOAEL = 8.5 mg/kg/day (30 ppm; 0.13 mg/L) from the 90-day subchronic inhalation toxicity study in rabbits. The NOAEL is based on vacuolation of white matter in the brain of females at the LOAEL of 28 mg/kg/day (100 ppm; 0.42 mg/L). The route and dosing regimen of this study is appropriate for the route and duration of exposure of concern.

Inhalation - Long-term (several months to lifetime). NOAEL = 8.5 mg/kg/day (30 ppm; 0.13 mg/L) from the 90-day subchronic inhalation toxicity study in rabbits. The NOAEL is based on vacuolation of white matter in the brain of females at the LOAEL of 28 mg/kg/day (100 ppm; 0.42 mg/L). This is the same study used to establish the chronic RfD.

Table 3.1.3. Summary of Dose and Endpoint Selection for use in Human Health Risk Assessments for Sulfuryl Fluoride.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary	None UF = N/A	Not applicable	No toxicological endpoint attributable to a single exposure was identified in the available toxicology studies on sulfuryl fluoride.
Chronic Dietary (All populations)	NOAEL= 8.5 mg/kg/day UF = 3000 **Chronic RfD** = **0.003** mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = **0.003** mg/kg/day	**90-Day Inhalation - Rabbit** LOAEL = 28 mg/kg/day based on vacuolation of white matter in the brain of females.
Incidental Oral (All durations)	None	Not applicable	Due to sulfuryl fluoride being a gas and pattern of use, no significant incidental oral exposure is anticipated.
Dermal (All durations)	None	Not applicable	Due to sulfuryl fluoride being a gas and pattern of use, no significant dermal exposure is anticipated. No hazard identified, therefore, no quantification is required.

[3]U.S. EPA, Structural fumigation using sulfuryl fluoride: DowElanco's Vikane ™ Gas Fumigant, Methyl bromide alternative case study, Part of EPA 430-R-021, 10 Case studies, volume 2, December 1996, p. 3. Available at http://www.epa.gov/spdpublc/mbr/sulfury2.html.

Table 3.1.3. Summary of Dose and Endpoint Selection for use in Human Health Risk Assessments for Sulfuryl Fluoride.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Inhalation (1 to 30 days)	Inhalation study NOAEL= **30** mg/kg/day (100 ppm; 0.42 mg/L)	**Residential** LOC for MOE = **1000** **Occupational** LOC for MOE = **100**	**2-Week Inhalation - Rabbit** LOAEL = 90 mg/kg/day (300 ppm; 1.25 mg/L) based on malacia (necrosis) and vacuolation in brain, inflammation of nasal tissues and trachea.
Intermediate-Term Inhalation (1 to 6 months)	Inhalation study NOAEL = **8.5** mg/kg/day (30 ppm; 0.13 mg/L)	**Residential** LOC for MOE = **1000** **Occupational** LOC for MOE = **100**	**90-Day Inhalation - Rabbit** LOAEL = 28 mg/kg/day (100 ppm; 0.42 mg/L) based on vacuolation of white matter in the brain of females.
Long-Term Inhalation (>6 months)	Inhalation study NOAEL = **8.5** mg/kg/day (30 ppm; 0.13 mg/L)	**Residential** LOC for MOE = **3000** **Occupational** LOC for MOE = **300**	**90-Day Inhalation - Rabbit** LOAEL = 28 mg/kg/day (100 ppm; 0.42 mg/L) based on vacuolation of white matter in the brain of females.
Cancer (oral, dermal, inhalation)	Classified as "Not likely to be carcinogenic to humans"		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

3.1.4 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). In the available toxicity studies on sulfuryl fluoride, there was no toxicologically significant evidence of endocrine disruptor effects. Follicular cell hypertrophy in the thyroid of mice in the 90-day toxicity study and in the 18-month carcinogenicity study, and in the thyroid of dogs in the 1-year chronic toxicity study was observed. At the same dose levels at which these effects were observed, however, considerably more serious effects (microscopic lesions in the brain in mice and dogs and increased mortality in dogs) were also observed.

Consequently, there is only minimal concern for potential endocrine disruptor effects at these dose levels in these species. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, sulfuryl fluoride may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

3.2 Fluoride Anion

3.2.1 Hazard Profile

A very large body of information regarding the toxicology of fluoride is available in the open literature. A complete review or re-presentation of that information is beyond the scope of this assessment. For a comprehensive review of the toxicology of fluoride, the reader is referred to publications by the World Health Organization (2002), the Department of Health and Human Services (2001), the National Research Council (1993), the Medical Research Council (2002), and NHS CRD (2000). In conducting the assessment for fluoride, HED has used the toxicological assessment and Maximum Contaminant Levels (MCLs) established by the Agency's Office of Water. A MCL is an enforceable level that is set as closely as feasible to the Maximum Contaminant Level Goal (MCLG) of a contaminant. The MCLG is the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, and which allows an adequate margin of safety. Maximum contaminant level goals are non-enforceable health goals. For fluoride, both the MCL and the MCLG have been set at 4.0 ppm in order to protect against crippling skeletal fluorosis. The MCLG was established in 1986 [FR 51 (63)] and is based on an LOAEL of 20 mg/day, a safety factor of 2.5, and an adult drinking water intake of 2 L/day. The use of a safety factor of 2.5 ensures public health criteria while still allowing sufficient concentration of fluoride in water to realize its beneficial effects in protecting against dental caries. The typical 100X factor used by the HED to account for inter- and intra-species variability have been removed due to the large amounts of human epidemiological data surrounding fluoride and skeletal fluorosis.

The Agency is aware of concern regarding dental fluorosis. The National Academy of Sciences has stated that "...dental fluorosis is accepted as a purely cosmetic defect with no general health ramifications. However, the most severe forms of dental fluorosis might be more than a cosmetic defect if enough fluorotic enamel is fractured and lost to cause pain, adversely affect food choices, compromise chewing efficiency and require complex dental treatment." (NRC, 1993). The Office of Water has established a secondary MCL (SMCL) for fluoride at 2.0 ppm to be protective against objectionable dental fluorosis. The SMCL is a non-enforceable level established to be protective against the cosmetic and aesthetic effects of a contaminant. Appendix I of this risk assessment addresses dental fluorosis.

3.2.2 FQPA Considerations

HED has not applied an additional FQPA safety factor to the fluoride assessment. Skeletal fluorosis is an effect that requires chronic (15-20 years) high exposures in order to be

manifested. As such, infants and children will not exhibit this effect and an additional factor to account for potential enhanced sensitivity is not necessary.

3.2.3 Dose-Response Assessment

Toxicological Dose for Use in Acute Risk Assessments. None. HED has not identified any toxicological endpoint attributable to a single exposure of fluoride that would be applicable to females (13-50 years old) or to the general population (including infants and children). The Agency is aware of cases of acute toxicity following exposure to extremely high concentrations of fluoride in drinking water. These incidents appear to be due to malfunctioning fluoridation equipment and fall far outside the realm of expected exposures. As such, HED has not tried to assess acute toxicity for fluoride.

Toxicological Dose for Use in Non-Acute Risk Assessments. For all short-term, intermediate-term, and chronic assessments, HED has converted the MCL to a mg/kg/day basis using standard water consumption estimates and body weight data from the NHANES III survey (Table 3.2.1; U.S. EPA, 2000). Body weight data from the NHANES survey were matched as closely as possible to the population subgroups addressed by the DEEM-FCID dietary exposure modelling software (See Section 4.2.3 and the dietary exposure analysis; M. Doherty, D283008, 1/13/04). Use of the NHANES data (Institute of Medicine, 1997), rather than the HED default body weights, avoids setting dose levels too high due to underestimated body weights. These doses in Table 3.2.1 were used for all risk assessment durations and pathways (oral, dermal, and inhalation) in a manner analogous to an RfD. That is, HED would have concerns about the level of estimated risk if the exposure estimates exceed 100% of the MCL.

Table 3.2.1. Conversion of the MCL to a mg/kg/day basis for use in the Fluoride Risk Assessment. The doses are used in a manner analogous to an RfD and are used for all exposure pathways.

Population Subgroup	Toxicological Effect	Water Consumption, L/day	Body Weight, kg	MCL, mg/L	MCL, mg/kg/day*
U.S. Population (total)	Skeletal Fluorosis	2	70	4	0.114
All infants (< 1 year)	Skeletal Fluorosis	1	7	4	0.571
Children 1-2 yrs	Skeletal Fluorosis	1	13	4	0.308
Children 3-5 yrs	Skeletal Fluorosis	1	22	4	0.182
Children 6-12 yrs	Skeletal Fluorosis	1	40	4	0.100
Youth 13-19 yrs	Skeletal Fluorosis	2	60	4	0.133
Adults 20+ yrs	Skeletal Fluorosis	2	70	4	0.114
Females 13-49 yrs	Skeletal Fluorosis	2	61	4	0.131

* MCL (mg/kg/day) = MCL (mg/L) × Water Consumption (L/day) ÷ Body Weight (kg)

Carcinogenicity. In its assessment of the health effects of fluoride, the National Research Council came to the following conclusion:

The subcommittee concludes that the available laboratory data are insufficient to demonstrate a carcinogenic effect of fluoride in animals. The subcommittee also concludes that the weight of the evidence from more than 50 epidemiological studies does not support the hypothesis of an association between fluoride exposure and increased cancer risk in humans. National Research Council, 1993.

The Agency for Toxic Substances and Disease Registry (ATSDR, 2001) and the World Health Organization (2002) have come to similar conclusions. Based on the findings of those bodies, HED believes that a cancer risk assessment for fluoride is not appropriate.

3.2.4 Endocrine Disruption

As noted in Section 3.1.4, HED is required to consider potential endocrine effects when conducting its risk assessments. The Agency is aware of potential endocrine effects of fluoride being noted in the open literature. From a preliminary review of this literature (Baetcke, et al., 2003), there does not appear to be a sufficient science foundation to permit confident conclusions regarding the ability of fluoride to produce endocrine effects. Thus, the available body of literature does not provide a compelling basis to depart from OPP's use of the current Agency MCL and SMCL in pesticide risk assessments at this time. This conclusion is supported by the recent York Review (2000) and the conclusions of the Medical Research Council (2002). The National Academy of Sciences is currently in the process of reviewing the toxicological data for fluoride. When their review is available, EPA will reexamine this conclusion.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Sulfuryl fluoride is being proposed as a methyl bromide replacement to control post-harvest insect and rodent pests in stored grain, dried fruit, and tree nut commodities, and in grain milling establishments. Sulfuryl fluoride is a fumigant and, in the form of ProFume™, is formulated as 99+% active ingredient. The fumigation rate for sulfuryl fluoride is the product of the fumigant concentration and exposure time. The maximum target rate is 1500 mg·hr/L for normal atmospheric fumigations and 200 mg·hr/L for vacuum fumigations. Double fumigations are recommended for insect infestations where eggs may be present, with the second fumigation timed to control newly hatched, immature stages. The proposed label specifies that all food commodities be aerated for a minimum of 24 hours prior to the foods entering commerce.

Sulfuryl fluoride is a highly volatile compound with a boiling point of -55°C and a vapor pressure of 0.02 Torr. At 20°C, sulfuryl fluoride has a vapor density of 4.3 g/L (heavier than air) and is both colorless and odorless. The log K_{OW} is estimated to be 0.41. Sulfuryl fluoride has a very low solubility in water (0.075 g/100 g). Solubilities in other solvents are 0.78 g/100 g in Wesson oil, 1.74 g/100 g in acetone, and 2.12 g/100 g in chloroform.

Table 4.1.1. Summary of Directions for the Post-harvest Use of Sulfuryl Fluoride from the Proposed Label.						
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Max. per Applic. Rate (mg·hr/L)	Max. No. Applic. per Season	Max. Cumulative Applic. Rate (mg·hr/L)	Aeration (hours)	Use Directions and Limitations
Post-harvest fumigation of sealed mills, warehouses, chambers, and other storage structures.	ProFume [62719-XXX]	1500 (ambient pressure) 200 (vacuum fumigation)	2	3000 (ambient pressure) 400 (vacuum fumigation)	24	Food commodities must be aerated for 24 hours prior to entering commerce.

The proposed label has sufficient information to allow the Agency to evaluate the residue trials in light of the proposed use patterns. Prior to registration, HED is requesting that the label be modified to specify maximum total rates of 1500 mg·hr/L for ambient-pressure fumigation and 200 mg·hr/L for reduced-pressure fumigation, that commodities be actively aerated (not less than one chamber volume per minute) for at least 24 hours prior to their entering commerce, and that corn oil be removed from any premises prior to fumigation.

Fluoride, as a chemical species, does not have a set of registered pesticidal uses. Pesticide chemicals that are known to increase fluoride residues in foods above background levels are cryolite and sulfuryl fluoride. This assessment addresses those pesticidal sources of fluoride as well as other, non-pesticidal sources.

4.2 Dietary Exposure/Risk Pathway

The residue chemistry databases for both sulfuryl fluoride and fluoride anion are considered marginally adequate to set tolerances based on the proposed use pattern. As a condition of registration, HED is recommending that further residue data are collected to ensure that the tolerances being recommended by HED are appropriate. Residue chemistry data needs, including label modifications, are listed in Section 8. Provided the label changes are made, HED is recommending a conditional registration with the sulfuryl fluoride and fluoride anion time-limited tolerances summarized in Table 8.1. Details regarding the dietary analyses and residue profiles used in this assessment are provided below.

4.2.1 Residue Profile

4.2.1.1 Sulfuryl Fluoride and Fluoride Residues from the use of Sulfuryl Fluoride

Tolerances are currently established under an experimental use permit for residues of sulfuryl fluoride in/on walnuts and raisins (40 CFR 180.575) and for residues of inorganic fluoride resulting from the use of either sulfuryl fluoride or cryolite (40 CFR 180.145). Sulfuryl fluoride is highly reactive and breaks down to form sulfate and fluoride anion. Parent sulfuryl fluoride and the fluoride anion are the residues of concern for both tolerance expression and risk assessment purposes.

Storage stability data were not submitted for sulfuryl fluoride. Samples were analyzed for sulfuryl fluoride residues as rapidly as possible following the post-fumigation aeration period. Because the storage interval was very short, storage stability data are not needed for sulfuryl fluoride, per se. Storage stability data for fluoride anion indicate that fluoride is stable in wheat grain, corn grain, corn meal, raisins, and walnuts for up to 140 days. Fluoride residues decline in wheat flour at a rate of 0.3% per day. It is unclear whether this reflects a true dissipation of fluoride from the samples or an increase in "bound" residues. Background residues of fluoride in the control samples for all commodities in the storage stability study decrease with time and the rate appears to be of the same order of magnitude as that observed for wheat flour. How this decline of fluoride anion in the control samples relates to residues in treated commodities or to the regulation of fluoride anion is unclear at this time.

The petitioner has proposed separate methods for the analysis of sulfuryl fluoride and fluoride anion. Residues of sulfuryl fluoride are extracted with water, allowed to volatilize, and then determined by a GC/ECD method that uses headspace analysis. Based on validation data, the limit of detection (LOD) is 0.004 ppm and the limit of quantitation (LOQ) is 0.008 ppm (0.02 ppm for corn grain and wheat germ). The method for the analysis of fluoride anion uses aqueous buffered extraction and a fluoride-selective electrode with the double-known-addition technique for quantifying residues. The petitioner initially reported that the LOD and LOQ for the fluoride method are 0.2 and 0.5 ppm, respectively. Following the independent laboratory validation, the LOQ for the fluoride method was increased to 2 ppm. The petitioner has not demonstrated that either method is capable of extracting incurred residues from cereal grain commodities. Both methods have been reviewed by the Agency's Analytical Chemistry Branch, which recommended that (1) the petitioner radiovalidate both methods and (2) OPP accept the analytical methods without a laboratory validation based on the submitted data (Method Review Memorandum, D. Wright, D282408, 8/14/03). The method has not been validated for sulfuryl fluoride in corn oil and, therefore, HED is recommending that corn oil be removed from facilities prior to fumigation.

The proposed tolerances are based on minimal data. Although the petitioner submitted a large quantity of data from studies investigating the effects of various fumigation parameters on sulfuryl fluoride and/or fluoride anion residue levels, very few studies were conducted according to the proposed label directions. In examining the residue data, HED has pooled data across

various fumigation parameters when those parameters appear to have little effect on residue levels.

Cereal Grains. Generally, residues of sulfuryl fluoride were below the limit of quantitation in the cereal grain commodities following fumigation at ~1500 mg·hr/L and an aeration period of 24 hours. Occasionally, quantifiable residues of sulfuryl fluoride were found in/on wheat grain (maximum residue = 0.095 ppm), rice grain (0.025 ppm), rice hulls (0.057 ppm), corn grain (0.026 ppm), and corn grits (0.014 ppm). All samples of fumigated corn oil had quantifiable residues of sulfuryl fluoride, with a maximum residue of 7.84 ppm. Apparent residues of sulfuryl fluoride were less than the LOQ in all control samples. For cereal grains, residues of fluoride anion were greater than the LOQ in all commodities except corn oil. Fluoride residues increase with multiple fumigations and appear to be recalcitrant, not declining following longer aeration intervals. Fluoride residues from mill fumigation studies were generally greater than those that resulted from laboratory fumigation studies of cereal grain commodities. Following a single fumigation at ~1500 mg·hr/L, maximum residues ranged from 5.3 ppm (corn grain) to 104 ppm (wheat germ). Measurable fluoride anion residues occurred in most control samples; the residue levels varied from one commodity to another and ranged from 0.03 to 2.08 ppm.

Processing studies conducted with whole grain corn and whole grain wheat showed that residues of fluoride concentrate in wheat shorts (1.26X), wheat bran (2.56X), wheat germ (4.82X), and corn "impurities" (5.49X). Impurities are described as being similar to aspirated grain fractions. Commercial processing practices were followed as closely as possible during the conduct of the processing studies. Sulfuryl fluoride analyses were not done for commodities processed from treated grain samples.

Dried Fruits and Tree Nuts. In dried fruits and tree nuts, residue levels of sulfuryl fluoride varied based on the commodity and the treatment regime. For most commodities, residues had dissipated to <2.1 ppb within 6 days of aeration following fumigation. Sulfuryl fluoride residues were more persistent in commodities with higher oil content (e.g, walnuts, pecans, almonds), typically requiring closer to 14 days for residues to dissipate to <2.1 ppb. At the same fumigation rate, residues of sulfuryl fluoride were greater following vacuum fumigation versus treatment at ambient pressure. In oily commodities, multiple fumigations resulted in higher residues of sulfuryl fluoride at a given aeration time. Pooled across all of the variables addressed in this study, sulfuryl fluoride residues ranged from <2.1 ppb to 6030 ppb (6.03 ppm). Residue levels of fluoride were measured only after residues of sulfuryl fluoride had dissipated to below detectable levels; therefore, the effect of aeration time on fluoride levels cannot be assessed from these data. Generally, fluoride residues appear to be more dependent on the number of fumigations than on the treatment rate, treatment pressure, or commodity. Overall, fluoride residue levels ranged from <1.4 ppm to 21.8 ppm.

The residue chemistry databases for both sulfuryl fluoride and fluoride anion are considered marginally adequate to set tolerances based on the proposed use pattern. As a condition of registration, HED is recommending that further residue data are collected to ensure that the tolerances being recommended by HED are appropriate. Residue chemistry data needs,

including label modifications, are listed in Section 8. Provided the label changes are made, HED is recommending a conditional registration with the sulfuryl fluoride and fluoride anion time-limited tolerances summarized in Table 8.1

Residues Used In Risk Assessment - Sulfuryl Fluoride. Average residue levels and percent crop treated estimates were incorporated into the dietary risk assessment for sulfuryl fluoride. These values are summarized in table 4.2.1.1, below. A 0.1X processing factor has been used for flour commodities to account for the practice of drawing down the grain in the mill prior to fumigation and then flushing any residual grain/flour out of the mill with fresh grain during startup and mill equilibration. This is essentially a dilution situation and the 0.1X factor is reasonable based on standard practices. For all other commodities, the DEEM-FCID default processing factor of 1 was used since the use of sulfuryl fluoride would result in the direct treatment of processed commodities. Where residue data for a specific food item were not available, translations were made based on HED SOP 2000.1 (Guidance for Translation of Field Trial Data from Representative Commodities in the Crop Group Regulation to Other Commodities in Each Crop Group/Subgroup, 9/12/2000). For foods not covered by SOP 2000.1, translations were made from similar foods or food types and assumed the highest residues when multiple similar commodities were available. Overall, these should be considered to be moderately refined estimates of residues.

Table 4.2.1.1. Average Residue Values of Sulfuryl Fluoride Resulting from the Requested Uses of Sulfuryl Fluoride, and Percent Crop Treated Estimates Used in the Chronic Dietary Exposure Assessment.

Food	Sulfuryl Fluoride, ppm	Proc. Factor	Est. Crop Treated, %	Remarks
Almond	0.03	1	20	—
Almond-babyfood	0.03	1	20	—
Almond, oil	0.03	1	20	—
Almond, oil-babyfood	0.03	1	20	—
Apple, dried	0.037	1	40	From Figs
Apple, dried-babyfood	0.037	1	40	From Figs
Apricot, dried	0.037	1	40	From Figs
Banana, dried	0.037	1	40	From Figs
Banana, dried-babyfood	0.037	1	40	From Figs
Barley, pearled barley	0.02	1	2	From Corn
Barley, pearled barley-babyfood	0.02	1	2	From Corn
Barley, flour	0.02	0.1	2	From Corn (0.1 is a drawdown factor)
Barley, flour-babyfood	0.02	0.1	2	From Corn (0.1 is a drawdown factor)
Barley, bran	0.02	1	2	From Corn
Brazil nut	2.4	1	20	From Pecan
Butternut	2.4	1	20	From Pecan
Cashew	2.4	1	20	From Pecan
Chestnut	2.4	1	20	From Pecan
Coconut, dried	0.037	1	40	From Figs
Corn, field, flour	0.02	0.1	2	0.1 is a drawdown factor
Corn, field, flour-babyfood	0.02	0.1	2	0.1 is a drawdown factor
Corn, field, meal	0.02	1	2	—
Corn, field, meal-babyfood	0.02	1	2	—
Corn, field, bran	0.02	1	2	—

Food	Sulfuryl Fluoride, ppm	Proc. Factor	Est. Crop Treated, %	Remarks
Corn, field, starch	0.02	1	2	—
Corn, field, starch-babyfood	0.02	1	2	—
Cranberry, dried	0.037	1	40	From Figs
Fig, dried	0.037	1	40	—
Filbert	2.4	1	20	From Pecan
Filbert, oil	2.4	1	20	From Pecan
Grape, raisin	0.001	1	40	—
Hickory nut	2.4	1	20	From Pecan
Lychee, dried	0.037	1	40	From Figs
Macadamia nut	2.4	1	20	From Pecan
Mango, dried	0.037	1	40	From Figs
Oat, bran	0.008	1	2	From Wheat
Oat, flour	0.008	0.1	2	From Wheat (0.1 is a drawdown factor)
Oat, flour-babyfood	0.008	0.1	2	From Wheat (0.1 is a drawdown factor)
Oat, groats/rolled oats	0.008	1	2	From Wheat
Oat, groats/rolled oats-babyfood	0.008	1	2	From Wheat
Papaya, dried	0.037	1	40	From Figs
Peach, dried	0.037	1	40	From Figs
Peach, dried-babyfood	0.037	1	40	From Figs
Pear, dried	0.037	1	40	From Figs
Pecan	2.4	1	20	—
Pineapple, dried	0.037	1	40	From Figs
Pistachio	0.3	1	20	—
Plantain, dried	0.037	1	40	From Figs
Plum, prune, dried	0.001	1	40	—
Plum, prune, dried-babyfood	0.001	1	40	—
Rice, white	0.008	1	2	—
Rice, white-babyfood	0.008	1	2	—
Rice, brown	0.021	1	2	—
Rice, brown-babyfood	0.021	1	2	—
Rice, flour	0.021	0.1	2	Translated from brown rice (0.1 drawdown factor)
Rice, flour-babyfood	0.021	0.1	2	Translated from brown rice (0.1 drawdown factor)
Rice, bran	0.008	1	2	—
Rice, bran-babyfood	0.008	1	2	—
Walnut	0.6	1	20	—
Wheat, grain	0.09	1	2	—
Wheat, grain-babyfood	0.09	1	2	—
Wheat, flour	0.008	0.1	2	0.1 is a drawdown factor
Wheat, flour-babyfood	0.008	0.1	2	0.1 is a drawdown factor
Wheat, germ	0.02	1	2	—
Wheat, bran	0.008	1	2	—

Residues Used in Risk Assessment - Fluoride Anion. This risk assessment used average fluoride residue values measured during residue trials conducted in fumigation chambers and grain processing mills, as summarized in the Summary of Analytical Chemistry and Residue Data for sulfuryl fluoride (M. Doherty, D283007, 1/13/04). These residues are presented in Table 4.2.1.2, which includes the percent market share estimates that were used in the assessment

(Memo from John Faulkner, BEAD to Dennis McNeilly, RD; D283699, 10/28/02). As with sulfuryl fluoride, a 0.1X drawdown factor has been used for flour commodities; however, since grains entering the processing facility may have been treated with sufluryl fluoride, the potentially elevated fluoride level in the grain was added to the average residue for treated flour multiplied by the drawdown factor. The contribution from potentially treated grain was estimated by multiplying the average residues in grain by the empirical processing factors of either 0.38 (wheat) or 0.73 (all other grains). Thus, the estimated residue in flour may be expressed as:

(Avg. Grain Residue × Processing Factor) + (Avg. Flour Residue × Drawdown Factor).

For all other commodities, the DEEM-FCID default processing factor of 1 was used since the use of sulfuryl fluoride could result in the direct treatment of processed commodities. Where residue data for a specific food item were not available, translations were made based on HED SOP/ 2000.1 (Guidance for Translation of Field Trial Data from Representative Commodities in the Crop Group Regulation to Other Commodities in Each Crop Group/Subgroup, 9/12/2000). For foods not covered by SOP 2000.1, translations were made from similar foods or food types and assumed the highest residues when multiple similar commodities were available. Overall, these should be considered to be moderately refined estimates of residues that likely overestimate dietary exposure to fluoride.

Table 4.2.1.2. Average Residue Values of Fluoride Anion Resulting from the Requested Uses of Sulfuryl Fluoride, and Percent Crop Treated Estimates Used in the Chronic Dietary Exposure Assessment.

Food	Fluoride Anion, ppm	Proc. Factor	Est. Crop Treated, %	Remarks
Almond	4.7	1	20	—
Almond-babyfood	4.7	1	20	—
Almond, oil	1.2	1	20	—
Almond, oil-babyfood	1.2	1	20	—
Apple, dried	1.2	1	40	—
Apple, dried-babyfood	1.2	1	40	—
Apricot, dried	1.2	1	40	—
Banana, dried	1.2	1	40	—
Banana, dried-babyfood	1.2	1	40	—
Barley, pearled barley	50	1	2	Xlated: grain x 5 (wheat/corn)
Barley, pearled barley-babyfood	50	1	2	Xlated: grain x 5 (wheat/corn)
Barley, flour	9.58	1	2	(Avg. grain residue*0.73 PF)+(Avg. flour*0.1 DF)
Barley, flour-babyfood	9.58	1	2	(Avg. grain residue*0.73 PF)+(Avg. flour*0.1 DF)
Barley, bran	50	1	2	Xlated: grain x 5 (wheat/corn)
Brazil nut	8.6	1	20	From Pecan
Butternut	8.6	1	20	From Pecan
Cashew	8.6	1	20	From Pecan
Chestnut	8.6	1	20	From Pecan
Coconut, dried	1.2	1	40	—
Corn, field, flour	4.11	1	2	(Avg. grain residue*0.73 PF)+(Avg.

Food	Fluoride Anion, ppm	Proc. Factor	Est. Crop Treated, %	Remarks
				flour*0.1 DF)
Corn, field, flour-babyfood	4.11	1	2	(Avg. grain residue*0.73 PF)+(Avg. flour*0.1 DF)
Corn, field, meal	24	1	2	—
Corn, field, meal-babyfood	24	1	2	—
Corn, field, bran	24	1	2	Translated from meal
Corn, field, starch	4.6	1	2	—
Corn, field, starch-babyfood	4.6	1	2	—
Cranberry, dried	1.2	1	40	—
Fig, dried	1.2	1	40	—
Filbert	8.6	1	20	From Pecan
Filbert, oil	1.2	1	20	—
Grape, raisin	1.2	1	40	—
Hickory nut	8.6	1	20	From Pecan
Lychee, dried	1.2	1	40	—
Macadamia nut	8.6	1	20	From Pecan
Mango, dried	1.2	1	40	—
Oat, bran	50	1	2	Xlated: grain x 5 (wheat/corn)
Oat, flour	12.14	1	2	(Avg. grain residue*0.73 PF)+(Avg. flour*0.1 DF)
Oat, flour-babyfood	12.14	1	2	(Avg. grain residue*0.73 PF)+(Avg. flour*0.1 DF)
Oat, groats/rolled oats	50	1	2	Xlated: grain x 5 (wheat/corn)
Oat, groats/rolled oats-babyfood	50	1	2	Xlated: grain x 5 (wheat/corn)
Papaya, dried	1.2	1	40	—
Peach, dried	1.2	1	40	—
Peach, dried-babyfood	1.2	1	40	—
Pear, dried	1.2	1	40	—
Pecan	8.6	1	20	—
Pineapple, dried	1.2	1	40	—
Pistachio	4.1	1	20	—
Plantain, dried	1.2	1	40	—
Plum, prune, dried	0.7	1	40	—
Plum, prune, dried-babyfood	0.7	1	40	—
Rice, white	5	1	2	—
Rice, white-babyfood	5	1	2	—
Rice, brown	5.3	1	2	—
Rice, brown-babyfood	5.3	1	2	—
Rice, flour	7.24	1	2	(Avg. grain residue*0.73 PF)+(Avg. flour*0.1 DF)
Rice, flour-babyfood	7.24	1	2	(Avg. grain residue*0.73 PF)+(Avg. flour*0.1 DF)
Rice, bran	25.9	1	2	—
Rice, bran-babyfood	25.9	1	2	—
Walnut	5.6	1	20	—
Wheat, grain	4	1	2	—
Wheat, grain-babyfood	4	1	2	—

Food	Fluoride Anion, ppm	Proc. Factor	Est. Crop Treated, %	Remarks
Wheat, flour	4.99	1	2	(Avg. grain residue*0.38 PF)+(Avg. flour*0.1 DF)
Wheat, flour-babyfood	4.99	1	2	(Avg. grain residue*0.38 PF)+(Avg. flour*0.1 DF)
Wheat, germ	58	1	2	—
Wheat, bran	35.95	1	2	—

4.2.1.2 Fluoride Residues from the use of Cryolite

In evaluating the exposure to fluoride from the agricultural uses of cryolite, residue trial data were matched as closely as possible to the current maximum use patterns for this active ingredient. Where there were discrepancies between the use pattern and the residue trial data, worst-case assumptions were made regarding residue levels. For foods without any empirical residue data, translations were made based on HED SOP 2000.1. Residue values and percent crop treated estimates are summarized in Table 4.2.1.3. Empirically derived processing factors were used for processed commodities of grapes, citrus, mint, and tomato. Default processing factors from DEEM Version 7.81 were used for all other commodities Overall, these should be considered to be moderately refined estimates of residues and may slightly overestimate exposure to fluoride from uses of cryolite. Percent crop treated estimates from the last dietary analysis for cryolite (D. Soderberg, D279010, 12/18/01) were incorporated into this assessment.

Table 4.2.1.3. Average Residue Values of Fluoride Anion Resulting from the Uses of Cryolite, and Percent Crop Treated Estimates Used in the Chronic Dietary Exposure Assessment.

Food	Fluoride Anion, ppm	Proc. Factor	Est. Crop Treated, %	Remarks
Apricot	4.5	1	1	From Peach
Apricot-babyfood	4.5	1	1	From Peach
Apricot, dried	4.5	6	1	From Peach
Apricot, juice	4.5	1	1	From Peach
Apricot, juice-babyfood	4.5	1	1	From Peach
Blackberry	0.25	1	100	From Raspberry
Blackberry, juice	0.25	1	100	From Raspberry
Blackberry, juice-babyfood	0.25	1	100	From Raspberry
Blueberry	0.11	1	100	MRID 44742401
Blueberry-babyfood	0.11	1	100	MRID 44742402
Boysenberry	0.25	1	100	From Raspberry
Broccoli	5	1	2	MRID 00158001
Broccoli-babyfood	5	1	2	MRID 00158001
Brussels sprouts	4	1	2	MRID 00158001
Cabbage	1.5	1	1	MRID 41380610
Cabbage, Chinese, bok choy	4	1	1	MRID 00158001
Cantaloupe	2.16	1	1	MRID 41380602
Casaba	2.16	1	1	From Cantaloupe
Cauliflower	3	1	2	MRID 00158001
Citrus citron	8	1	4	From Orange
Collards	4	1	2	MRID 41380601

Food	Fluoride Anion, ppm	Proc. Factor	Est. Crop Treated, %	Remarks
Cranberry	0.5	1	100	D231384
Cranberry-babyfood	0.5	1	100	D231384
Cranberry, dried	0.5	1	100	D231384
Cranberry, juice	0.5	1.1	100	D231384
Cranberry, juice-babyfood	0.5	1.1	100	D231384
Cucumber	2.5	1	1	MRID 43867501
Currant	0.11	1	100	From Blueberry
Currant, dried	0.11	1	100	From Blueberry
Dewberry	0.25	1	100	From Raspberry
Eggplant	1.5	1	1	From Tomato
Elderberry	0.11	1	100	From Blueberry
Gooseberry	0.11	1	100	From Blueberry
Grape	3.5	1	33	MRID 00158001
Grape, juice	3.5	0.83	33	MRID 00158001+470178022
Grape, juice-babyfood	3.5	0.83	33	MRID 00158001+470178022
Grape, leaves	3.5	1	33	MRID 00158001
Grape, raisin	3.5	1.35	33	MRID 00158001+470178022
Grape, wine and sherry	3.5	0.83	33	MRID 00158001
Grapefruit	9	1	4	MRID 41380604+42751710
Grapefruit, juice	9	0.026	4	MRID 41380604+42751710+41380607
Honeydew melon	2.16	1	1	From Cantaloupe
Huckleberry	0.11	1	100	From Blueberry
Kale	4	1	2	From Collards
Kiwifruit	4.5	1	14	MRID 40635601
Kohlrabi	5	1	2	From Broccoli
Kumquat	8	1	4	From Orange
Lemon	13.5	1	2	MRID 41380605
Lemon, juice	13.5	0.024	2	MRID 41380605+41380607
Lemon, juice-babyfood	13.5	0.024	2	MRID 41380605+41380607
Lemon, peel	13.5	0.28	2	MRID 41380605
Lettuce, head	2.5	1	1	MRID 00158001+41380611
Lettuce, leaf	15	1	1	MRID 00158001+41380611+40901303
Lime	13.5	1	4	From Lemon
Lime, juice	13.5	0.024	4	From Lemon
Lime, juice-babyfood	13.5	0.024	4	From Lemon
Loganberry	0.25	1	100	From Raspberry
Nectarine	4.5	1	1	From Peach
Orange	8	1	2	MRID 41380606
Orange, juice	8	0.022	2	MRID 41380606+41380607
Orange, juice-babyfood	8	0.022	2	MRID 41380606+41380607
Orange, peel	8	0.28	2	MRID 41380606
Peach	4.5	1	1	MRID 43077601
Peach-babyfood	4.5	1	1	MRID 43077601
Peach, dried	4.5	7	1	MRID 43077601
Peach, dried-babyfood	4.5	7	1	MRID 43077601
Peach, juice	4.5	1	1	MRID 43077601
Peach, juice-babyfood	4.5	1	1	MRID 43077601
Pepper, bell	3.5	1	1	MRID 42659301
Pepper, bell-babyfood	3.5	1	1	MRID 42659301

Food	Fluoride Anion, ppm	Proc. Factor	Est. Crop Treated, %	Remarks
Pepper, bell, dried	3.5	1	1	MRID 42659301
Pepper, bell, dried-babyfood	3.5	1	1	MRID 42659301
Pepper, nonbell	3.5	1	1	MRID 42659301
Pepper, nonbell-babyfood	3.5	1	1	MRID 42659301
Pepper, nonbell, dried	3.5	1	1	MRID 42659301
Peppermint	19.5	1	100	MRID 45113801
Peppermint, oil	19.5	0.026	100	D276350
Plum	0.5	1	1	MRID 43830201
Plum-babyfood	0.5	1	1	MRID 43830201
Plum, prune, fresh	2	1	1	MRID 43830201, 4X factor
Plum, prune, fresh-babyfood	2	1	1	MRID 43830201
Plum, prune, dried	2	5	1	MRID 43830201
Plum, prune, dried-babyfood	2	5	1	MRID 43830201
Plum, prune, juice	2	1.4	1	MRID 43830201
Plum, prune, juice-babyfood	2	1.4	1	MRID 43830201
Potato, chips	0.65	1	3	MRID 42067901
Potato, dry (granules/ flakes)	0.65	6.5	3	MRID 42067901
Potato, dry (granules/ flakes)-babyfood	0.65	6.5	3	MRID 42067901
Potato, flour	0.65	6.5	3	MRID 42067901
Potato, flour-babyfood	0.65	6.5	3	MRID 42067901
Potato, tuber, w/peel	0.65	1	3	MRID 42067901
Potato, tuber, w/peel-babyfood	0.65	1	3	MRID 42067901
Potato, tuber, w/o peel	0.65	1	3	MRID 42067901
Potato, tuber, w/o peel-babyfood	0.65	1	3	MRID 42067901
Pummelo	9	1	4	From Grapefruit
Pumpkin	2.5	1	1	MRID 00158001
Pumpkin, seed	2.5	1	1	MRID 00158001
Raspberry	0.25	1	100	MRID 45162301
Raspberry-babyfood	0.25	1	100	MRID 45162301
Raspberry, juice	0.25	1	100	MRID 45162301
Raspberry, juice-babyfood	0.25	1	100	MRID 45162301
Spearmint	19.5	1	100	MRID 45113801
Spearmint, oil	19.5	0.026	100	D276350
Squash, summer	2.5	1	1	MRID 41380603
Squash, summer-babyfood	2.5	1	1	MRID 41380603
Squash, winter	2.5	1	1	From Summer Squash
Squash, winter-babyfood	2.5	1	1	From Summer Squash
Strawberry	1	1	2	MRID 45009001
Strawberry-babyfood	1	1	2	MRID 45009001
Strawberry, juice	1	1	2	MRID 45009001
Strawberry, juice-babyfood	1	1	2	MRID 45009001
Tangerine	8	1	4	From Orange
Tangerine, juice	8	0.028	4	From Orange
Tomato	1.5	1	1	MRID 42656901+41380608
Tomato-babyfood	1.5	1	1	MRID 42656901+41380608
Tomato, paste	1.5	1.5	1	MRID 42656901+41380608+41380609
Tomato, paste-babyfood	1.5	1.5	1	MRID 42656901+41380608+41380609
Tomato, puree	1.5	1	1	MRID 42656901+41380608+41380609

Food	Fluoride Anion, ppm	Proc. Factor	Est. Crop Treated, %	Remarks
Tomato, puree-babyfood	1.5	1	1	MRID 42656901+41380608+41380609
Tomato, dried	1.5	14.3	1	MRID 42656901+41380608
Tomato, dried-babyfood	1.5	14.3	1	MRID 42656901+41380608
Tomato, juice	1.5	1.5	1	MRID 42656901+41380608+41380609
Watermelon	2.16	1	1	From Cantaloupe
Watermelon, juice	2.16	1	1	From Cantaloupe

4.2.1.3 Background Levels of Fluoride in Foods

Monitoring studies indicate fluoride is ubiquitous in the food supply (e.g., World Health Organization. 2002; Rao, G. S. 1984; Sherlock, J. C. 1984). The primary sources for residues used in this background food assessment were Taves, D. R. (1983) for plant-based foods, bovine and porcine commodities, and eggs; Fein, N. J. and Cerklewski F. L. (2001) for poultry; and residue trials for tree nuts and dried fruits (MRID 45510304). Average residue values were used when available. In cases where a range was listed, the maximum value in the range was used. When a specific food in the DEEM-FCID input listing was not addressed by one of the monitoring studies, residues were translated from similar commodities using HED SOP 2000.1. In the 1983 study by Taves, 93 food items from a hospital in an area with fluoridated water were analyzed for fluoride content. The use of the Taves data accounts for the increase in fluoride residues that may occur when foods are processed/prepared in fluoridated water. For a number of commodities, the highest fluoride residue value (from beans cooked in fluoridated water) was used. Due to the inclusion of fluoride residues for all of the food items in DEEM-FCID (543 entries), the residue values are not listed as a separate table within the body of this document. The residue estimates are provided in Attachment 4 of the dietary exposure assessment memorandum (M. Doherty, D283008, 1/13/04). Note that the residue estimates for dried fruits and tree nuts are at ½ the LOQ for the residue trial method and are most likely overestimates of fluoride, based on the residue levels in other commodities. Overall, these should be considered to be moderately to slightly refined estimates of fluoride residues that provide some overestimation of chronic exposure to fluoride from food.

4.2.1.4 Fluoride Residues in Water

Monitoring data based on 16 states from 1983 to 1998 that have been extrapolated to the U.S. (U.S. EPA, 2003) indicate that approximately 99% of the U.S. population is supplied with water containing, on average, less than 2 ppm fluoride anion (Figure 4.2.1). In the current risk assessment, HED has assumed a residue level of 2 ppm for tap water and 0.4 ppm (50^{th} percentile value) for water sources other than tap water. The optimal fluoridation level for water is approximately 1 ppm for prevention of dental caries. The use of 2 ppm fluoride in tap water and 0.4 ppm in other water sources likely results in an overestimation of exposure for the general population, especially those on public water systems (93% of the U.S. population based on 2002 Census figures). However, it may underestimate exposures to certain individuals in the U.S. who are supplied by well water that is naturally high in fluoride. In monitoring data (1991-2002) from

the National Water Quality Assessment (NAWQA) Program (http://water.usgs.gov/nawqa/), the concentration of fluoride in groundwater samples designated as being used for domestic purposes exceeded 2 ppm in at least one sample from 13 of 49 study units. Study units are major river basins and aquifers across the nation and typically encompass approximately 4000 square miles. Examination of data from each of those 13 study units indicates that there is a fair degree of spatial variability in fluoride levels (Table 4.2.1.4). Similar finding regarding spatial difference in fluoride concentration have been noted in local monitoring studies. For example, data from Lakewood Township, Minnesota show a fluoride concentration of 0.4 ppm in a well located at a similar depth and only a few hundred feet from a well with a fluoride concentration of 14.0 ppm (Hastreiter, et al., 1992). Similar variations in fluoride levels over small geographic areas were noted. Data are not available describing fluoride levels for a specific source over time, and it is unclear whether or not there is temporal, as well as spatial, variability in well water fluoride concentrations. If temporal variability is similar in magnitude to the spatial variability, then the 2-ppm estimate for fluoride in tap water is conservative for even those populations living in high-fluoride areas.

Table 4.2.1.4. Summary of Fluoride Residues in NAWQA Study Units with Maximum Residue Levels Greater than 2 ppm. Data are from samples marked for domestic use. Data are from 1991 - 2002

Study Unit ID	n	Minimum F, ppm	Maximum F, ppm	Median F, ppm	Average F, ppm
ALMN	94	0.100	2.200	0.186	0.227
CAZB	78	0.100	7.805	0.600	1.289
EIWA	69	0.066	2.300	0.300	0.462
HDSN	47	0.100	4.600	0.100	0.379
HPGW	135	0.147	7.036	1.222	1.590
KANA	58	0.100	2.523	0.100	0.244
NECB	58	0.088	6.162	0.197	0.614
RIOG	25	0.200	4.600	0.400	0.692
SANT	60	0.100	5.515	0.129	0.508
SCTX	52	0.100	3.900	0.258	0.925
SPLT	34	0.100	3.100	0.700	0.924
USNK	199	0.100	2.800	0.400	0.480
YELL	24	0.377	6.966	0.886	1.599

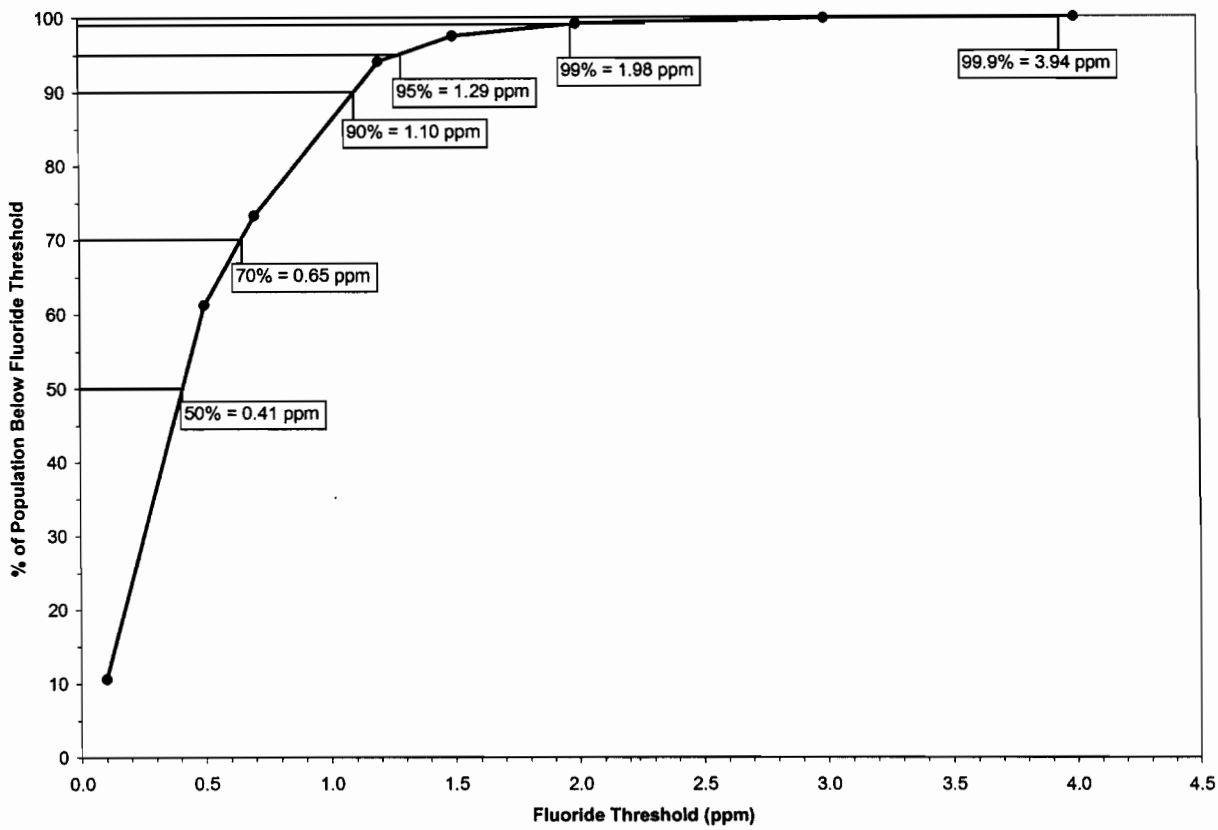

Figure 4.2.1. Cumulative Distribution of Fluoride Concentrations in Drinking Water for the U.S. Population (1986 - 1998). Derived from *Occurrence Estimation Methodology and Occurrence Findings Report for the Six-Year Review of Existing National Primary Drinking Water Regulations.* U.S. EPA. 2003. Office of Water EPA-815-R-03-006. Washington, DC.

4.2.1.5 Other Sources of Fluoride

This risk assessment includes quantitative estimates of fluoride exposure from residues in foods from the use of sulfuryl fluoride and/or cryolite, background levels in foods, and consumption of fluoride-containing water. Also addressed quantitatively are exposure from the use of fluoridated toothpaste and inhalation of fluoride from the atmosphere. These sources are addressed in Section 4.4. Other known potential sources of fluoride exposure were not addressed quantitatively either due to lack of data regarding residues and/or data regarding the demographics of exposure. Sections 4.4 and 5 provide more information.

4.2.2 Acute Dietary

No toxicological endpoint attributable to a single exposure was identified in the available toxicology studies on sulfuryl fluoride or fluoride anion. Therefore, acute dietary assessments were not conducted.

4.2.3 Chronic Dietary

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 1.30), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. For the water assessment, DEEM Version 7.87 was used. The 7.87 version of DEEM uses proprietary recipes that better account for "commercial" water (water in processed foods and beverages) than the Food Commodity Intake Database (FCID) recipes. This previous release of DEEM was used to ensure that the water assessment does not underestimate exposure from water. The following information summarizes the dietary assessments for sulfuryl fluoride and fluoride anion (M. Doherty, D283008, 1/13/04).

Sulfuryl Fluoride. The chronic analysis for sulfuryl fluoride used average residue values from residue trials reflecting the maximum proposed use, percent market share estimates, and a dilution factor for flour commodities to reflect the pre-fumigation draw-down practice in grain processing mills. Based on these assumptions, the refined chronic dietary risk estimates for all population subgroups are less than 1% of the chronic population-adjusted dose (cPAD) of 0.003 mg/kg/day.

Table 4.2.3.1. Results of the Refined Chronic Dietary Exposure Assessment for Sulfuryl Fluoride.

Population Subgroup	Chronic PAD, mg/kg/day	Estimated Exposure, mg/kg/day	Risk, % of cPAD
U.S. Population (total)	0.003	0.000003	<1
All infants (< 1 year)	0.003	0.000002	<1
Children 1-2 yrs	0.003	0.000004	<1
Children 3-5 yrs	0.003	0.000004	<1
Children 6-12 yrs	0.003	0.000003	<1
Youth 13-19 yrs	0.003	0.000001	<1
Adults 20-49 yrs	0.003	0.000003	<1
Adults 50+ yrs	0.003	0.000004	<1
Females 13-49 yrs	0.003	0.000003	<1

The chronic analyses for fluoride are presented in Table 4.2.3.2. In addition to showing the combined dietary fluoride exposure estimate, Table 4.2.3.2 illustrates the relative contributions of the various sources to dietary fluoride exposure. Based on the inputs for these analyses, fluoride from water is the primary contributor to dietary fluoride exposure, with exposure to background levels of fluoride in food being approximately 2 - 16 times less than that from water. The fluoride exposures resulting from the uses of cryolite and sulfuryl fluoride each are 4-9 times less than that coming from food and 13-360 times less than that from water. Overall, the combined dietary fluoride risk estimates are below HED's level of concern for all population subgroups.

Table 4.2.3.2. Total Chronic Exposure and Risk Estimates for Fluoride from Dietary Sources.							
Population Subgroup	MCL, mg/kg/day	Dietary Fluoride Anion Exposure Estimates, mg/kg/day					Risk, % of MCL
		Sulfuryl Fluoride	Cryolite	Food	Water	Total Dietary	
U.S. Population (total)	0.114	0.0004	0.0007	0.0068	0.0269	0.0348	31
All infants (< 1 year)	0.571	0.0005	0.0010	0.0093	0.1424	0.1532	27
Children 1-2 yrs	0.308	0.0013	0.0033	0.0175	0.0407	0.0627	20
Children 3-5 yrs	0.182	0.0012	0.0021	0.0149	0.0338	0.0521	29
Children 6-12 yrs	0.100	0.0007	0.0009	0.0094	0.0227	0.0337	34
Youth 13-19 yrs	0.133	0.0004	0.0003	0.0062	0.0176	0.0246	18
Adults 20-49 yrs	0.114	0.0003	0.0004	0.0057	0.0252	0.0317	28
Adults 50+ yrs	0.114	0.0003	0.0005	0.0050	0.0256	0.0315	28
Females 13-49 yrs	0.131	0.0003	0.0005	0.0054	0.0238	0.0300	23

4.2.4 Cancer Dietary

As noted in Section 3, sulfuryl fluoride has been classified as "not likely to be carcinogenic to humans" and there is no evidence showing an increased risk of cancer following exposure to fluoride. HED has not conducted an assessment of cancer risk from dietary exposures for either sulfuryl fluoride or fluoride anion.

4.3 Water Exposure/Risk Pathway

Sulfuryl Fluoride. For the Agency's EUP assessment of sulfuryl fluoride, the Environmental Fate and Effects Division (EFED) determined that neither residues of sulfuryl fluoride nor of inorganic fluoride are expected to reach surface or groundwater due to the post-harvest fumigation of walnuts and raisins. This finding was made based on the use pattern and physicochemical characteristics of sulfuryl fluoride (e-mail from Sid Abel, EFED to Donna Davis, HED dated 4/3/01; Attachment 1). The use patterns reviewed by EFED are identical to those being proposed in the current petition; therefore, HED has applied EFED previous conclusions to this petition.

Fluoride. Fluoride may occur in drinking water due to naturally occurring residues or due to intentional fluoridation of the water supply. The exposure to fluoride residues in drinking water has been addressed in the dietary analysis for fluoride (Section 4.2.1.4).

4.4 Residential Exposure/Risk Pathway

Sulfuryl fluoride is registered for the fumigation of domestic structures. Exposure to sulfuryl fluoride could occur when residents re-occupy a fumigated home. HED has determined that there is sufficient evidence to show that risks to residents from exposure to sulfuryl fluoride resulting from home fumigation are negligible (B. Daiss, 5/15/2001, DP Barcode 274960).

Fluoride exposure may occur from non-dietary sources, including incidental ingestion of toothpaste and inhalation of airborne fluoride. Other non-dietary exposures may occur; however, HED has included only these two in its quantitative assessment due to lack of data regarding residue levels and/or exposure demographics. In order to take into account these other sources of non-dietary exposure, HED has used conservative assumptions when estimating exposure from toothpaste and air in an effort to ensure that overall exposures are not underestimated. Exposure estimates for fluoride from toothpaste and air for all of the population subgroups addressed in DEEM-FCID are presented in Table 4.4.1, below.

Toothpaste. A number of studies are available in the open literature that address the exposure to fluoride from the incidental ingestion of toothpaste (e.g., Levy et al., 1995; Naccache et al., 1992, 1990; Simard et al., 1989; Bruun and Thylstrup, 1988; Barnhart et al., 1974). Due to the different techniques used to assess toothpaste ingestion and the different foci in those studies, the estimates of fluoride exposure from toothpaste are quite varied. However, a few conclusions can be made:

- Incidental toothpaste ingestion decreases with age as children gain better control of the swallowing reflex
- Ingestion of toothpaste can be a significant contributor to overall fluoride exposure.

Despite the variability in the estimates of ingested toothpaste, maximum exposures to fluoride observed in those studies appear to converge to approximately 0.3 mg/day (assuming 2 brushings per day). In assessing fluoride from toothpaste, HED has used this maximum estimate of 0.3 mg/day and normalized to body weight using the closest-matching NHANES data for the various population subgroups. The exposure estimates range from 0.004 to 0.04 mg/kg/day (Table 4.4.1) and should be considered conservative in nature; especially for older population subgroups since exposure estimates were not adjusted for the age-related decrease in toothpaste ingestion. These exposure estimates result in risk estimates that are below HED's level of concern. HED notes that the American Academy of Pediatric Dentistry recommends that children less than 2 years of age not use fluoridated toothpaste[4].

Air. Estimates of fluoride residues in air are presented in a number of review articles (e.g., World Health Organization, 2002; Burt, 1992). In the U.S., airborne fluoride concentrations are highest around smelters and industrialized area. In such areas, the fluoride concentration does not typically exceed 3 $\mu g/m^3$. HED has used standard respiration rates derived from OPP/HED Science Advisory Council for Exposure Policy No. 12 (2/22/2001; See Table 4.4.1) and NHANES body weights to convert 3 $\mu g/m^3$ to a mg/kg/day basis. Exposure estimates range from 0.0006 to 0.002 mg/kg/day. As with toothpaste, the risk estimates derived from these exposure estimates are below HED's level of concern.

[4] http://www.aapd.org/pediatricinformation/faq.asp

Table 4.4.1. Estimated Fluoride Exposure from Non-Dietary Sources.				
Population Subgroup	Body Weight, kg	Standard Respiration, m^3/day	Estimated Exposure, mg/kg/day	
			Toothpaste	Air
U.S. Population (total)	70	13.3	0.0043	0.0006
All infants (< 1 year)	7	4.5	0.0429	0.0019
Children 1-2 yrs	13	8.7	0.0231	0.0020
Children 3-5 yrs	22	8.7	0.0136	0.0012
Children 6-12 yrs	40	8.7	0.0075	0.0007
Youth 13-19 yrs	60	13.3	0.0050	0.0007
Adults 20-49 yrs	70	13.3	0.0043	0.0006
Adults 50+ yrs	70	13.3	0.0043	0.0006
Females 13-49 yrs	61	11.3	0.0049	0.0006

4.4.1 Other

HED has not conducted a quantitative assessment for persons living near fumigation activities (i.e., bystanders). Due to the rapid dissipation of sulfuryl fluoride, the infrequency of fumigations of grain processing facilities, and the general location of such facilities away from residential areas, HED is not concerned with potential bystander exposures associated with fumigation of grain processing facilities. For tree nut and dried fruit fumigations of sulfuryl fluoride, there is more of a potential for more regular bystander exposure to sulfuryl fluoride. As sulfuryl fluoride is a candidate to replace methyl bromide for these uses, and facilities using methyl bromide have buffer zones to assure bystander safety, HED will assume that such precautions are adequate for sulfuryl fluoride. As a condition of registration and in conjunction with the monitoring of fumigation workers (see Section 7), HED is requesting air monitoring data from areas surrounding tree nut and dried fruit fumigation facilities.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Sulfuryl Fluoride. In estimating aggregate risks from exposure to sulfuryl fluoride, HED has examined potential dietary and non-dietary exposure pathways. The only potential non-dietary exposure pathway is from fumigation of domestic structures and, as noted in Section 4.4, that exposure is negligible. Therefore, HED has not included non-dietary exposure in a quantitative aggregate exposure assessment. Due to the use pattern and toxicology of sulfuryl fluoride, HED has determined that a chronic aggregate assessment is appropriate and has not calculated acute, short-term, or intermediate-term aggregate risks. As discussed in Section 4.3, residues of sulfuryl fluoride will not occur in drinking water. Therefore, drinking water does not contribute to aggregate exposure, leaving residues in or on food as the only quantifiable exposure pathway for estimating aggregate risks. Estimated chronic dietary risks, and therefore chronic aggregate risks, are less than 1% of the cPAD for the U.S. population and all population subgroups (Table 4.2.3). These risk estimates are well below HED's level of concern.

Fluoride. In estimating aggregate risks for skeletal fluorosis, HED has examined potential dietary and non-dietary exposure pathways. Based on the toxicology of fluoride and the

behaviors associated with fluoride exposure (e.g., brushing teeth), HED has examined only chronic aggregate exposure scenarios. As discussed in Section 4.2.2.3, moderately conservative estimates of dietary exposure were quantified based on fluoride residues coming from the pesticidal uses of sulfuryl fluoride and cryolite, from background residue levels in food, and the fluoride content of drinking water. Non-dietary sources for which sufficient information was available to quantitate exposure were toothpaste and air. As noted in Section 4.4, the exposure estimates from these sources are considered to be conservative. Aggregate exposures are summarized in Table 5.1 for the repesentative population subgroups addressed in the chronic exposure module of the DEEM-FCID software (the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old) . The aggregate risks for those populations are also presented in Table 5.1 as a percentage of the MCL. The aggregate risk estimates for the representative subgroups in DEEM-FCID range from 23% (youth 13-19 years of age) to 42% (children 6-12 years of age) of the MCL. The aggregate risk estimates for the U.S. population and all subgroups, including those of infants and children, are below HED's level of concern. HED notes that based on the assumptions in these assessments, sulfuryl fluoride is an insignificant source of fluoride relative to that coming from water, toothpaste, and background residues in foods. Risk estimates associated with dental fluorosis are presented in Appendix I.

Table 5.1. Aggregate Exposure and Risk Estimates for Skeletal Fluorosis.

Population Subgroup	MCL, mg/kg/day	Estimated Fluoride Exposure by Source, mg/kg/day							Risk, % of MCL
		Sulfuryl Fluoride	Cryolite	Back-ground Food	Water	Tooth-paste	Air	Total	
U.S. Population (total)	0.114	0.0004	0.0007	0.0068	0.0269	0.0043	0.0006	0.0397	35
All infants (< 1 year)	0.571	0.0005	0.0010	0.0093	0.1424	0.0429	0.0019	0.1980	35
Children 1-2 yrs	0.308	0.0013	0.0033	0.0175	0.0407	0.0231	0.0020	0.0878	29
Children 3-5 yrs	0.182	0.0012	0.0021	0.0149	0.0338	0.0136	0.0012	0.0669	37
Children 6-12 yrs	0.100	0.0007	0.0009	0.0094	0.0227	0.0075	0.0007	0.0419	42
Youth 13-19 yrs	0.133	0.0004	0.0003	0.0062	0.0176	0.0050	0.0007	0.0303	23
Adults 20-49 yrs	0.114	0.0003	0.0004	0.0057	0.0252	0.0043	0.0006	0.0366	32
Adults 50+ yrs	0.114	0.0003	0.0005	0.0050	0.0256	0.0043	0.0006	0.0364	32
Females 13-49 yrs	0.131	0.0003	0.0005	0.0054	0.0238	0.0049	0.0006	0.0355	27

Other Sources of Fluoride Exposure. HED is aware that exposure to fluoride may come from sources other than those quantified above. Although those sources have not been incorporated directly in the aggregate risk assessment, HED believes that the assessment is sufficiently conservative to ensure that it does not underestimate actual fluoride exposures experienced by members of the U.S. population.

In response to the Experimental Use Permit for sulfuryl fluoride, the Agency received comments regarding, among other things, sources of fluoride that were not considered in the EUP assessment. Most of those sources have been addressed quantitatively above; however, the

use of fluoride supplements and the potential for increased exposure following food preparation in fluoropolymer-treated cookware were specific issues that were not addressed numerically.

Fluoride Supplements. Fluoride supplements are prescribed only by a health care professional. The community of health care professionals is aware of the potential for fluorosis and the use of supplements is only advocated when aggregate exposure is insufficient to provide protection against dental caries. Because the amount of fluoride prescribed is made in consideration of other fluoride sources, the use of fluoride supplements should not result in overexposure to fluoride.

Treated Cookware. The non-stick coating of fluoropolymer-treated cookware represents a potential source of fluoride exposure. A 1975 study (Full and Parkins) reported an increase in the fluoride concentration of water boiled in a non-stick coated pan compared to stainless steel or Pyrex glass. Due to their experimental design and the manner in which final fluoride concentrations are expressed, it is not possible to discern whether or not the increased fluoride concentration was due to leaching of fluoride from the cookware surface or differential evaporation noted for the treated cookware versus other materials. The EPA [Office of Pollution Prevention and Toxics (OPPT)], in conjunction with other governmental agencies [FDA and CPSC], has been working with the manufacturers of these coatings to test these commercial articles under conditions of regular and misuse conditions to determine any decomposition products and their amounts. HED will coordinate with OPPT and will review the results of the cookware testing when the data become available.

6.0 CUMULATIVE RISK

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this risk assessment for sulfuryl fluoride because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of sulfuryl fluoride. For purposes of this petition, EPA has assumed that sulfuryl fluoride does not have a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA□s request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in

order to evaluate issues related to whether sulfuryl fluoride shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for sulfuryl fluoride need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with sulfuryl fluoride, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

HED has recently finalized its guidance for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance will be available from the OPP Website (http://www.epa.gov/pesticides). In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity* (64 FR 5795-5796, February 5, 1999).

7.0 OCCUPATIONAL EXPOSURE

ProFume will be dispensed as a pressurized gas from a steel cylinder through a hose into the interior of an enclosed, sealed structure. People must be evacuated from the structure before it is treated. After treatment, the structure remains closed for a period of time after which the applicator reenters and begins to aerate the area. The proposed label prohibits people not wearing a NIOSH-approved self contained breathing apparatus (SCBA) from reentering the treated structure until air levels of sulfuryl fluoride have declined to 1 part per million (ppm) or less. Because sulfuryl fluoride is a Restricted Use Pesticide, it may only be applied by or under the direct supervision of a trained, certified applicator.

No data regarding the number of exposure days per year for occupational workers were provided. Use data included in California EPA's assessment of workers fumigating walnuts and raisins with methyl bromide indicate worker exposures may occur for short to chronic/long-term periods. HED believes that chronic exposure may also occur for sulfuryl fluoride, and requests confirmatory use data from the petitioner.

Dermal Exposure. Because of its use pattern, the likelihood of dermal exposure to toxicologically significant amounts of sulfuryl fluoride is very low. Therefore, no dermal endpoint was selected and HED has not estimated occupational risks associated with dermal exposures.

Inhalation Exposure. As noted in Section 3.1.3, the NOAELs for use in short-, intermediate-, and long-term inhalation assessments are as follows:

Short-term exposures (1 to7 days) = 100 ppm (30 mg/kg/day)
Intermediate-term (7 days to several months) = 30 ppm (8.5 mg/kg/day)
Long-term exposures (several months to lifetime) = 30 ppm (8.5 mg/kg/day).

A human activity factor of 2.0, representing light activity, was assumed for all durations when assessing occupational exposures. For short- and intermediate-term exposures the HIARC recommended the target margin of exposure (MOE) for workers be ≥100 (based on the conventional uncertainty factor of 100X). For long-term inhalation exposure occupational risk assessments, the target MOE is ≥300 [based on extra factor of 3X applied to the conventional uncertainty factor of 100X to account for using a subchronic (90-day) study, rather than a chronic study] for this risk assessment.

The American Conference of Governmental Industrial Hygienists (ACGIH) has a Threshold Limit Value (TLV) of 5 ppm as an 8-hour time-weighted average for sulfuryl fluoride, and a 15-minute short-term exposure limit (STEL) of 10 ppm.

No worker exposure data were submitted to the Agency regarding the fumigation of food commodities. HED previously reviewed worker exposure data from the fumigation of numerous tarped structures with sulfuryl fluoride. The geometric means of full-shift exposures (8.6 hours) for fumigator and tent-workers in the study were reported to be 0.08 ppm and 0.17 ppm, respectively (fumigator value includes 1,000-fold protection factor for SCBA). Using the latest endpoints and a human activity factor of 2.0, the short-term inhalation Vikane MOEs for the fumigator and tent-workers are 440 and 210, respectively. The intermediate- and long-term inhalation Vikane MOEs are 130 for the fumigator and 60 for tent workers. It was also reported that average exposures during many tasks while not wearing SCBA were approximately 1 to 2 ppm (geometric means) and that there may have been some high-end exposures above the ACGIH 10 ppm STEL. The above exposure estimates and subsequent MOEs are based on the 5-ppm reentry concentration for Vikane. The activities and exposures that may occur for workers involved in post-fumigation activities with ProFume are expected to be similar to those experienced by the Vikane tent workers. The Agency is recommending that for ProFume, the reentry concentration be set at 1 ppm. Assuming a 5-fold reduction in residues based on the 1-ppm recommended reentry concentration versus the 5-ppm level used during collection of the exposure data, the MOEs associated with ProFume show that risk estimates are at or below HED's level of concern (Table 7.1). These MOEs assume a constant sulfuryl fluoride concentration of 1 ppm. Since sulfuryl fluoride will continue to dissipate following the 1-ppm reentry threshold, the MOEs likely overestimate risks.

Table 7.1. Occupational Exposure MOEs for ProFume. MOEs assume one fifth the geometric mean exposure concentrations of 0.08 ppm (fumigators) and 0.17 ppm (tent workers) determined from structural fumigation studies with Vikane, and an Activity Factor of 2. The 5-fold reduction factor is due to differences in reentry concentrations (5 ppm for Vikane vs. 1 ppm for ProFume). MOEs are rounded down to 2 significant figures.

Work Activity	Short-Term (NOAEL = 100 ppm)		Intermediate-Term (NOAEL = 30 ppm)		Long-Term (NOAEL = 30 ppm)	
	Target MOE	Estimated MOE	Target MOE	Estimated MOE	Target MOE	Estimated MOE
Fumigator	100	2100	100	650	300	650
Tent Worker	100	1000	100	300	300	300

MOE = [NOAEL × Animal Exposure Duration (6 hrs/day) × Animal Activity Factor (1)] ÷ [Human Exposure Concentration × Human Exposure Duration (8.6 hrs/day) × Human Activity Factor (2)]

The current and proposed labels for sulfuryl fluoride require that only an approved detection device of sufficient sensitivity, such as the INTERSCAN or MIRAN can be used to confirm a concentration of 1 ppm or less. These devices give real-time results and reportedly have a limit of detection (LOD) of 1 ppm when used in the field. Personal breathing zone sampling is performed using charcoal sorbent tubes that reportedly have a LOD of 0.07 ppm for a four-hour sample and 1.1 ppm for a 15-minute sample.

The registrant should be required to conduct a comprehensive air monitoring study as a condition of registration. The reentry concentration can be reevaluated upon analysis of the new study data.

8.0 DATA NEEDS AND LABEL REQUIREMENTS

Toxicology

Based on the available evidence, HIARC recommends that an inhalation developmental neurotoxicity (DNT) study in rats (Guideline No. 870.6300) be conducted in order to more clearly and fully characterize the potential for neurotoxic effects in young animals.

Residue Chemistry Deficiencies

- The number of cereal grain magnitude of the residue studies conducted at the maximum proposed use rate is marginally adequate. Residue data for both sulfuryl fluoride and fluoride anion should be submitted. The data should be from samples in at least three different grain mills that were treated according to the proposed maximum use. The matrices to be analyzed should include raw and processed commodities of wheat, rice, sorghum, and corn. If the petitioner would like HED-recommended label restriction regarding corn oil (see below) to be removed, then data should be collected for corn oil.
- The number of dried nut and tree fruit magnitude of the residue studies conducted at the maximum proposed use rate is marginally adequate. Residue data for both sulfuryl fluoride and fluoride anion should be submitted for representative

commodities for these two groups. Samples should be treated according to the proposed maximum use.

- Both HED and the Analytical Chemistry Branch are concerned about the ability of the analytical methods to extract incurred residues. Data showing the ability of the sulfuryl fluoride and fluoride anion methods to extract and accurately quantify incurred residues in raw and processed cereal grain matrices should be submitted. Furthermore, HED is requesting that the sulfuryl fluoride method be validated for corn oil.
- The sulfuryl fluoride method has not been shown to be specific to sulfuryl fluoride. An interference study for sulfuryl fluoride should be submitted.
- Cereal grain commodities, including aspirated grain fractions, are significant livestock feed items. Feeding studies were not submitted to determine the extent of secondary residues that may occur in livestock commodities. HED is requesting data showing the transfer of fluoride from feedstuffs into livestock commodities. A feeding study is not being requested for sulfuryl fluoride.
- A revised Section F (Proposed Tolerances) is required. HED notes that the Office of Water, via the National Academy of Sciences, is reevaluating the available information regarding fluoride. Therefore, HED is recommending that these tolerances be time-limited.

HED notes that data are sufficient to set sulfuryl fluoride and fluoride anion tolerances provided that the following modifications are made to the label:

- The total fumigation rate at ambient pressure should not exceed 1500 mg·hr/L and under reduced pressure should not exceed 200 mg·hr/L,
- Active aeration of at least 24 hours at not less than 1 chamber volume/min shall occur for all commodities prior to their entering commerce,
- Corn oil shall be removed from the premises prior to fumigation.

Occupational and Residential Exposoure

As a condition of registration, data describing actual sulfuryl fluoride exposure to workers involved in fumigation and post-fumigation activities should be provided for the various use sites under consideration. Additionally, data depicting residues of sulfuryl fluoride in air from areas surrounding fumigation facilities for tree nuts and dried fruit should be provided to ensure adequate protection of bystanders, including persons living nearby to fumigation facilities.

Table 8.1. Tolerance Summary for Sulfuryl Fluoride

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Sulfuryl Fluoride			
Barley, bran	None	0.05	Translated from wheat, flour
Barley, flour	None	0.05	Translated from wheat, flour
Barley, grain	0.01	0.10	Translated from wheat, grain

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Barley, pearled	None	0.05	Translated from wheat, flour
Corn, aspirated grain fractions	None	0.05	Translated from wheat, flour
Corn, field, flour	0.01	0.01	–
Corn, field, grain	0.04	0.05	–
Corn, field, grits	0.01	0.02	–
Corn, field, meal	0.01	0.01	–
Corn, field, refined oil	9	None	Recommend use restriction on corn, oil.
Corn, pop, grain	0.04	0.05	–
Millet, grain	0.05	0.10	Translated from wheat, grain
Oat, flour	0.08	0.05	Translated from wheat, flour
Oat, grain	0.01	0.10	Translated from wheat, grain
Oat, rolled	0.08	0.10	Translated from wheat, grain
Rice, bran	0.01	0.01	–
Rice, brown	0.01	None	Covered by rice, grain
Rice, grain	0.04	0.05	–
Rice, hulls	0.08	0.10	–
Rice, polished	0.01	0.01	–
Rice, wild, grain	0.05	0.05	–
Sorghum, grain	0.05	0.10	Translated from wheat, grain
Triticale, grain	0.05	0.10	Translated from wheat, grain
Wheat, bran	0.01	0.05	Translated from wheat, flour
Wheat, flour	0.03	0.05	–
Wheat, germ	0.01	0.02	–
Wheat, grain	0.05	0.10	–
Wheat, milled by-products	0.01	0.05	Translated from wheat, flour
Wheat, shorts	0.01	0.05	Translated from wheat, flour
Nut, tree, group 14	6	3.0	–
Fruit, dried	—	0.05	A dried fruit group tolerance was not proposed. Tolerances for "fruit, dried" should be proposed and the individual listings omitted.
Dates	0.03	See Fruit, dried	–
Figs	0.05	See Fruit, dried	–
Plums, dried	0.01	See Fruit, dried	–
Raisins	0.01	See Fruit, dried	–

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
All other dried fruits	0.05	See Fruit, dried	–
Fluoride			
Barley, bran	98	45.0	–
Barley, flour	98	45.0	–
Barley, grain	10	15.0	–
Barley, pearled	98	45.0	–
Corn, aspirated grain fractions	98	55.0	–
Corn, field, flour	26	35.0	Translated from 24 ppm at 1012 mg·hr/L
Corn, field, grain	7	10.0	–
Corn, field, grits	10	10.0	–
Corn, field, meal	28	30.0	Translated from 21 ppm at 1012 mg·hr/L
Corn, field, refined oil	3	None	Recommend use restriction on corn, oil.
Corn, pop, grain	7	10.0	–
Millet, grain	24	40.0	–
Oat, flour	98	75.0	–
Oat, grain	17	25.0	–
Oat, rolled	98	75.0	–
Rice, bran	31	30.0	Translated from 11.8 ppm at 1012 mg·hr/L
Rice, brown	14	20.0	–
Rice, grain	10	12.0	–
Rice, hulls	35	35.0	–
Rice, polished	18	25.0	–
Rice, wild, grain	24	12.0	–
Sorghum, grain	24	40.0	–
Triticale, grain	24	40.0	–
Wheat, bran	40	40.0	–
Wheat, flour	10	125.0	–
Wheat, germ	98	130.0	Translated from 89.7 ppm at 1012 mg·hr/L
Wheat, grain	25	40.0	–
Wheat, milled by-products	98	130.0	Translated from wheat, germ
Wheat, shorts	38	40.0	–
Nut, tree, group 14	30	10.0	–

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Fruit, dried, except grape, raisins	—	3.0	A dried fruit group tolerance was not proposed. Tolerances for "fruit, dried" should be proposed and the individual listings omitted.
Dates	5	See Fruit, dried	–
Figs	5	See Fruit, dried	–
Plums, dried	5	See Fruit, dried	–
Raisins	5	7.0	**Grape, raisin** - This tolerance is higher than other dried fruits because of the potential for fluoride residues from cryolite on this commodity.
All other dried fruits	5	See Fruit, dried	–

9.0 References

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cc: M. Doherty (RAB2), B. Daiss (RRB4), RAB2 Reading File

Attachments:

Appendix I - Risk Estimates for Development of Dental Fluorosis

Attachment 1. E-mail of 4/3/2001 from Sid Abel to Donna Davis regarding contamination of water with sulfuryl fluoride.

APPENDIX I - Risk Estimates for Development of Dental Fluorosis

At this time, based on the information available to the Agency, EPA is not concluding that dental fluorosis associated with fluoride exposure is an adverse health effect under the FFDCA. The current arguments that dental fluorosis is more than a cosmetic effect are not sufficiently persuasive to warrant regulation as an adverse health effect under the FFDCA. Accordingly, consistent with the action taken by the Office of Water under the Safe Drinking Water Act, 40 FR 47142 (November 14, 1985) (WH-FRL-2913-8(b)), the Agency believes that the appropriate endpoint for regulation under the FFDCA is skeletal fluorosis.

While the tolerance safety determination under the FFDCA is a health based standard, FIFRA requires the balancing of all costs, taking into account the economic, social, and environmental effects as well as health based risks, against the benefits associated with the pesticide use. Therefore, the Agency will consider dental fluorosis in determining whether sulfuryl fluoride meets the requisite standard under FIFRA.

The Agency, through the Office of Water, has set a Secondary MCL (SMCL) for fluoride at 2 ppm. This SMCL is set to be protective against moderate to severe dental fluorosis. Therefore, at exposures from 2 ppm fluoride in water, and assuming a source contribution of 100% from water, moderate to severe dental fluorosis is not expected to occur; mild to moderate dental fluorosis may occur. HED notes that the EPA's Integrated Risk Information System (IRIS) lists an oral RfD of 1 ppm fluoride in water for dental fluorosis (IRIS Database). That RfD is based on a NOEL of 1 ppm with an LOEL of 2 ppm and no modifying or uncertainty factors since the effect was noted in a sensitive population and the duration of exposure was appropriate for the effect and the population. The information in IRIS supports the SMCL of 2 ppm given that mild dental fluorosis is a cosmetic effect. In addition to findings by the Agency, the National Academy of Sciences Institute of Medicine has published Tolerable Upper Intakes for fluoride. The Agency's SMCL and the Institute of Medicine values are presented on a mg/kg/day basis in Table I-1.

Table I-1. Reference Exposure Levels used to Estimate Risk of Developing Dental Fluorosis.

Population Subgroup	Body Weight, kg	Water Consumption, L/day	SMCL, mg/kg/day*	Tolerable Upper Intake, mg/kg/day†
All Infants (<1 year)	7	1	0.286	0.1
Children 1-2 years	13	1	0.154	0.07
Children 3-5 years	22	1	0.091	0.06
Children 6-12 years	40	1	0.05	0.05

* SMCL (mg/kg/day) = SMCL (mg/L) × Water Consumption (L/day) ÷ Body Weight (kg).

† Tolerable Upper Intake from Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride. Report of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Washington, DC: National Academy Press, 1997.

HED has not estimated risks for dental fluorosis for population subgroups greater than 12 years of age. Dental fluorosis is an effect that occurs prior to eruption of the teeth, at the time

that the tooth enamel is being formed. In evaluating dental fluorosis, the National Academy of Sciences and the Office of Water use age cutoffs of 8 years and 9 years, respectively, as ages above which it is not appropriate to assess this effect. In this assessment, HED has used a maximum age of 12 years due to the population grouping of the exposure modelling software.

The risk estimates for dental fluorosis are presented in Table I-2. They are based on the aggregate exposure assessment discussed in Section 5 of this document. The use of both the MCL and the Tolerable Upper Intake values provides a range of risk estimates for each population subgroup. Both estimates should be considered when looking at the potential for fluoride exposures to result in dental fluorosis.

Table I-2. Aggregate Exposure and Risk Estimates for Dental Fluorosis.

Population Subgroup	Aggregate Exposure, mg/kg/day (without toothpaste)	MCL, mg/kg/day	% of MCL (without toothpaste)	Tolerable Upper Intake, mg/kg/day*	% of Tolerable Upper Intake (without toothpaste)
All infants (< 1 year)	0.1980 (0.1550)	0.286	69 (54)	0.10	198 (155)
Children 1-2 yrs	0.0878 (0.0647)	0.154	57 (42)	0.07	125 (92)
Children 3-5 yrs	0.0669	0.091	74	0.06	112
Children 6-12 yrs	0.0419	0.050	84	0.05	84

Based on the MCL values, risks do not exceed HED's level of concern for any of the assessed population subgroups (risk estimates range from 57 to 84% of the MCL). When risk estimates are based on the Institute of Medicine's Tolerable Upper Intake values, the values indicate that there may be concern for infants, children 1-2 years old, and children 3-5 years old. The exposure estimates for the "all infants" and "children 1-2 years" groups include exposure from fluoridated toothpaste. Provided parents follow the recommendations of the American Academy of Pediatric Dentistry that fluoridated toothpaste not be introduced into oral hygiene until children are at a minimum of 2 years old, the aggregate exposure estimates presented in Table I-2 represent an overestimate of exposure. Exposure and risk estimates without toothpaste are included parenthetically in the table for populations less than 2 years old. We note that dental fluorosis that occurs in the infant population subgroup will be to their deciduous teeth[5]. Therefore, the risk estimate of 198% (155% without toothpaste) of the Tolerable Upper Intake does not pertain to fluorosis of the permanent teeth. Given the assumptions in the exposure assessments and the range of numbers presented in Table I-2, HED does not believe that these risk estimates warrant critical concern regarding development of objectionable dental fluorosis

[5] Centers for Disease Control. "Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States". http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5014a1.htm.

Attachment 1. E-mail of 4/3/2001 from Sid Abel to Donna Davis regarding contamination of water with sulfuryl fluoride.

To: Donna Davis/DC/USEPA/US@EPA
cc: Dennis McNeilly/DC/USEPA/US@EPA, Meredith Laws/DC/USEPA/US@EPA, Donald Stubbs/DC/USEPA/US@EPA
Subject: Re: Can you help?

Donna,

This e-mail is in response to HED's request to determine whether a drinking water assessment is necessary for the proposed use of sulfuryl fluoride, under an EUP and as a potential replacement for methyl bromide, for fumigation uses, raisins and walnuts. EFED would not conduct an assessment of impacts to drinking water from surface or ground water sources. The nature of the use pattern would limit exposures to ambient waters to at most non-quantifiable fugitive deposition. Any releases to wastewater treatment plants would be "stripped" from the wastestream during the aeration of the activated sludge or trickling filter processes (secondary treatment). Releases from these operation would generally be controlled by NPDES permits for down-the-drain releases, if applicable, and air emissions would be controlled by similar local regulations.

If you need any further assistance on this matter, please feel free to contact me.

Sid