D R A F T

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: June 2, 2005 – DRAFT

MEMORANDUM

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

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

Class: Fumigant

From: Michael Doherty, Chemist
Registration Action Branch 2
Health Effects Division (7509C)

Through: Richard Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

To: Dan Kenny/Meredith Laws
Insecticide/Rodenticide Branch
Registration Division (7505C)

D R A F T

Table of Contents

1.0 EXECUTIVE SUMMARY

Dow AgroSciences has petitioned the Agency to register sulfuryl fluoride to control numerous pests in 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, 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.

HED has reviewed the toxicology and residue chemistry data submitted to support the petition and has examined the potential for exposures via dietary (food and drinking water), non-dietary oral, inhalation, and dermal routes. Residues of concern for sulfuryl fluoride are sulfuryl fluoride, *per se*, and fluoride anion (also referred to as "fluoride" in this document). This assessment addresses the human health risk associated with sulfuryl fluoride and fluoride anion. Due to the different toxicological effects elicited by these two chemicals, their risks have been assessed separately. 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, other uses of sulfuryl fluoride, and use of cryolite 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 conservative market share estimates. Additionally, we assumed that commodities might be serially fumigated, first as part of a post-harvest 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 a 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 2% 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. Target MOEs are 100 for short- and intermediate-term exposures, and 300 for long-term exposures.

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

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

U.S. Population	0.114	mg/kg/day
Infants (< 1 year old)	0.571	mg/kg/day
Children 1-2 years old	0.308	mg/kg/day
Children 3-5 years old	0.182	mg/kg/day
Children 6-12 years old	0.100	mg/kg/day
Youth 13-19 years old	0.133	mg/kg/day
Adults 20+ years old	0.114	mg/kg/day
Females 13-49 years old	0.131	mg/kg/day

For fluoride risk assessments addressed in this document, these MCL values have been used in a manner analogous to a reference dose (RfD). In addition to the converted MCL values, HED has also used recommendations made by the National Academies of Sciences Institute of Medicine to develop risk estimates for skeletal fluorosis (Appendix II).

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

Risk estimates for individual fluoride exposure pathways are below 100% of the MCLs for the general U.S. population and all population subgroups, including those of infants and children. When all quantified dietary and non-dietary exposure pathways are combined, risk estimates range from 23 to 43% of the MCL. These aggregate risk estimates are below HED's level of concern for all population subgroups. HED believes that the assessment is sufficiently conservative to ensure that it does not underestimate actual fluoride exposures experienced by members of the U.S. population. HED further notes that the fluoride exposures due to the uses of sulfuryl fluoride, the primary subject of this petition, are minuscule in comparison to exposures from water, toothpaste, and background residues already occurring in foods.

Deficiencies in the sulfuryl fluoride data are noted in Section 8 and HED's recommended tolerance levels are summarized in Table 8.1. HED notes that the Office of Water, via the National Academy of Sciences, is reevaluating the available information regarding fluoride. Furthermore, HED's recommendations involving the method for fluoride may impact tolerance

levels. Because of these issues, HED is recommending that these tolerances be time-limited and that OPP reexamine this risk assessment once the Office of Water has completed its review.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Sulfuryl fluoride (SO_2F_2) is a fumigant that is being proposed as a methyl bromide replacement for the post-harvest control of pests in stored commodities and grain processing facilities. Sulfuryl fluoride is a gas at standard temperature and pressure. It has a melting point of -136°C, a boiling point of -55°C, and a vapor pressure of 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
-------- (inhalation study)	2-Week inhalation toxicity, rats 0, 100, 300, 600 ppm (0/0, 83/89, 249/267, 498/534 mg/kg/day) (M/F)	**NOAEL**: 83/89 mg/kg/day (M/F) **LOAEL**: 249/267 mg/kg/day (M/F): M&F = slightly increased kidney weights, minimal histopathology in kidney. At 498/534 mg/kg/day (M/F): M&F = high mortality, decreased body weights, severe histopathology in kidney, gross and histopathology in many tissues/organs (secondary to kidney effects); severe inflammation of respiratory tissues in 1 survivor. No treatment-related neurotoxicity.
-------- (inhalation study)	2-Week inhalation toxicity, dogs 0, 30, 100, 300 ppm (0/0, 7.9/8.0, 26/27, 79/80 mg/kg/day) (M/F)	**NOAEL**: 26/27 mg/kg/day (M/F) **LOAEL**: 79/80 mg/kg/day (M/F): M&F = intermittant tremors and tetany during exposures, minimal inflammatory changes in upper respiratory tract, decreased body weight (F only). Note–increased serum fluoride at ≥26/27 mg/kg/day.
-------- (inhalation study)	2-Week inhalation toxicity, rabbits 0, 100, 300, 600 ppm (0/0, 30/30, 90/90, 180/180 mg/kg/day) (M/F)	**NOAEL**: 30/30 mg/kg/day (M/F) **LOAEL**: 90/90 mg/kg/day (M/F): M&F = malacia (necrosis) in cerebrum, vacuolation of cerebrum, moderate inflammation of respiratory tissues. At 180/180 mg/kg/day (M/F): M&F = convulsions, hyperactivity, malacia (necrosis) in cerebrum, vacuolation of cerebrum, moderate inflammation of respiratory tissues.
(870.3100) (inhalation study)	90-Day inhalation toxicity, rats 0, 30, 100, 300 ppm (0/0, 24/25, 80/83, 240/250 mg/kg/day) (M/F)	**NOAEL**: 24/25 mg/kg/day (M/F) **LOAEL**: 80/83 mg/kg/day (M/F): M&F = dental fluorosis. At 240/250 mg/kg/day (M/F): M&F = vacuolation of caudate-putamen nucleus and white fiber tracts of the internal capsule of the brain, decreased body weight, inflammation of nasal passages, alveolar histiocytosis; slight hyperplasia of renal collecting ducts (F only).
(870.3100) (inhalation study)	90-Day inhalation toxicity, mice 0, 10, 30, 100 ppm (0/0, 12.5/12.1, 38/36, 125/121 mg/kg/day) (M/F)	**NOAEL**: 38/36 mg/kg/day (M/F) **LOAEL**: 125/121 mg/kg/day (M/F): M&F = microscoic lesions in caudate-putamen nucleus and external capsule, decreased body weight, decreased body weight gain, follicular cell hypertrophy in thyroid. Note–increased serum fluoride at ≥38/36 mg/kg/day.
(870.3150) (inhalation study)	90-Day inhalation toxicity, dogs 0, 30, 100, 200 ppm (0/0, 7.5/7.6, 25/26, 50/51 mg/kg/day) (M/F)	**NOAEL**: 25/26 mg/kg/day (M/F) **LOAEL**: 50/51 mg/kg/day (M/F): M&F = slight histopathology of the caudate nucleus of the basal ganglia, decreaed bodyweight, decreased body weight gain, transient neurological signs (lateral recumbancy, tremors, incoordination, salivation, tetany, inactivity) starting at day 19 in 1 M.
(870.3150) (inhalation study)	90-Day inhalation toxicity, rabbits 0, 30, 100, 600/300* ppm (0/0, 8.6/8.5, 29/28, 86/85 mg/kg/day) (M/F)	**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.

Table 3.1.2. Toxicity Profile of Technical Grade Sulfuryl Fluoride (99.8% active ingredient)		
Guideline No.	Study Type	Results
	* 600 ppm reduced to 300 ppm after 9 exposures due to convulsions and hind leg paralysis .	Note–increased serum fluoride at all dose levels (≥8.6/8.5 mg/kg/day).
(870.3700) (inhalation study)	Developmental toxicity inhalation study, rats 0, 25, 75, 225 ppm (0, 27, 81, 243 mg/kg/day)(F)	**Maternal NOAEL**: 243 mg/kg/day (F): highest dose tested. **Maternal LOAEL**: >243 mg/kg/day (F). Note-significant maternal toxicity observed in range-finding study at 300 ppm. **Developmental NOAEL**: 243 mg/kg/day (F): highest dose tested. **Developmental LOAEL**: >243 mg/kg/day (F)
(870.3700) (inhalation study)	Developmental toxicity inhalation study , rabbits 0, 25, 75, 225 ppm (0, 9.5, 29, 86 mg/kg/day)(F)	**Maternal NOAEL**: 29 mg/kg/day (F) **Maternal LOAEL**: 86 mg/kg/day (F): F = decreased body weight and decreased body weight gain during treatment. Note-significant maternal toxicity observed in range-finding study at 300 ppm. **Developmental NOAEL**: 29 mg/kg/day (F) **Developmental LOAEL**: 86 mg/kg/day (F): F = decreased fetal body weight, decreased crown-rump length, possibly incresed fetal liver pathology (pale liver).
(870.3800) (inhalation study)	2-Generation reproduction inhalation study, rats 0, 5, 20, 150 ppm (0/0, 3.6/3.6, 14/14, 108/108 mg/kg/day) (M/F)	**Parental NOAEL**: 3.6/3.6 mg/kg/day (M/F) **Parental LOAEL**: 14/14 mg/kg/day (M/F): M&F = pale foci in lungs, increased alveolar macrophages in lungs. At 108/108 mg/kg/day (M/F): M&F = vacuolation of caudate putamen tracts in brain, decreased body weight, histopathology in lungs, dental fluorosis. **Offspring NOAEL**: 14/14 mg/kg/day (M/F) **Offspring LOAEL**: 108/108 (M/F): Decreased pup weights in F1 and F2 generations (probably secondary to maternal body weight loss).
870.41	Chronic toxicity, rats	See (870.4300)
(870.4100) (inhalation study)	1-Year chronic inhalation toxicity, dogs 0, 20, 80, 200 ppm (0/0, 5.0/5.1, 20/20, 50/51 mg/kg/day) (M/F)	**NOAEL**: 5.0/5.1 mg/kg/day (M/F) **LOAEL**: 20/20 mg/kg/day (M/F): M&F = decreased body weight gain, increased alveolar macrophages in lungs, dental fluorosis. At 50/51 mg/kg/day (M/F): M&F = increased mortality, malacia (necrosis) in caudate nucleus of brain, follicular cell hypertrophy in thyroid, histopathology in lung.
870.42	Carcinogenicity, rats	See (870.4300)
(870.4200) (inhalation study)	18-Month carcino-genicity inhalation study, mice 0, 5, 20, 80 ppm (0/0, 5.3/6.3, 25/25, 101/101 mg/kg/day) (M/F)	**NOAEL**: 25/25 mg/kg/day (M/F) **LOAEL**: 101/101 mg/kg/day (M/F): M&F = cerebral vacuolation in brain, decreased body weight gain; follicular cell hypertrophy in thyroid (M only); increased mortality (F only), heart thrombus (F only), lung congestion (F only). Negative for carcinogenicity in M and F.
(870.4300)	2-Year combined chronic toxicity/ carcinogenicity	**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.

Table 3.1.2. Toxicity Profile of Technical Grade Sulfuryl Fluoride (99.8% active ingredient)		
Guideline No.	Study Type	Results
(inhalation study)	inhalation study, rats 0, 5, 20, 80 ppm (0/0, 3.5/3.9, 14/16, 56/62 mg/kg/day) (M/F)	**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 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).

Table 3.1.2. Toxicity Profile of Technical Grade Sulfuryl Fluoride (99.8% active ingredient)		
Guideline No.	Study Type	Results
870.7485	Metabolism and pharmacokinetics, rats	No study available. Study waived in Reregistration Eligibility Document (RED) published by EPA in 1993.
870.7600	Dermal Penetration, rats	No study available. Not required.

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

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

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

In chronic (1-2 year) inhalation studies in rats, dogs and mice, target organs were the same as in the 90-day studies. In rats, severe kidney damage caused renal failure and mortality in many animals. Additional gross and histopathological lesions in numerous organs and tissues were considered to be secondary to the primary effect on the kidneys. Other treatment-related effects in rats included effects in the brain (vacuolation of the cerebrum and thalamus/ hypothalamus) and respiratory tract (reactive hyperplasia and inflammation of the respiratory epithelium of the nasal turbinates, lung congestion, aggregates of alveolar macrophages). In dogs and mice, increased mortality, malacia and/or vacuolation in the white matter in the brain, histopathology in the lungs, and follicular cell hypertrophy in the thyroid gland were observed. Decreased body weights and body weight gains were also noted in all three species. No evidence of carcinogenicity was observed in either the combined chronic toxicity/carcinogenicity study in rats or in the 18-month carcinogenicity study in mice.

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

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

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

qualitative evidence of increased susceptibility of fetuses or pups was observed in the developmental toxicity or reproduction studies on sulfuryl fluoride.

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

In carcinogenicity studies in male and female rats and in male and female mice, sulfuryl fluoride did not demonstrate evidence of carcinogenic potential. Sulfuryl fluoride is classified as "not likely to be carcinogenic to humans" according to the July 2, 1999 EPA *Draft Proposed Guidelines for Carcinogen Risk Assessment.*

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

3.1.2 FQPA Considerations

On October 21, 2003, the HED Hazard Identification Assessment Review Committee (HIARC) met to re-evaluate the potential for increased susceptibility of infants and children from exposure to sulfuryl fluoride, as required by the Food Quality Protection Act (FQPA) of 1996,

---

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

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

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 assessments. The current dose for the short-term inhalation exposure risk assessment is the NOAEL of 30 mg/kg/day (100 ppm; 0.42 mg/L) from a 2-week inhalation toxicity study in rabbits.

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

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

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

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

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

3.1.3 Dose-Response Assessment

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

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

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

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

- A higher and more persistent level of parent test material in the body may occur following inhalation exposure as compared to an oral exposure because the parent

test material is immediately distributed throughout the circulatory system following inhalation, rather than first being directly shunted to the liver (where most metabolism occurs) as in the case of oral exposure.

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

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

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

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

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

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

The HIARC determined there is no need to quantify the inhalation risk resulting from a single residential or occupational inhalation exposure to sulfuryl fluoride. No treatment-related neurotoxic or other effects were observed in a specially designed acute neurotoxicity inhalation study (MRID 42772001) in which rats were exposed on two consecutive days for 6 hours/day to concentrations up to 300 ppm of sulfuryl fluoride (equivalent to 1.25 mg/L). Further, no appropriate endpoints resulting from a single inhalation exposure were identified in any of the available toxicity studies on sulfuryl fluoride. Therefore, no hazard attributable to a single inhalation exposure was identified and quantification of risk for single inhalation exposures was determined to be unnecessary. The HIARC noted that poisonings and fatalities have been reported in humans following inhalation exposure to sulfuryl fluoride. The severity of these effects has depended on the concentration of sulfuryl fluoride and the duration of exposure. Short-term inhalation exposure to high concentrations has caused respiratory irritation, pulmonary edema, nausea, abdominal pain, central nervous system depression, and numbness in the extremities[3]. In addition, there have been two reports of deaths of persons entering houses treated with sulfuryl fluoride (see end of section 3.1.1). As previously stated, these acute poisonings in humans, however, occurred only after label directions were grossly violated and persons were subsequently exposed to extremely high concentrations of sulfuryl fluoride.

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

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

---

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

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

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary	None UF = N/A	Not applicable	No toxicological endpoint attributable to a single exposure was identified in the available toxicology studies on sulfuryl fluoride.
Chronic Dietary (All populations)	NOAEL= 8.5 mg/kg/day UF = 3000 **Chronic RfD = 0.003** mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = **0.003** mg/kg/day	**90-Day Inhalation - Rabbit** LOAEL = 28 mg/kg/day based on vacuolation of white matter in the brain of females.
Incidental Oral (All durations)	None	Not applicable	Due to sulfuryl fluoride being a gas and pattern of use, no significant incidental oral exposure is anticipated.
Dermal (All durations)	None	Not applicable	Due to sulfuryl fluoride being a gas and pattern of use, no significant dermal exposure is anticipated. No hazard identified, therefore, no quantification is required.
Short-Term Inhalation (1 to 30 days)	Inhalation study NOAEL= **30** mg/kg/day (100 ppm; 0.42 mg/L)	**Residential** LOC for MOE = **1000** **Occupational** LOC for MOE = **100**	**2-Week Inhalation - Rabbit** LOAEL = 90 mg/kg/day (300 ppm; 1.25 mg/L) based on malacia (necrosis) and vacuolation in brain, inflammation of nasal tissues and trachea.
Intermediate-Term Inhalation (1 to 6 months)	Inhalation study NOAEL = **8.5** mg/kg/day (30 ppm; 0.13 mg/L)	**Residential** LOC for MOE = **1000** **Occupational** LOC for MOE = **100**	**90-Day Inhalation - Rabbit** LOAEL = 28 mg/kg/day (100 ppm; 0.42 mg/L) based on vacuolation of white matter in the brain of females.
Long-Term Inhalation (>6 months)	Inhalation study NOAEL = **8.5** mg/kg/day (30 ppm; 0.13 mg/L)	**Residential** LOC for MOE = **3000** **Occupational** LOC for MOE = **300**	**90-Day Inhalation - Rabbit** LOAEL = 28 mg/kg/day (100 ppm; 0.42 mg/L) based on vacuolation of white matter in the brain of females.
Cancer (oral, dermal, inhalation)	Classified as "Not likely to be carcinogenic to humans"		

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

3.1.4 Endocrine Disruption

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

3.2 Fluoride Anion

3.2.1 Hazard Profile

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

ensures public health criteria while still allowing sufficient concentration of fluoride in water to realize its beneficial effects in protecting against dental caries. The typical 100X factor used by the HED to account for inter- and intra-species variability have been removed due to the large amounts of human epidemiological data surrounding fluoride and skeletal fluorosis.

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

3.2.2 FQPA Considerations

HED has not applied an additional FQPA safety factor to the fluoride assessment. Skeletal fluorosis is an effect that requires chronic (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 converted the MCL to a mg/kg/day basis using standard water consumption estimates and body weight data from the NHANES III survey (Table 3.2.1; U.S. EPA, 2000). Body weight data from the NHANES survey were matched as closely as possible to the population subgroups addressed by the DEEM-FCID dietary exposure modelling software (See Section 4.2.3 and the dietary exposure analysis; M. Doherty, D283008, 1/13/04). Use of the NHANES data (Institute of Medicine, 1997), rather than the HED default body weights, avoids setting dose levels too high due to underestimated body weights. These doses in Table 3.2.1 were used for all risk assessment durations and pathways (oral, dermal, and inhalation) in a manner analogous to an RfD. That is, HED would have concerns about the level of estimated risk if the exposure estimates exceed 100% of the MCL.

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

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

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

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

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

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

3.2.4 Endocrine Disruption

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

4.0 EXPOSURE ASSESSMENT

4.1 Summary of 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 Season	Max. Cumulative Applic. Rate (mg·hr/L)	Aeration (hours)	Use Directions and Limitations
Fumigation of sealed food processing facilities	ProFume [62719-XXX]	1500 (ambient pressure) 200 (vacuum fumigation)	2	3000 (ambient pressure) 400 (vacuum fumigation)	24	Food commodities must be aerated for 24 hours prior to entering commerce.

The proposed label has sufficient information to allow the Agency to evaluate the residue trials in light of the proposed use patterns.

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

4.2 Dietary Exposure/Risk Pathway

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

that the tolerances being recommended by HED are appropriate. Residue chemistry data needs, including label modifications, are listed in Section 8. Provided the label changes are made, HED is recommending a conditional registration with the sulfuryl fluoride and fluoride anion time-limited tolerances summarized in Table 8.1. Details regarding the dietary analyses and residue profiles used in this assessment are provided below. HED notes that the proposed uses are intended to treat spaces and equipment and do not specifically target finished foods or their ingredients. Nevertheless, ingredients remaining in the machinery following drawdown and cleanout as well as finished products being held in treated areas may be exposed to the fumigant during treatment.

4.2.1 Residue Profile

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

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 was 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. HED notes that 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 (e.g., Taves DR. Separation of fluoride by rapid diffusion using hexamethyldisiloxane. Talanta, 1968; 15: 969-74.), using representative commodities from all crop groups and animal commodities (meat, fat, milk, eggs). Since many foods naturally contain detectable levels of fluoride, a total fluoride method may result in higher apparent residue following sulfuryl fluoride treatment than is found with the current method. Therefore, the recommendation for a total fluoride method is coupled with a recommendation for time-limited tolerances, based on the current method, as follows:

Sulfuryl fluoride:	2.0 ppm for all commodities unless otherwise listed
Fluoride:	900 ppm for powdered eggs
	70 ppm for all commodities unless otherwise listed

Prior to establishment of permanent tolerances, HED is requesting that representative residue data be submitted. Data should reflect total post-treatment fluoride residues and should be of sufficient quantity and scope to allow re-evaluation of current and requested tolerances. HED further recommends that data focus on agricultural commodities rather than finished foods.

4.2.1.5 Other Sources of Fluoride

This risk assessment includes quantitative estimates of fluoride exposure from residues in foods from the use of sulfuryl fluoride and/or cryolite, background levels in foods, and consumption of fluoride-containing water. Also addressed quantitatively are exposure from the use of fluoridated toothpaste and inhalation of fluoride from the atmosphere. These sources are addressed in Section 4.4 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

Chronic dietary risk 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. Due to the potential for serial fumigation of a commodity or ingredient, first as part of a post-harvest or grain mill fumigation and then again due to food processing facility fumigation, HED is combining dietary exposure estimates from the previous assessment with those from the current assessment. The actual probability of this occurring is likely to be very small; therefore, this assumption results in an overestimate of exposure.

Sulfuryl Fluoride. The chronic analysis for sulfuryl fluoride used average residue values from residue trials reflecting the maximum proposed use, percent market share estimates, and an estimate of the amount of yearly production that might be within the processing facility during fumigation. Based on these assumptions, the refined chronic dietary risk estimates for all population subgroups are less than 2% of the chronic population-adjusted dose (cPAD) of 0.003 mg/kg/day.

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

Population Subgroup	Chronic PAD, mg/kg/day	Estimated Exposure, mg/kg/day			Risk, % of cPAD
		Current Request	Previous Estimate	Total	
U.S. Population (total)	0.003	0.000021	0.000003	0.000024	0.8
All infants (< 1 year)	0.003	0.000097	0.000002	0.000099	3.3
Children 1-2 yrs	0.003	0.000041	0.000004	0.000045	1.5
Children 3-5 yrs	0.003	0.000045	0.000004	0.000049	1.6
Children 6-12 yrs	0.003	0.000035	0.000003	0.000038	1.3
Youth 13-19 yrs	0.003	0.000021	0.000001	0.000022	0.7
Adults 20-49 yrs	0.003	0.000015	0.000003	0.000018	0.6
Adults 50+ yrs	0.003	0.000012	0.000004	0.000016	0.5
Females 13-49 yrs	0.003	0.000015	0.000003	0.000018	0.6

The chronic analyses for fluoride are presented in Table 4.2.3.2. In addition to showing the combined dietary fluoride exposure estimate, Table 4.2.3.2 illustrates the relative contributions of the various sources to dietary fluoride exposure. Based on the assumptions used in these assessments, drinking water and background levels in food are the principal sources of

dietary exposure to fluoride. Overall, the combined dietary fluoride risk estimates are below HED's level of concern for all population subgroups.

Table 4.2.3.2. Total Chronic Exposure and Risk Estimates for Fluoride from Dietary Sources.

Population Subgroup	MCL, mg/kg/day	Dietary Fluoride Anion Exposure Estimates, mg/kg/day						Risk, % of MCL
		Current Request	Previous Sulfuryl Fluoride	Cryolite	Food	Water	Total Dietary	
U.S. Population (total)	0.114	0.0006	0.0004	0.0007	0.0068	0.0269	0.0354	31
All infants (< 1 year)	0.571	0.0002	0.0005	0.0010	0.0093	0.1424	0.1534	27
Children 1-2 yrs	0.308	0.0012	0.0013	0.0033	0.0175	0.0407	0.0640	21
Children 3-5 yrs	0.182	0.0017	0.0012	0.0021	0.0149	0.0338	0.0538	30
Children 6-12 yrs	0.100	0.0015	0.0007	0.0009	0.0094	0.0227	0.0351	35
Youth 13-19 yrs	0.133	0.0007	0.0004	0.0003	0.0062	0.0176	0.0253	19
Adults 20-49 yrs	0.114	0.0004	0.0003	0.0004	0.0057	0.0252	0.0321	28
Adults 50+ yrs	0.114	0.0003	0.0003	0.0005	0.0050	0.0256	0.0318	28
Females 13-49 yrs	0.131	0.0005	0.0003	0.0005	0.0054	0.0238	0.0305	23

4.2.4 Cancer Dietary

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

4.3 Water Exposure/Risk Pathway

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).

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	Body Weight, kg	Standard Respiration, m^3/day	Estimated Exposure, mg/kg/day	
			Toothpaste	Air
U.S. Population (total)	70	13.3	0.0043	0.0006

All infants (< 1 year)	7	4.5	0.0429	0.0019
Children 1-2 yrs	13	8.7	0.0231	0.0020
Children 3-5 yrs	22	8.7	0.0136	0.0012
Children 6-12 yrs	40	8.7	0.0075	0.0007
Youth 13-19 yrs	60	13.3	0.0050	0.0007
Adults 20-49 yrs	70	13.3	0.0043	0.0006
Adults 50+ yrs	70	13.3	0.0043	0.0006
Females 13-49 yrs	61	11.3	0.0049	0.0006

4.4.1 Other

HED has not conducted a quantitative assessment for persons living near fumigation activities (i.e., bystanders). Due to the rapid dissipation of sulfuryl fluoride, the infrequency of fumigations of grain processing facilities, and the general location of such facilities away from residential areas, HED is not concerned with potential bystander exposures associated with fumigation of grain processing facilities. For tree nut and dried fruit fumigations, 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 facilites, 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 is requesting 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. The potential non-dietary exposure pathway 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 2% of the cPAD for the U.S. population and all population subgroups (Table 4.2.3). These risk estimates are well below HED's level of concern.

Fluoride. In estimating aggregate risks for skeletal fluorosis, HED has examined potential dietary and non-dietary exposure pathways. Based on the toxicology of fluoride and the behaviors associated with fluoride exposure (e.g., brushing teeth), HED has examined only chronic aggregate exposure scenarios. As discussed in Section 4.2.2.3, moderately conservative estimates of dietary exposure were quantified based on fluoride residues coming from the pesticidal uses of sulfuryl fluoride and cryolite, from background residue levels in food, and the

fluoride content of drinking water. Non-dietary sources for which sufficient information was available to quantitate exposure were toothpaste and air. As noted in Section 4.4, the exposure estimates from these sources are considered to be conservative. Aggregate exposures are summarized in Table 5.1 for the repesentative population subgroups addressed in the chronic exposure module of the DEEM-FCID software (the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old) . The aggregate risks for those populations are also presented in Table 5.1 as a percentage of the MCL. The aggregate risk estimates for the representative subgroups in DEEM-FCID range from 23% (youth 13-19 years of age) to 43% (children 6-12 years of age) of the MCL. The aggregate risk estimates for the U.S. population and all subgroups, including those of infants and children, are below HED's level of concern. HED notes that based on the assumptions in these assessments, sulfuryl fluoride is an insignificant source of fluoride relative to that coming from water, toothpaste, and background residues in foods. Risk estimates 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	MCL, mg/kg/day	Estimated Fluoride Exposure by Source, mg/kg/day							Risk, % of MCL
		Total from Sulfuryl Fluoride	From Cryolite	Back-ground Food	Water	Tooth-paste	Air	Total	
U.S. Population (total)	0.114	0.0010	0.0007	0.0068	0.0269	0.0043	0.0006	0.0403	35
All infants (< 1 year)	0.571	0.0007	0.0010	0.0093	0.1424	0.0429	0.0019	0.1982	35
Children 1-2 yrs	0.308	0.0025	0.0033	0.0175	0.0407	0.0231	0.0020	0.0890	29
Children 3-5 yrs	0.182	0.0029	0.0021	0.0149	0.0338	0.0136	0.0012	0.0686	38
Children 6-12 yrs	0.100	0.0022	0.0009	0.0094	0.0227	0.0075	0.0007	0.0434	43
Youth 13-19 yrs	0.133	0.0011	0.0003	0.0062	0.0176	0.0050	0.0007	0.0310	23
Adults 20-49 yrs	0.114	0.0007	0.0004	0.0057	0.0252	0.0043	0.0006	0.0369	32
Adults 50+ yrs	0.114	0.0006	0.0005	0.0050	0.0256	0.0043	0.0006	0.0367	32
Females 13-49 yrs	0.131	0.0008	0.0005	0.0054	0.0238	0.0049	0.0006	0.0360	27

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

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. Data 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 petition and recommends that the petitioner investigate and, if necessary, validate a total fluoride method (e.g., Taves DR. Separation of fluoride by rapid diffusion using hexamethyldisiloxane. Talanta, 1968; 15: 969-74.), using representative commodities from all crop groups and animal commodities (meat, fat, milk, eggs). Since many foods naturally contain detectable levels of fluoride, a total fluoride method may result in higher apparent residue following sulfuryl fluoride treatment than is found with the current method. Prior to establishment of permanent tolerances, HED is requesting that representative residue data be submitted. Data should reflect total post-treatment fluoride residues and should be of sufficient quantity and scope to allow re-evaluation of current and requested tolerances. HED further recommends that data focus on agricultural commodities rather than finished foods. If this increase is significant, higher tolerances may be required.

Occupational and Residential Exposoure

- 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)
Sulfuryl Fluoride			
Flavorings, leavening agents (except yeast), dry garlic, dry onion, dry pepper, baking powder, baking soda	0.05	None	–
Other herbs, spices, chili pepper	0.3	None	–
Salt, sugars, high-fructose corn syrup	0.02	None	–
Peanuts	0.2	None	–
Coffee, cocoa beans	0.8	None	–
Dried legume vegetables (beans, peas, soybean, etc.)	0.02	None	–
Powdered milk, powdered cheese	1.5	None	–
All other processed foods	1.2	None	–
All commodities unless otherwise listed	None	2.0	–
Fluoride			
Flavorings, leavening agents (except yeast), dry garlic, dry onion, dry pepper, baking powder, baking soda	8	None	–
Other herbs, spices, chili pepper	70	None	–
Salt, sugars, high-fructose corn syrup	2	None	–
Peanuts	13	None	–
Coffee, cocoa beans	12	None	–
Dried legume vegetables (beans, peas, soybean, etc.)	6	None	–
Powdered milk, powdered cheese	3	None	–
All other processed foods	70	None	–
Eggs, powdered	None	900	–
All commodities unless otherwise listed	None	70	–

9.0 References

OPP Documents

Baetcke, K., Blondell, J., Burnam, W., Dellarco, V. L., Donohue, J., and Hill, R. 11/18/2003. A Preliminary Evaluation of Articles Related to Fluoride Cited by the Fluoride Action Network (FAN) as Objections to the Sulfruryl Fluoride Pesticide Tolerance Rule.

Daiss, B. D274960. 5/15/01. Residential Risk from Dissipation of Sulfuryl Fluoride after Structural Fumigation (62719-EUP-45).

Doherty, M. D309015. 10/12/04. PP#1F06312 – Sulfuryl Fluoride. Section 3 Registration for the Post-harvest Fumigation of Stored Cereal Grains, Dried Fruits, and Tree Nuts, and Fumigation of Grain Milling Establishments. Corrected Summary of Analytical Chemistry and Residue Data.

Doherty, M. D309014. 10/12/04. Corrected Chronic Dietary Exposure Assessments for Sulfuryl Fluoride and Fluoride Anion, Addressing the Section 3 Registration of Sulfuryl Fluoride on Stored Cereal Grains, Grain Processing Facilities, Dried Fruits, and Tree Nuts. PP# 1F6312.

Doherty, M. D317730. 6/2/05. Sulfuryl Fluoride. Evaluation of the Proposed Fumigation of Food Processing Establishments. Summary of Analytical Chemistry and Residue Data. Petition Number 3F6573.

Doherty, M. D317731. 6/2/05. Sulfuryl Fluoride and Fluoride Chronic Dietary Exposure Assessments for the Section 3 Registration of Sulfuryl Fluoride as a Fumigant for Food Processing Facilities.

Kidwell, J. TXR No. 0052208. 10/31/03. Sulfuryl Fluoride - Second Report of the Hazard Identification Assessment Review Committee.

Open Literature

CDC. 2001. Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States. Centers for Disease Control and Prevention, Recommendations and Reports. August 17, 2001 / 50(RR14);1-42.

Institute of Medicine. 1997. Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride. Institute of Medicine. National Academy of Sciences. National Academy Press. Washington, DC.

IRIS Database. Fluorine (soluble fluoride). Entry No. 0053. Search Date: 12/9/03 http://www.epa.gov/iris/subst/0053.htm

Medical Research Council. 2002. *Water fluoridation and health*. Medical Research Council, London.

National Research Council. 1993. *Health Effects of Ingested Fluoride*. National Academy Press, Washington D.C.

NHS CRD. 2000. A Systematic Review of Public Water Fluoridation (CRD Report No. 18). NHS Centre for Review and Dissemination, University of York, York, UK. Available at http://www.york.ac.uk/inst/crd/fluorid.htm

U.S. Dept. of Health and Human Services, Agency for Toxic Substances and Disease Registry. 2002. *Toxicological Profile for Fluorides*. U.S. Government. Printing Office.

World Health Organization. 2002. *Fluorides. Environmental Health Criteria 227.* World Health Organization, Geneva.

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

Attachments:

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

Appendix II - Risk Estimates for Development of Dental Fluorosis

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. Their 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. Using the body weight data discussed in Section 4.4 and the uncertainty factor of 1gives the cPAD values in Table I-1, below. 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.

Table I-1. Derivation of Skeletal Fluorosis cPAD Based on Analysis by the Institute of Medicine of the National Academies.

Population Subgroup	NOAEL, mg/day	Body Weight, kg	cPAD, mg/kg/day
U.S. Population (total)	10	70	0.143
Children 6-12 yrs	10	40	0.250
Youth 13-19 yrs	10	60	0.167
Adults 20-49 yrs	10	70	0.143
Adults 50+ yrs	10	70	0.143
Females 13-49 yrs	10	61	0.164

When the dietary and non-dietary exposure estimates summarized in Section 5 are compared to the IOM-based cPAD, the risk estimates are slightly less (ranging from 17 to 28% cPAD; Table I-2) than those that are based on the MCL (27 to 43% MCL; 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	cPAD, mg/kg/day	Estimated Fluoride Exposure by Source, mg/kg/day							Risk, % of cPAD
		Total from Sulfuryl Fluoride	From Cryolite	Back-ground Food	Water	Tooth-paste	Air	Total	
U.S. Population (total)	0.143	0.0010	0.0007	0.0068	0.0269	0.0043	0.0006	0.0403	28
Children 6-12 yrs	0.250	0.0022	0.0009	0.0094	0.0227	0.0075	0.0007	0.0434	17
Youth 13-19 yrs	0.167	0.0011	0.0003	0.0062	0.0176	0.0050	0.0007	0.0310	19
Adults 20-49 yrs	0.143	0.0007	0.0004	0.0057	0.0252	0.0043	0.0006	0.0369	26
Adults 50+ yrs	0.143	0.0006	0.0005	0.0050	0.0256	0.0043	0.0006	0.0367	26

Females 13-49 yrs	0.164	0.0008	0.0005	0.0054	0.0238	0.0049	0.0006	0.0360	22

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/kg/day basis in Table II-1.

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

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

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

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

HED has not estimated risks for dental fluorosis for population subgroups greater than 12 years of age. Dental fluorosis is an effect that occurs prior to eruption of the teeth, at the time that the tooth enamel is being formed. In evaluating dental fluorosis, the National Academy of Sciences and the Office of Water use age cutoffs of 8 years and 9 years, respectively, as ages above which it is not appropriate to assess this effect. In this assessment, HED has used a maximum age of 12 years due to the population grouping of the exposure 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 MCL and the Tolerable Upper Intake values provides a range of risk estimates for each population subgroup. Both estimates should be considered when looking at the potential for fluoride exposures to result in dental fluorosis.

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

Population Subgroup	Aggregate Exposure, mg/kg/day (without toothpaste)	SMCL, mg/kg/day	% of SMCL (without toothpaste)	Tolerable Upper Intake, mg/kg/day*	% of Tolerable Upper Intake (without toothpaste)
All infants (< 1 year)	0.1982 (0.1553)	0.286	69 (54)	0.10	198 (155)
Children 1-2 yrs	0.0890 (0.0659)	0.154	57 (43)	0.07	127 (94)
Children 3-5 yrs	0.0686	0.091	75	0.06	114
Children 6-12 yrs	0.0434	0.050	87	0.05	87

Based on the MCL values, risks do not exceed HED's level of concern for any of the assessed population subgroups (risk estimates range from 57 to 84% of the MCL). When risk estimates are based on the Institute of Medicine's Tolerable Upper Intake values, the values indicate that there may be concern for infants, children 1-2 years old, and children 3-5 years old. The exposure estimates for the "all infants" and "children 1-2 years" groups include exposure from fluoridated toothpaste. Provided parents follow the recommendations of the American Academy of Pediatric Dentistry that fluoridated toothpaste not be introduced into oral hygiene until children are at a minimum of 2 years old, the aggregate exposure estimates presented in Table 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 that occurs in the infant population subgroup will be to their deciduous teeth[4]. Therefore, the risk estimate of 198% (155% without toothpaste) of the Tolerable Upper Intake does not pertain to fluorosis of the permanent teeth. Given the assumptions in the exposure assessments and the range of numbers presented in Table II-2, HED does not believe that these risk estimates warrant critical concern regarding development of objectionable dental fluorosis.

[4] 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.