UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: January 18, 2006

Subject: Human Health Risk Assessment for Sulfuryl Fluoride and Fluoride Anion Addressing the Section 3 Registration of Sulfuryl Fluoride as a Fumigant for Foods and Food Processing Facilities. PP# 3F6573.

DP Number: 312659
PC Code: 078003
40 CFR 180: 575 (sulfuryl fluoride)
145 (fluorine compounds)

Class: Fumigant

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Note: This risk assessment post-dates the Federal Register notice establishing tolerances for residues of sulfuryl fluoride and fluoride resulting from fumigation of some foods and of food processing facilities [Federal Register - July 15, 2005 (Volume 70, Number 135)]. During the internal peer-review process in OPP, errors were noted in the residue files used to estimate dietary exposure and it was found that there were discrepancies between the assumptions made in the risk assessment and the uses that were being allowed on the product label. Those errors and discrepancies have been resolved. While the dietary and aggregate exposure and risk estimates presented in this document are slightly greater than those presented in the Federal Register notice, HED's conclusions and regulatory recommendations remain unchanged. HED is still recommending for a conditional registration of sulfuryl fluoride for the sought after uses and the establishment of permanent tolerances for residues of sulfuryl fluoride and fluoride anion.

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1.0 EXECUTIVE SUMMARY

Dow AgroSciences has petitioned the Agency to register sulfuryl fluoride for the control of numerous pests in foods and food processing facilities. In conjunction with that petition, Dow AgroSciences has requested the establishment of permanent tolerances for residues of sulfuryl fluoride and of fluoride anion on a suite of commodities related to the proposed use. Sulfuryl fluoride is a potential methyl bromide replacement for these uses. Under the proposed use, foods and food processing facilities will be fumigated with sulfuryl fluoride formulated as the 99% a.i. ProFume. Fumigation may be carried out at ambient pressures or, where practical, 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.

This assessment also addresses a revised use pattern for the previously registered use of sulfuryl fluoride in cereal grain milling facilities. The directions for that use have been revised to eliminate the required blending of fumigated flour with untreated flour.

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 risks associated with sulfuryl fluoride and fluoride anion. Due to the different toxicological effects elicited by these two chemicals, their risks have been assessed separately. This risk assessment builds on the previous human health risk assessment issued by HED (M. Doherty, D309013, 10/12/04). Much of the detail regarding exposure estimates to fluoride from water, background residues in food, toothpaste, inhalation, and use of cryolite (which also results in fluoride residues in food) can be found in that document.

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 estimates of the percent of commodities treated. Additionally, we assumed that commodities might be serially fumigated, first as part of a post-harvest and/or grain mill fumigation and then again due to food processing facility fumigation. The actual probability of this occurring is likely to be very small; therefore, this assumption results in an overestimate of exposure. Even with this assumption, the estimated dietary exposures for the general U.S. population and all population subgroups, including those of infants and children, are less than or equal to 8% 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. The Vikane data were collected based on a 5-ppm reentry concentration. ProFume has a 1-ppm reentry concentration. Therefore, the exposure estimates from Vikane were reduced by 5-fold. Occupational MOEs for ProFume range from 300 to 2100. Since levels of concern are 100 for short- and intermediate-term exposures, and 300 for long-term exposures, the risk estimates represented by the occupational MOEs are below HEDs level of concern.

Fluoride Anion. In assessing the risks associated with exposure to fluoride, HED has relied on the toxicological assessment completed by the Agency's Office of Water. That assessment identified crippling skeletal fluorosis as the endpoint of regulatory concern and determined that a value of 8 mg/day is protective against skeletal fluorosis without being so low as to negate the beneficial, cavity-fighting effects of fluoride exposure. The Office of Water has acknowledged that dental fluorosis may occur at exposures of less than 8 mg/day. At this time, based on the information available to the Agency, EPA is not concluding that mild to moderate 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 considered dental fluorosis in determining whether sulfuryl fluoride meets the requisite standard under FIFRA (see Appendix II).

OPP notes that a more recent assessment of fluoride by the National Academy of Sciences' Institute of Medicine (IOM) identified a skeletal fluorosis NOAEL at 10 mg/day[1].

[1]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.

Their assessment of the data concluded that no safety or uncertainty factors were needed. The IOM also notes that high exposures for long durations (on the order of 10 years) are required to develop skeletal fluorosis and that such a condition is not expected to occur in children under the age of 8. Although the values of 8 mg/day and 10 mg/day are equally appropriate for use in a human health risk assessment, OPP has used the 8-mg/day value in order to be slightly more conservative in assessing risk. For fluoride risk assessments addressed in this document, the 8 mg/day value has been used in a manner analogous to a reference dose (RfD) and for ease of communication will be referred to as such.

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. For foods, we have assumed that all commodities are serially fumigated (as described above for sulfuryl fluoride), with cryolite included as a potential addition source of elevated fluoride residues. 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 RfD 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 17 to 43% of the RfD. These aggregate risk estimates are below HED's level of concern for all population subgroups.

HED notes that this assessment is predicated upon the removal of dried eggs from the list of "Commodities That Can Be Fumigated" on the ProFume Label. Dow AgroSciences recently submitted a proposed label with that deletion.

Deficiencies in the sulfuryl fluoride data are noted in Section 8 and HED's recommended tolerance levels are summarized in Table 8.1. HED's recommendations involving the method for fluoride may impact tolerance levels. Because of this, we are recommending that the registration, if granted, be conditional upon receipt and evaluation of the data outlined in Section 8. Furthermore, HED notes that the Office of Water, via the National Academy of Sciences, is reevaluating the available information regarding fluoride and recommends 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 control of pests in food 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 11552 mm Hg (Torr) at 20°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 fluorine's 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

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 = intermittent 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 = microscopic 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, decreased 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 increased 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). That requirement has subsequently been waived (2004, see attachment)
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 liquefied 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 toxicological 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. Intermittent 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[2]. 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[3]. 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. Fluorosis results from the binding of fluoride anion to teeth (causing mottling of the teeth) and to bone.

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:

- 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

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[2]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.

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

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.

In April 2004, the Health Effects Division evaluated rational submitted by the registrant requesting a waiver of the DNT study. HED granted the waiver request (Attachment 1) because, given the relatively minimal exposure to sulfuryl fluoride relative to the identified endpoints, any lowering of the regulatory endpoints due to DNT study results would be unlikely to affect the safety determination. However, because there remains uncertainty with regard to the regulatory endpoints for sulfuryl fluoride in the absence of a DNT, EPA has retained the FQPA 10X factor in assessing the risk posed by sulfuryl fluoride.

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[4]. 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

[4]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**
			is required.
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 conducted by the Agency's Office of Water. The regulatory findings in that assessment [FR 51 (63)] are based on a LOAEL of 20 mg/day and a safety factor of 2.5, giving a maximum allowable intake of 8 mg/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 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. In a more recent review of the data, the National Academy of Sciences' Institute of Medicine (IOM) identified a skeletal fluorosis NOAEL at 10 mg/day[5]. Their assessment of the data concludes that no safety or uncertainty factors are needed. The IOM also notes that high exposures for long durations (on the order of 10 years) are required to develop skeletal fluorosis and that such a condition is not expected to occur in children under the age of 8. The findings of the IOM are nearly identical with respect to upper limits of exposure as those of the Office of Water. Although the values of 8 mg/day and 10 mg/day are essentially equivalent, OPP has used the 8-mg/day value in order to be slightly more conservative in assessing risk. For fluoride risk assessments addressed in this document, the 8 mg/day value has been used in a manner analogous to a reference dose (RfD) and is referred to as such for ease of communication. We note that the previous human health risk assessment for sulfuryl fluoride (M. Doherty, 10/12/2004, D309013) expressed toxicology and exposure in terms of mg/kg/day in order to match the units used by the dietary exposure model. In this assessment, those values are being expressed in mg/day to better harmonize with the more typical units found in the open literature describing fluoride exposures. In both cases, the values listed are derived from the same toxicological data and conclusions.

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

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[5]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.

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 maximum contaminant level (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 II 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 (10+ 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 used the 8-mg/day value derived by the Office of Water in a manner analogous to a chronic PAD.

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 scientific 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 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 Proposed Uses

Sulfuryl fluoride is being proposed as a methyl bromide replacement to control pests in food processing facilities. 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 11552 Torr (20°C). 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 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 Batch	Max. Cumulative Applic. Rate (mg·hr/L)	Aeration (hours)	Use Directions and Limitations
Fumigation of foods and sealed food processing facilities	ProFume [62719-XXX]	1500 (ambient pressure) 200 (vacuum fumigation)	2	1500 (ambient pressure) 200 (vacuum fumigation)	24	Food commodities must be aerated for 24 hours prior to entering commerce.

Provided the proposed label is amended to remove dried eggs as a targeted commodity for food fumigations and to prohibit targeted fumigation of edible oils, the label has sufficient information to allow the Agency to evaluate the residue trials in light of the proposed use patterns. Dow AgroSciences has submitted a draft label in which dried egg has been deleted as a targeted commodity for food fumigations.

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 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
(M. Doherty, DP Number 317730, 7/13/05 and M. Doherty, DP Number 317731, 1/18/06)

Tolerances are currently established for sulfuryl fluoride (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.

To support the requested uses, Dow AgroSciences has submitted residue data for sulfuryl fluoride and fluoride anion from a number of finished food products (chips, cookies, etc.) as well as foods considered to be "key" ingredients (salt, sugar, powdered milk, etc.). Foods were fumigated at approximately the maximum label rate (1500 mg·hr/L) and allowed to aerate for 24 hours prior to residue analysis. Fumigation, aeration, and storage were all done at 30°C in order to maximize the potential conversion of sulfuryl fluoride to fluoride anion. For finished foods, items were fumigated in an open configuration (i.e., a box or other open container) as well as in their original packaging. Key ingredients were fumigated only in the open configuration. HED has matched the available data to the various food types in the dietary exposure model to obtain dietary exposure estimates.

Separate analytical methods for each residue of concern are available for most commodities; however, the data submitted to support this petition shows that the methods are not suitable for all commodities that may be treated. Furthermore, storage stability data for fluoride were not submitted and there is concern that fluoride may have reacted with food components during storage and become "bound." There is evidence from previous storage stability studies with fluoride (MRID 45510302) that this may occur.

Residues of sulfuryl fluoride were highly dependent on the nature of the fumigated material and ranged from <0.004 ppm to approximately 2 ppm. Similarly, fluoride residues were dependent on the commodity and ranged from <1 to approximately 820 ppm. Generally, commodities with higher protein and/or fat content have higher residues of sulfuryl fluoride or fluoride (an extreme case being powdered eggs). For a number of finished products, the residues of sulfuryl fluoride in the packaged configuration were greater than in the open configuration. In all such cases, the packaging contained a polymer film, either as a bag liner or as lined paper. The phenomena were not mirrored in the fluoride residue levels. HED does not have a satisfactory theory to explain these observations at this time. Method performance leaves a high degree of uncertainty surrounding residues of sulfuryl fluoride in Oreo® cookies, powdered eggs, and baking soda; and for residues of fluoride in white cake mix, pet foods, parsley, and baking powder. Given the transient nature of sulfuryl fluoride residues and the potential for fluoride to serve as a marker compound, HED does not believe that the lack of a universal method for sulfuryl fluoride warrants development of a new sulfuryl fluoride method. HED is, however, concerned about the lack of performance of the fluoride method for some commodities and the fluoride storage stability issue noted above. The use of a total fluoride analysis method would resolve both the method and the storage stability issues and recommends that the petitioner investigate and, if necessary, validate a total fluoride method using representative commodities from all crop groups and animal commodities (meat, fat, milk, eggs). Further, HED recommends that the petitioner consult with the HED prior to the onset of any such investigation. HED is recommending that the registration, if granted, be made conditional on the proposal of a more universal fluoride method, acceptance of that method by the Agency, and submission of residue data collected from control and fumigated representative commodities. As of 1/13/06, the Analytical Chemistry Laboratory had not received reference standards of either sulfuryl fluoride or a suitable fluoride salt. Due to the nature of sulfuryl fluoride, the laboratory is not requesting that a standard be submitted at this time; however, a reference standard for fluoride should be provided.

Based on the data available at this time, HED is recommending that the following tolerances be established:

Commodity	Tolerance, ppm	
	Sulfuryl Fluoride	Fluoride Ion
All processed food commodities not otherwise listed	2.0	70
Cattle, meat, dried	0.01	40
Cheese	2.0	5.0
Cocoa bean, postharvest	0.2	20
Coconut, postharvest	1.0	40
Coffee, postharvest	1.0	15
Cottonseed, postharvest	0.5	70
Eggs, dried	1.0	900
Ginger, postharvest	0.5	70
Ham	0.02	20

Herbs and Spices, Group 19, postharvest	0.5	70
Milk, powdered	2.0	5.0
Nut, pine, postharvest	0.2	20
Peanut, postharvest	0.5	15
Rice, flour, postharvest	0.05	45
Vegetables, Legume, Group 6, postharvest	0.5	70

4.2.1.5 Other Sources of Fluoride

(M. Doherty, DP Number 309013)

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 of the previous risk assessment. The exposure estimates are summarized in Table 4.2.3.2, below. 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

The Health Effects Division has conducted two dietary assessments to evaluate the potential dietary exposures to sulfuryl fluoride and fluoride anion associated with the requested uses. The first assessment addresses food fumigations and includes use on dried fruits, stored cereal grains, herbs and spices, dried peas and beans, tree nuts, cocoa beans, coconut, coffee beans, cottonseed, ginger, powdered milk, cheese, peanut, pine nut, and ham. The second analysis addresses inadvertent residues that may occur during space fumigations of grain milling facilities and food processing facilities. Both assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. There is the potential for a given commodity to receive post-harvest treatment with sulfuryl fluoride and to then be exposed to the fumigant again as part of a space fumigation. Therefore, the dietary exposure estimates from the food fumigation and space fumigation analyses have been combined to give total dietary exposure estimates. Since the likelihood of this serial treatment is highly unlikely, adding the exposure estimates is considered to be a highly health-protective assumption.

The Biological and Economic Analysis Division has supplied HED with information regarding the amount of commodities that may be treated per year. For food fumigations, estimates are 2%

for stored cereal grains, 20% for tree nuts, and 40% for dried fruits. All other commodities in the food fumigation assessments were assigned a percent crop treated value of 100%. The space fumigation assessments include estimates of the fraction of commodities treated. The estimates include the percentage of facilities that may be fumigated per year as well as the amount of the various commodities that may be exposed to sulfuryl fluoride during fumigation. It is estimated that approximately 40% of the processing facilities would receive sulfuryl fluoride fumigation with, on average, 2.5 fumigations per year. Approximately one day's worth of production could be stored on-site and the facilities typically operate over 300 days per year. Combining these estimates gives a fraction of commodity treated estimate of $0.4 \times 2.5 \times 1 \div 300 = 0.003$. This estimate was rounded up to 0.004 for the space fumigation analyses. For grain mills, HED assumed that 40% of the facilities would be treated, that there could be 3 fumigations per year, and 2 days worth of production exposed, giving an estimate of $0.4 \times 3 \times 2 \div 300 = 0.008$. Since cereal grain commodities could be exposed to sulfuryl fluoride at the mill and at the food processing facility, these two percent-commodity-treated estimates were added together for an overall inadvertent cereal grain commodity treated estimate of 1.1%.

The previous human health risk assessment included a 0.1X processing factor for flour commodities to account for the practice of drawing down grain in the mills prior to fumigation and then flushing any residual grain/flour out of the mill with fresh material during startup and mill equilibration. The present assessment has removed that 0.1X factor to account for the ProFume label having been revised in 2005 to eliminate blending of fumigated flour with untreated flour.

Sulfuryl Fluoride. The chronic analysis for sulfuryl fluoride used average residue values from residue trials reflecting the maximum proposed use. The refined chronic dietary risk estimates for all population subgroups are less than or equal to 8% of the chronic population-adjusted dose (cPAD) of 0.003 mg/kg/day when combined for the food fumigation and space fumigation uses.

Table 4.2.3.1. Sulfuryl Fluoride Chronic Dietary Exposure and Risk Estimates for Fumigation of Food and Food Processing Facilities with Sulfuryl Fluoride. The cPAD for sulfuryl fluoride is 0.003 mg/kg/day for all population subgroups.

Population Subgroup	Food Fumigations		Space Fumigations		Food + Space	
	Exposure Estimate, mg/kg/day	% cPAD	Exposure Estimate, mg/kg/day	% cPAD	Exposure Estimate, mg/kg/day	% cPAD
U.S. Pop. (total)	0.000064	2	0.000017	1	0.000082	3
All infants (< 1 year)	0.000041	1	0.000097	3	0.000138	5
Children 1-2 yrs	0.000189	6	0.000036	1	0.000225	8
Children 3-5 yrs	0.000177	6	0.000036	1	0.000213	7
Children 6-12 yrs	0.000100	3	0.000026	1	0.000126	4
Youth 13-19 yrs	0.000058	2	0.000017	1	0.000075	3
Adults 20-49 yrs	0.000047	2	0.000014	<1	0.000061	2
Adults 50+ yrs	0.000045	2	0.000011	<1	0.000056	2
Females 13-49 yrs	0.000046	2	0.000013	<1	0.000059	2

Fluoride. The chronic analyses for fluoride are presented in Table 4.2.3.2. The separate food-fumigation and space-fumigation risk estimates are below HED's level of concern for all population subgroups. It should be noted that crippling skeletal fluorosis requires high exposure

for extended time (on the order of decades); therefore, it is not really appropriate to include children in an assessment for this condition. Children are included in Table 4.2.3.2, and subsequent tables, for completeness.

Table 4.2.3.3 combines dietary exposure estimates from sulfuryl fluoride, cryolite, background levels in food, and drinking water to give an overall dietary exposure estimate. Note that exposure estimates in Tables 4.2.3.2 and 4.2.3.3 are expressed in mg/day. Total dietary risk estimates range from 13 to 38% of the RfD and are below HED's level of concern for all population subgroups.

Table 4.2.3.2. Fluoride Chronic Dietary Exposure and Risk Estimates for Fumigation of Food and Food Processing Facilities with Sulfuryl Fluoride. The RfD for fluoride is 8 mg/day for all population subgroups.

Population Subgroup	NHANES Estimated Body Weight, kg*	Food Fumigations			Space Fumigations			Food + Space	
		Exposure Estimate,		% RfD	Exposure Estimate,		% RfD	Exposure Estimate, mg/day	% RfD
		mg/kg/day	mg/day		mg/kg/day	mg/day			
U.S. Pop. (total)	70	0.008701	0.6091	8	0.000820	0.0574	1	0.6665	8
All infants (< 1 year)	7	0.010972	0.0768	1	0.000876	0.0061	<1	0.0829	1
Children 1-2 yrs	13	0.017980	0.2337	3	0.002052	0.0267	<1	0.2604	3
Children 3-5 yrs	22	0.019274	0.4240	5	0.002009	0.0442	1	0.4682	6
Children 6-12 yrs	40	0.012879	0.5152	6	0.001361	0.0544	1	0.5696	7
Youth 13-19 yrs	60	0.008014	0.4808	6	0.000795	0.0477	1	0.5285	7
Adults 20-49 yrs	70	0.007212	0.5048	6	0.000660	0.0462	1	0.5510	7
Adults 50+ yrs	70	0.006670	0.4669	6	0.000516	0.0361	<1	0.5030	6
Females 13-49 yrs	61	0.006398	0.3903	5	0.000603	0.0368	<1	0.4271	5

*National Health and Nutrition Examination Survey. U.S. EPA. 2000. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. Office of Science and Technology, Office of Water EPA-822-B-00-004. Washington, DC.

Table 4.2.3.3. Total Chronic Exposure and Risk Estimates for Fluoride from Dietary Sources.

Population Subgroup	RfD, mg/day	Dietary Fluoride Anion Exposure Estimates, mg/day					Risk, % RfD
		Sulfuryl Fluoride	Cryolite	Food	Water	Total Dietary	
U.S. Population (total)	8	0.667	0.049	0.476	1.883	3.075	38
All infants (< 1 year)	8	0.083	0.007	0.065	0.997	1.152	14
Children 1-2 yrs	8	0.260	0.043	0.228	0.529	1.060	13
Children 3-5 yrs	8	0.468	0.046	0.328	0.744	1.586	20
Children 6-12 yrs	8	0.570	0.036	0.376	0.908	1.890	24
Youth 13-19 yrs	8	0.529	0.018	0.372	1.056	1.975	25
Adults 20-49 yrs	8	0.551	0.028	0.399	1.764	2.742	34
Adults 50+ yrs	8	0.503	0.035	0.35	1.792	2.680	34
Females 13-49 yrs	8	0.427	0.031	0.329	1.452	2.239	28

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

Please see the previous human health risk assessment for sulfuryl fluoride/fluoride for a discussion of water exposures and risks (M. Doherty, D309013, 10/12/04). This risk assessment assumed an average 2 ppm level of fluoride in drinking water (see M. Doherty 10/12/04 memo, D309014). This level represents the 99th percentile of exposure for the US population as presented in a 2003 Office of Water publication ("Occurrence Estimation Methodology and Occurrence Findings Report for the Six-Year Review of Existing National Primary Drinking Water Regulations"). The latter also concluded that a subpopulation of about 191,000 is served by drinking water sources containing average fluoride residues greater than the MCL of 4 ppm. An additional 535,900 and 1.98 million individuals are estimated to be served by sources containing more than 3 ppm and 2 ppm average fluoride, respectively. Public notice regulations have been established by EPA under Chapter 40, Part 141, Subpart Q of the Code of Federal Regulations to address situations wherein fluoride levels exceed 2 ppm[6]. These regulations require operators of public water systems to inform consumers when fluoride levels exceed the secondary MCL (SMCL) of 2 ppm or the MCL of 4 ppm. Exceedances of the SMCL must be reported as soon as practical but within 12 months, while levels higher than the 4 ppm MCL must be reported within 30 days. In both cases the public notices state that children under the age of nine should be provided with an alternative source of drinking water low in fluoride. The SMCL exceedance notice states that older children and adults may safely drink the water, but the notice for levels greater than the MCL advises adults and older children to consult their dentist or doctor to determine if an alternate source of water low in fluoride should be used. Based on the existence of this public notice system for consumers in areas with higher fluoride levels, HED considers the use of 2 ppm fluoride in drinking water as a reasonable upper limit for the purposes of chronic risk assessment.

4.4 Residential Exposure/Risk Pathway

Please see the previous human health risk assessment for sulfuryl fluoride/fluoride for a discussion of non-dietary exposures and risks (M. Doherty, D309013, 10/12/04). Exposure estimates for these pathways are summarized in Table 4.4.1, below.

Table 4.4.1. Estimated Fluoride Exposure from Non-Dietary Sources.

Population Subgroup	Standard Respiration, m^3/day	Estimated Exposure, mg/day	
		Toothpaste	Air
U.S. Population (total)	13.3	0.30	0.0420
All infants (< 1 year)	4.5	0.30	0.0133
Children 1-2 yrs	8.7	0.30	0.0260
Children 3-5 yrs	8.7	0.30	0.0264
Children 6-12 yrs	8.7	0.30	0.0280

[6] For guidance on the public notice regulations, the reader is referred to the "Public Notification Handbook" at www.epa.gov/safewater/pws/pn/handbook.pdf.

Youth 13-19 yrs	13.3	0.30	0.0420
Adults 20-49 yrs	13.3	0.30	0.0420
Adults 50+ yrs	13.3	0.30	0.0420
Females 13-49 yrs	11.3	0.30	0.0366

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 and the infrequency of fumigations of food processing facilities, HED is not concerned with potential bystander exposures associated with fumigation of those facilities. As noted in the previous assessment, for tree nut and dried fruit fumigations, there is more of a potential for more regular bystander exposure to sulfuryl fluoride. Based on the properties of sulfuryl fluoride and the practices associated with fumigation facilities, HED does not believe that there will be significant exposure to bystanders; however, as a condition of registration and in conjunction with the monitoring of fumigation workers (see Section 7), HED has requested air monitoring data from areas surrounding fumigation sites.

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. Due to the use pattern of sulfuryl fluoride and associated label restrictions, the potential non-dietary exposure pathways are believed to result in negligible exposures. 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 or equal to 8% of the cPAD for the U.S. population and all population subgroups (Table 4.2.3.1). 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 representative 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 RfD. The aggregate risk estimates for the representative subgroups in DEEM-FCID range from 17% (children 1-2 year of age) to 43% (general U.S. population) of the RfD. 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. Risk estimates based on toxicological findings of the Institute of Medicine (1997) are presented in Appendix I. Risk estimates associated with dental fluorosis are presented in Appendix II.

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

Population Subgroup	RfD, mg/day	Estimated Fluoride Exposure by Source, mg/day				Risk, % of RfD
		Dietary	Toothpaste	Air	Total	
U.S. Population (total)	8	3.075	0.3	0.0420	3.417	43
All infants (< 1 year)	8	1.152	0.3	0.0133	1.465	18
Children 1-2 yrs	8	1.060	0.3	0.0260	1.386	17
Children 3-5 yrs	8	1.586	0.3	0.0264	1.912	24
Children 6-12 yrs	8	1.890	0.3	0.0280	2.218	28
Youth 13-19 yrs	8	1.975	0.3	0.0420	2.317	29
Adults 20-49 yrs	8	2.742	0.3	0.0420	3.084	39
Adults 50+ yrs	8	2.680	0.3	0.0420	3.022	38
Females 13-49 yrs	8	2.239	0.3	0.0366	2.576	32

In developing the exposure estimates for fluoride from water, HED has used the national median fluoride concentration of 0.4 ppm for non-tap water (i.e., food-based water, commercially processed water, and bottled water). While we believe that the median value is a reasonable estimate given that such water, as a whole, will come from various sources, we acknowledge that certain water within that designation may come from a fairly localized region and therefore fluoride levels may be underestimated by use of a national median. In order to ascertain the impact of using the 0.4-ppm value on the aggregate exposure estimates, HED has also estimated fluoride exposure from water using the 2-ppm concentration for all water sources. Using the 2-ppm value results in total dietary fluoride exposure estimates that range from 20% to 67% of the RfD, giving a maximum aggregate risk estimate of approximately 71% of the RfD (details not shown). Although HED believes that this risk estimate is based on unreasonably high exposure levels, it still falls below our level of concern.

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.

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

The proposed use of sulfuryl fluoride is identical with respect to occupational exposure to the previously assessed uses. Please see the previous human health risk assessment for a discussion of occupational exposure (M. Doherty, D309013, 10/12/04). For convenience, the estimates from that assessment have been reproduced in Table 7.1, below.

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. Values from M. Doherty, D309013, 10/12/04.

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)]

8.0 DATA NEEDS AND LABEL REQUIREMENTS

Toxicology

- None associated with this petition.

Residue Chemistry Deficiencies

- HED believes that a total fluoride analysis method would resolve the method performance and the storage stability issues that came to light as a result of this and the previous petition, and recommends that the petitioner investigate and validate a total fluoride method using control and fumigated representative commodities from all crop groups and animal commodities (meat, fat, milk, eggs). HED further recommends that the petitioner consult with the Agency prior to initiating any such validation.
- HED has not included dried eggs in dietary exposure and risk estimates associated with food fumigations, and is recommending that food fumigation of dried eggs be removed from the label section titled "Commodities That Can Be Fumigated." Dow AgroSciences has submitted a draft label making that change. Incidental treatment of dried eggs resulting from space fumigations may be permitted.
- HED has not included edible oils in dietary exposure and risk estimates associated with food fumigations, and is recommending that the label be modified to state that edible oils may not be directly fumigated. Incidental treatment of edible oils resulting from space fumigations may be permitted.
- As of 1/13/06, the Analytical Chemistry Laboratory had not received reference standards of either sulfuryl fluoride or a suitable fluoride salt. Due to the nature of sulfuryl fluoride, the laboratory is not requesting that a standard be submitted at this time; however, a suitable reference standard of a fluoride salt should be provided.

- The previous risk assessment requested information regarding the transfer of fluoride from feedstuffs into livestock commodities. To date, HED has not received any such information.
- The previous risk assessment also requested that the label be modified to specify that 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.

Occupational and Residential Exposure

- None associated with this petition. Air monitoring data around fumigation sites have been received by the Agency but have not yet been reviewed.

Table 8.1. Tolerance Summary for Sulfuryl Fluoride

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Flavorings, leavening agents (except yeast), dry garlic, dry onion, dry pepper, baking powder, baking soda	0.05	None	Covered under "All processed food commodities not otherwise listed."
Other herbs, spices, chili pepper	0.3	0.5	Herbs and spices, group 19, postharvest
Salt, sugars, high-fructose corn syrup	0.02	None	Covered under "All processed food commodities not otherwise listed."
Peanuts	0.2	0.5	Peanut, postharvest
Coffee, cocoa beans	0.8	See below	Separate listings should be made for Coffee, postharvest and Cocoa bean, postharvest
Cocoa beans, postharvest	0.8	0.2	
Coffee, postharvest	0.8	1.0	
Dried legume vegetables (beans, peas, soybean, etc.)	0.02	0.5	Vegetables, legume, group 19, postharvest
Powdered milk, powdered cheese	1.5	See below	Separate listings should be made for milk, powdered and cheese
Cheese	1.5	2.0	
Milk, powdered	1.5	2.0	
All other processed foods	1.2	2.0	All processed food commodities not otherwise listed
Cattle, meat, dried	0.01	0.01	
Coconut, postharvest	1.0	1.0	
Egg	0.7	1.0	Eggs, dried
Ginger, postharvest	0.2	0.5	

Table 8.1. Tolerance Summary for Sulfuryl Fluoride			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Ham	0.01	0.02	
Nut, pine, postharvest	3.0	0.2	
Rice, flour, postharvest	0.08	0.05	
Grain, cereal forage, fodder, and straw, group 16, postharvest	2.0	None	No data to support tolerance
Grass, forage, fodder, and hay, group 17, postharvest	2.0	None	No data to support tolerance
Animal Feed	2.0	None	Covered under "All processed food commodities not otherwise listed."

Table 8.2. Tolerance Summary for Fluoride			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Flavorings, leavening agents (except yeast), dry garlic, dry onion, dry pepper, baking powder, baking soda	8	None	Covered under "All processed food commodities not otherwise listed."
Other herbs, spices, chili pepper	70	70	Herbs and spices, group 19, postharvest
Salt, sugars, high-fructose corn syrup	2	None	Covered under "All processed food commodities not otherwise listed."
Peanuts	13	15	Peanut, postharvest
Coffee, cocoa beans	12	See below	Separate listings should be made for Coffee, postharvest and Cocoa bean, postharvest
Cocoa beans, postharvest	12	20	
Coffee, postharvest	12	15	
Dried legume vegetables (beans, peas, soybean, etc.)	6	70	Vegetables, legume, group 19, postharvest
Powdered milk, powdered cheese	3	See below	Separate listings should be made for milk, powdered and cheese
Cheese	3	5.0	
Milk, powdered	3	5.0	
All other processed foods	70	70	All processed food commodities not otherwise listed
Cattle, meat, dried	40	40	

Table 8.2. Tolerance Summary for Fluoride			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Coconut, postharvest	40	40	
Egg	850	900	Eggs, dried
Ginger, postharvest	13	70	
Ham	20	20	
Nut, pine, postharvest	10	20	
Rice, flour, postharvest	98	45	
Grain, cereal forage, fodder, and straw, group 16, postharvest	130	None	No data to support tolerance
Grass, forage, fodder, and hay, group 17, postharvest	130	None	No data to support tolerance
Animal Feed	130	None	Covered under "All processed food commodities not otherwise listed."

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cc: M. Doherty (RAB2)

Attachments: Waiver of Rat Developmental Neurotoxicity Study with Sulfuryl Fluoride.

APPENDIX I - Risk Estimates for Development of Skeletal Fluorosis Based on Institute of Medicine Toxicological Findings

The Institute of Medicine of the National Academies (IOM) published, in 1997, dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Their examination of the available data identified a NOAEL of 10 mg/day as relates to fluoride intake and skeletal fluorosis. They further point out that exposures of 10 or more years are required to develop this condition and focus their attention on people greater than 8 years of age. OPP has included all age groups in its assessment for the sake of completeness. The IOM analysis results in a tolerable upper intake level of 10 mg/day for children (> 8 years old) and adults, including pregnant or lactating females. In deriving their recommended upper limit for exposure, the Institute used an uncertainty factor of 1, noting that the NOAEL is derived from human studies and that symptomatic skeletal fluorosis is not observed at intakes of 10 mg/day. As noted in the general discussion of fluoride toxicity, the FQPA safety factor can be reduced to 1X; therefore, the cPAD for skeletal fluorosis based on the IOM analysis is 10 mg/day. Due to the constraints of the chronic dietary exposure model output, HED has included children aged 6-12 in this assessment even though such a group includes people too young to develop skeletal fluorosis.

When the dietary and non-dietary exposure estimates summarized in Section 5 are compared to the IOM-based toxicological threshold, the risk estimates are slightly less (ranging from 14 to 33% cPAD; Table I-2) than those that are based on the RfD (17 to 41% RfD; Table 5.1).

Table I-2. Aggregate Exposure and Risk Estimates for Skeletal Fluorosis Based on Analysis by the Institute of Medicine of the National Academies.

Population Subgroup	RfD, mg/day	Estimated Fluoride Exposure by Source, mg/day				Risk, % of RfD
		Dietary	Toothpaste	Air	Total	
U.S. Population (total)	10	3.075	0.3	0.0420	3.417	34
All infants (< 1 year)	10	1.152	0.3	0.0133	1.465	15
Children 1-2 yrs	10	1.060	0.3	0.0260	1.386	14
Children 3-5 yrs	10	1.586	0.3	0.0264	1.912	19
Children 6-12 yrs	10	1.890	0.3	0.0280	2.218	22
Youth 13-19 yrs	10	1.975	0.3	0.0420	2.317	23
Adults 20-49 yrs	10	2.742	0.3	0.0420	3.084	31
Adults 50+ yrs	10	2.680	0.3	0.0420	3.022	30
Females 13-49 yrs	10	2.239	0.3	0.0366	2.576	26

APPENDIX II - 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, dental fluorosis in the moderate-to-severe category is not expected to occur; dental fluorosis in the mild-to-moderate category 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 Institute of Medicine of the National Academies (IOM) has published Tolerable Upper Intakes for fluoride as relates to dental fluorosis. The Agency's SMCL and the IOM values are presented on a mg/day basis in Table II-1.

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

Population Subgroup	Water Consumption, L/day	SMCL, mg/day*	Tolerable Upper Intake, mg/day†
All Infants (<1 year)	1	2	0.7
Children 1-2 years	1	2	1.3
Children 3-5 years	1	2	1.9
Children 6-12 years	1	2	2.2

* SMCL (mg/day) = SMCL (mg/L) × Water Consumption (L/day).

† 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. Values have been matched to the listed age groups using a weighted average.

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 modeling software.

The risk estimates for dental fluorosis are presented in Table II-2. They are based on the aggregate exposure assessment discussed in Section 5 of this document. The use of both the SMCL 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 II-2. Aggregate Exposure and Risk Estimates for Dental Fluorosis.

Population Subgroup	Aggregate Exposure, mg/day (without toothpaste)	SMCL, mg/day	% of SMCL (without toothpaste)	Tolerable Upper Intake, mg/day	% of Tolerable Upper Intake (without toothpaste)
All infants (< 1 year)	1.465 (1.165)	2	73 (58)	0.70	209 (166)
Children 1-2 yrs	1.386 (1.086)	2	69 (54)	1.30	107 (84)
Children 3-5 yrs	1.912	2	96	1.90	101
Children 6-12 yrs	2.218	2	111	2.20	101

Based on the SMCL values, risks slightly exceed HED's level of concern for children aged 6 to 12 years old. When risk estimates are based on the Institute of Medicine's Tolerable Upper Intake values, those estimates indicate that there may be concern for infants. The exposure estimates for the "all infants" group includes 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 II-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 which occurs in the infant population subgroup will be to their deciduous teeth[7]. Therefore, the risk estimate of 209% (166% 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 II-2, HED does not believe that these risk estimates warrant critical concern regarding development of objectionable dental fluorosis.

[7] 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.