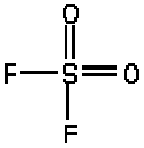
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
SULFURYL FLUORIDE
2699-79-8

SO_2F_2



INTERIM

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
SULFURYL FLUORIDE
2699-79-8

INTERIM

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL

TABLE OF CONTENTS

PREFACE 3
LIST OF TABLES 6
EXECUTIVE SUMMARY 7
1. INTRODUCTION 8
2. HUMAN TOXICITY DATA 9
2.1. Acute Lethality 9
2.1.1. Case Reports 9
2.2. Nonlethal Toxicity 10
2.2.1. Odor Threshold/Odor Awareness 10
2.2.2. Case Reports 10
2.2.3. Epidemiologic Studies 10
2.3. Neurotoxicity 10
2.4. Developmental/Reproductive Toxicity 11
2.5. Genotoxicity 11
2.6. Carcinogenicity 11
2.7. Summary 11
3. ANIMAL TOXICITY DATA 11
3.1. Acute Lethality 11
3.1.1. Rats 11
3.1.2. Mice 13
3.2. Nonlethal Toxicity 14
3.2.1. Rats 14
3.2.2. Mice 14
3.3. Repeat-Dose Studies 15
3.3.1. Dogs 15
3.3.2. Rats 15
3.3.3. Mice 16
3.3.4. Rabbits 16
3.4. Developmental/Reproductive Toxicity 17
3.5. Genotoxicity 18
3.7. Summary 19
4. SPECIAL CONSIDERATIONS 19
4.1. Metabolism and Disposition 19
4.2. Mechanism of Toxicity 20
4.3. Structure Activity Relationships 20
4.4. Other Relevant Information 20
4.4.1. Species Variability 20
4.4.2. Susceptible Populations 20
4.4.3. Concentration-Exposure Duration Relationship 21
4.4.4. Concurrent Exposure Issues 21
5. DATA ANALYSIS FOR AEGL-1 21
5.1. Summary of Human Data Relevant to AEGL-1 21
5.2. Summary of Animal Data Relevant to AEGL-1 21
5.3. Derivation of AEGL-1 21
6. DATA ANALYSIS FOR AEGL-2 21
6.1. Summary of Human Data Relevant to AEGL-2 21
6.2. Summary of Animal Data Relevant to AEGL-2 21
6.3. Derivation of AEGL-2 22
7. DATA ANALYSIS FOR AEGL-3 22
7.1. Summary of Human Data Relevant to AEGL-3 22
7.2. Summary of Animal Data Relevant to AEGL-3 22

7.3. Derivation of AEGL-3 22
8. SUMMARY OF AEGLS 23
8.1. AEGL Values and Toxicity Endpoints 23
8.2. Comparison with Other Standards and Guidelines 24
8.3. Data Adequacy and Research 25
9. REFERENCES 26
APPENDIX A: DERIVATION OF AEGL VALUES 29
APPENDIX B: TIME-SCALING CALCULATIONS 34
APPENDIX C: DERIVATION SUMMARY FOR SULFURYL FLUORIDE AEGLS 36
APPENDIX E: CATEGORY PLOT FOR SULFURYL FLUORIDE 40

LIST OF TABLES

TABLE 1. Summary of AEGL Values for Sulfuryl Fluoride 8
TABLE 2. Sulfuryl Fluoride Chemical and Physical Properties 9
TABLE 3. Data from Rats Exposed to Sulfuryl Fluoride (Torkelson 1959) 12
TABLE 4. Summary of Acute Inhalation Data in Laboratory Animals 15
TABLE 5. Summary of Repeat-Dose Data in Laboratory Animals 17
TABLE 6. AEGL-1 Values for Sulfuryl Fluoride 21
TABLE 7. AEGL-2 Values for Sulfuryl Fluoride 22
TABLE 8. AEGL-3 Values for Sulfuryl Fluoride 23
TABLE 9. Summary of AEGL Values 24
TABLE 10. Extant Standards and Guidelines for Sulfuryl Fluoride 24

EXECUTIVE SUMMARY

Sulfuryl fluoride, also known as Vikane or ProFume, is a restricted use broad spectrum insecticide and rodenticide fumigant created by heating barium difluorosulfite or from silver fluoride and sulfur dioxide. It is also used in organic drug and dye synthesis. It is used to control infestations of pests in residential structures, processed-food and pet food facilities, warehouses, and shipping containers. It is non corrosive and not very reactive. It is hydrolyzed by sodium hydroxide but not water. It breaks down into sulfate and fluoride anions. It is a gas at ambient temperatures, but marketed as a liquefied gas in pressurized steel cylinders.

Exposure-response data from a rat study were used to derive acute exposure guideline level (AEGL) values for sulfuryl fluoride due to lack of quantitative data from human case reports. The AEGL values for the exposure periods of concern are scaled from the experimental exposure duration using exponential scaling ($C^n \times t = k$, where C= exposure concentration, t= exposure duration, and k= a constant). Data are unavailable to empirically derive a scaling factor (n) for sulfuryl fluoride. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Temporal scaling was performed using n = 3, when extrapolating to shorter time points and n = 1 when extrapolating to longer time points for AEGL values (NRC 2001). The 30-minute AEGL value was adopted for the 10-minute value according to the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001).

Data are not available from human studies to derive AEGL-1 values. The data available from animal studies are not sufficient to derive AEGL-1 values. Therefore, AEGL-1 values are not recommended.

In the absence of empirical data and the presence of a steep dose response relationship, the AEGL-2 values were derived by dividing the AEGL-3 values by 3 according to AEGL guidelines (NRC 2001). In 4-hr acute studies with the most sensitive species tested (mouse), no signs of toxicity were found at 404 or 596 ppm, but mortality occurred at 603 (100%) and 692 (90%), respectively, in two different strains of mouse (Nitschke and Lomax 1989; Nitschke and Quast 1990). Rats exposed for 4-hr to 790 ppm had cyanosis, and mortality occurred at the next highest concentration, 1000 ppm-10% male, 100% female (Miller et al. 1980).

The highest concentration with no mortality (404 ppm, 4-hr exposure in rats) was identified as the basis of the AEGL-3 derivation (Nitschke and Lomax 1989). Mice exposed to 603 ppm for four hours experienced 100% mortality within 5 days of exposure. A total uncertainty factor of 10 was applied to account for interspecies extrapolation (1) and intraspecies variability (10). A 1 was applied for interspecies extrapolation because the most sensitive species was used (mouse) and sulfuryl fluoride has a steep concentration-response curve. The mouse was considered the most sensitive species because mortality occurred at 603 ppm in after a 4-hr exposure vs. 1000 pppm in rat for the same duration (Nitschke and Lomax 1989; Nitschke and Quast 1990; Miller et al. 1980). In longer studies rats and mice were exposed to the same concentrations 30, 100, or 300 ppm for 2 weeks (mice) and 13 weeks (rats), and 90% of the mice exposed to 300 ppm died, but no mortality was experienced by the rats. The rats had minimal brain vacuolation at 300 ppm and mice exposed to 100 ppm showed the same effect (Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002). In acute studies, no signs of toxicity were found

at 404 or 596 ppm, but mortality occurred at 603 (100%) and 692 (90%), respectively, in two different strains of mouse (Nitschke and Lomax 1989; Nitschke and Quast 1990). The use of a factor of 1 is also supported by the results of the acute and repeat-dose studies. Both rats and mice experienced tremors or convulsions after an acute exposure to sulfuryl fluoride (Miller et al. 1980, Nitschke et al. 1986; Nitschke and Lomax 1989; Nitschke and Quast 1990). Dogs, rats, mice, and rabbits exposed to 100-300 ppm sulfuryl fluoride from 2 weeks to 1 year showed central nervous system effects including tremors and lethargy and histological evaluation showed evidence of brain vacuolization in the same area of the brain of all the species (Nitschke et al. 1992; Quast et al. 1993b; Eisenbrandt et al. 1993; Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002; Nitschke and Quast 1993). A 10 was applied for intraspecies extrapolation because only qualitative human data were available, and it is unknown if sulfuryl fluoride would elicit the same response in humans as that observed in animals.

The calculated values are listed in the table below.

TABLE 1. Summary of AEGL Values for Sulfuryl Fluoride

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Notable Discomfort)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	27 ppm (110 mg/m^3)	27 ppm (110 mg/m^3)	21 ppm (88 mg/m^3)	13 ppm (54 mg/m^3)	6.7 ppm (28 mg/m^3)	Reduction of AEGL-3 for steep dose response relationship (NRC 2001)
AEGL-3 (Lethal)	81 ppm (340 mg/m^3)	81 ppm (340 mg/m^3)	64 ppm (270 mg/m^3)	40 ppm (170 mg/m^3)	20 ppm (83 mg/m^3)	Highest concentration with no lethality (Nitschke and Lomax 1989)

NR= Not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

1. INTRODUCTION

Sulfuryl fluoride, also known as Vikane or ProFume, is a restricted use broad spectrum insecticide and rodenticide fumigant created by heating barium difluorosulfite or from silver fluoride and sulfur dioxide. It is also used in organic drug and dye synthesis. It is used to control infestations of pests in residential structures, processed-food and pet food facilities, warehouses, and shipping containers. It is non corrosive and not very reactive. It is hydrolyzed by sodium hydroxide but not water. It breaks down into sulfate and fluoride anions. It is a gas at ambient temperatures, but marketed as a liquefied gas in pressurized steel cylinders. Chloropicrin is added to the 99+% (a.i.) sulfuryl fluoride (Vikane) as a warning agent to give it an irritating odor. Vikane is used in dwellings buildings, construction materials, furnishings, and vehicles. ProFume, a methyl bromide replacement, is used for postharvest fumigation for a variety of food commodities and has no warning agent. It is a central nervous system depressant and pulmonary irritant in animals. The chemical and physical properties of sulfuryl fluoride are listed in Table 2.

TABLE 2. Sulfuryl Fluoride Chemical and Physical Properties

Parameter	Value	References
Synonyms	Sulfonyl fluoride; sulfur dioxide difluoride; sulfur fluoride oxide, sulfuric oxyfluoride, Vikane, fluorure de sulfuryle, fluoro de sulfurilo, sulphuryl fluoride, Vikane fumigant, sulfuryl difluoride, ProFume	HSDB 2005
Chemical formula	F_2O_2S	HSDB 2005
Molecular weight	102.1	HSDB 2005
CAS Reg. No.	2699-79-8	HSDB 2005
Physical state	Colorless gas	HSDB 2005
Solubility in water	750 mg/kg @ 25ºC	HSDB 2005
Vapor pressure	12,750 mmHg @ 21.1ºC	HSDB 2005
Vapor density (air =1)	3.5	HSDB 2005
Melting point	-135.82ºC	HSDB 2005
Boiling point	-55.38ºC	HSDB 2005
Flammability limits	None; nonflammable gas	ACGIH 1991
Conversion factors	1 ppm = 4.17 mg/m^3 1 mg/m^3 = 0.2392 ppm	NIOSH 2005

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

Scheuerman (1986) reported three cases of fatal sulfuryl fluoride exposure. A 29-yr old male entered an apartment complex that had been treated with 50 pounds of sulfuryl fluoride 6 hr post fumigation. He was found dead the following morning and autopsy revealed congested larynx, trachea, and bronchi. Pulmonary congestion and edema were also found. A 22-yr old pest control worker was found dead next to an open container of sulfuryl fluoride. The empty container had held 70 pounds of the gas. Autopsy found pulmonary congestion and brain edema. A 19-yr old female entered her residence the afternoon of the fumigation to collect personal items and lost consciousness. She was rescued and taken to the hospital. Her symptoms included coughing, chest discomfort, and hypotension. Six hours post exposure she became hyperexcitable and began hyperventilating and drooling. She developed severe pulmonary edema, tetany of the hands and feet, cardiac dysrhythmias, and died shortly after.

In 1986, a home in Virginia was fumigated with 250 pounds of sulfuryl fluoride (Nuckolls et al. 1987). The owners, an elderly couple, were allowed to enter the home approximately 5-8 hours post ventilation. The following day, the wife experienced weakness, nausea, and repeated vomiting while her husband suffered from dyspnea and restlessness. The husband's dyspnea became severe the next day and, he experienced a generalized seizure and cardiopulmonary arrest that led to death. Three days later, the wife still suffered from weakness and had chills, dyspnea, and anorexia. Examination at the hospital revealed hypoxemia and diffuse pulmonary infiltrates. She died the following day. It was later revealed that the exterminators failed to measure the air concentration of sulfuryl fluoride before allowing the couple to re-enter the home.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

Sulfuryl fluoride is an odorless gas (HSDB 2005).

2.2.2. Case Reports

Taxay (1966) reported the symptoms of a male worker who had breathed Vikane for 4 hr in a place with limited ventilation. He also breathed chloropicrin, the irritant used as a warning of exposure, mixed with the Vikane. His symptoms included nausea, vomiting, crampy abdominal pain, and pruritus. He was admitted to the hospital with normal vital signs, reddened conjunctivae and pharyngeal and nasal mucosa, and diffuse rhonchi. He was discharged 4 days later. The concentration of Vikane in the air several hours after his exposure was found to be 5 ppm.

2.2.3. Epidemiologic Studies

Contardi and Lambesis (1994) evaluated respiratory exposures of workers using sulfuryl fluoride during typical work days. Participants (17 male workers in California and Florida) had a training session in which the purposes of the study and health/safety issues were discussed and Informed Consent forms were signed. The activities that the workers were involved in included tarping a structure, introducing the fumigant, and removing the tarp and clearing the structure for re-entry. Personal air samples were collected for the full shift and for short term tasks. For full shift exposures, the range was from non-detectable to 2.3 ppm. These values take into account the use of self contained breathing apparatus (SCBA) for specific tasks. Short term exposures ranged from 0.5 to 2 ppm for specific tasks not requiring SCBA (fumigant introduction, seam opening, tarp folding, etc.). For specific tasks requiring SCBA, exposures averaged 0.07 ppm.

2.3. Neurotoxicity

Calvert et al. (1998) studied the health effects associated with sulfuryl fluoride fumigation work. The targeted workers were those who physically applied the fumigant and those who raised and dismantled the structural tarp coverings. The participants (123 males) had been exposed to methyl bromide and sulfuryl fluoride, except 11 who had only been exposed to sulfuryl fluoride. The median lifetime duration of sulfuryl fluoride was 2.85 years (range-0.11-20.5 yrs). Neurological function, neurobehavioral, visual function, and olfactory function tests were conducted on the participants and a reference group (120 males). In the neuron-function tests, the fumigants had significantly slower nerve conduction velocity of the median motor nerve in the forearm. They also had significantly worse performance on the pattern memory neurobehavioral test, especially the workers exposed to high levels of sulfuryl fluoride during the preceding year. High exposure was defined as having used sulfuryl fluoride on 50% or more jobs during the preceding year. The high sulfuryl fluoride exposed workers also had lower performance on the olfactory function tests. The authors suggested that exposure to occupational sulfuryl fluoride may be associated with central nervous system toxicity including cognitive and olfactory functions.

2.4. Developmental/Reproductive Toxicity

No data regarding developmental/reproductive toxicity in humans were located.

2.5. Genotoxicity

No data regarding genotoxicity in humans were located.

2.6. Carcinogenicity

The US EPA has not classified sulfuryl fluoride for carcinogenicity. The International Agency for Research on Cancer has not evaluated sulfuryl fluoride for carcinogenicity.

2.7. Summary

Sulfuryl fluoride is a fumigant with no odor. Human exposure mainly occurs during use or when entering a structure has been fumigated with the gas. The effects of lethal exposure include pulmonary congestion and edema, dyspnea, and cardiac arrest. A case report listed respiratory and ocular irritation as well as nervous system effects following a nonlethal exposure. Studies of workers regularly exposed to sulfuryl fluoride found that they are exposed to levels less than 2 ppm.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Torkelson (1959) reported on the exposure of male and females rats to 1000, 2000, 4000, 8000, or 15000 ppm sulfuryl fluoride (>99% pure). Exposure duration ranged from 6 min to 6 hr. The males (18-20/group) and females (10/group) were placed in a 160 L glass and Monel chamber. Chamber atmosphere was monitored by a Recording IR with a 4.5 m cell and were within 10% of calculated levels. Chamber atmosphere was analyzed by the Thorium-Alizarin method during the male rat exposure to 1000 ppm. Exposure at the highest concentration for 12 minutes caused the rats to be drowsy, have labored breathing, and tremors when removed. Forty-eight minutes post exposure, convulsions began and the rats died after 3 hours post exposure. At a shorter exposure time, 6 minutes, the rats were slow moving on removal. The male rat that died experienced convulsions before death. Rats were exposed to 8000 ppm for 30 minutes. Tremors began 8 minutes into the exposure, but the animals were able to move after 15 minutes of exposure. They all began convulsing and died in less than 2.5 hours. One male and female rat died following exposure to 8000 ppm for 12 minutes. At 4000 ppm for 60 minutes, rats were conscious but weak on removal. Half died within 2 hours, 3 overnight, and one died 4 days after exposure. Exposure to 4000 ppm for 30 minutes caused death in 5/20 males and 7/10 females. At 2000 ppm for 2 hr, the rats were drowsy at removal. Two hours post exposure, rats were sick, slow moving, and had tremors with 12/18 males and 10/10 females dying. Only one male rat died after exposure to 2000 ppm for 1 hr. Mortality was noted in all groups of rats exposed to 1000 ppm for 4-6 hr. The rats started having tremors and slight convulsions after 4 hours that increased in intensity and frequency during exposure. Death occurred after 5 hr of exposure. One female rat died following exposure to 1000 ppm for 2 hours.

TABLE 3. Data from Rats Exposed to Sulfuryl Fluoride (Torkelson 1959)

Concentration (ppm)	Time (hr)	Sex	No. Animals Exposed	No. Animals Dead	Effects
1000	2	F	10	1	Slight tremors post exposure; slight weight loss
	2	M	10	0	
	3	M	8	0	
	4	F	10	2	Tremors and slight convulsions after 4 hr of exposure; survivors sick and trembling; slight weight loss
	4	M	10	4	
	5.6	F	10	2	
	5.6	M	10	2	
	6	M	8	4	
2000	1	F	10	0	Slight weight loss
	1	M	18	1	
	2	F	10	10	Drowsy upon removal; slow moving; slight tremors
	2	M	18	12	
4000	0.5	F	10	7	No weight loss
	0.5	M	20	5	
	1	F	10	10	Weak but conscious upon removal, half dead within 2 hours
	1	M	20	19	
8000	0.2	F	10	1	Slight weight loss; rapid recovery
	0.2	M	18	1	
	0.5	F	10	10	Tremors after 8 min exposure; convulsions and death within 2.5 hr
	0.5	M	18	18	
15000	0.1	F	10	0	Slow moving upon removal; convulsions and death after 2 hours
	0.1	M	18	1	
	0.2	F	10	9	Drowsy and labored breathing upon removal; tremors; convulsions; death after 3 hours
	0.2	M	18	18	

Miller et al. (1980) exposed male and female Fischer 344 rats (10/sex/group) to 99.7% pure Vikane vapors for 4 hr. Males were exposed to 0, 450, 1000, 1250, 1425, or 2025 ppm and females were exposed to 0, 320, 450, 700, 790, 1000, 1020, 1200, 1425, or 2025 ppm Vikane (analytical concentration). Exposures were conducted in 112 L stainless steel and glass chambers under dynamic airflow conditions. Infrared spectrophotometry was used to measure sulfuryl fluoride concentration. Rats were observed closely during exposure, 4 hours post exposure, and twice daily for 14 days. All deaths occurred within 6 days post exposure. Mortality (100%) was observed at 1425 and 2025 ppm in both males and females and at 1000 ppm in females. Some mortality occurred at 1000 ppm (10% males), 1020 ppm (10% female), 1200 ppm (90% female), and 1250 (60% male). The authors report that the dose-response curve is sharp around 1000 ppm and may account for the mortality in females. Central nervous system depression was apparent in these animals within 20-40 minutes of exposure. Ocular irritation was evident through discharge and frequent blinking. Convulsions and death occurred within 3-4 hours. Lesions were observed in the upper and lower respiratory tract, kidneys, and liver. Perivascular edema of the lungs, hepatocellular cytoplasmic vacuolar degeneration, and renal tubular degeneration with sloughing of the renal tubular epithelium were some of the effects

observed. The LC_{50} for male rats was 1122 ppm and 991 ppm for female rats.

Gorzinski and Streeter (1985) monitored physiological parameters in male and female Fischer 344 rats exposed to 4000 or 20000 ppm 99.8% pure sulfuryl fluoride. The rats were exposed nose/head only. Three males and one female were exposed at 20000 ppm, and three males and two females were exposed at 4000 ppm. Body temperature (low dose), heart rate, blood pressure, and electroencephalogram were monitored. The lungs of the rats were also examined. Mortality and/or absence of brain electrical activity or blood pressure occurred within 9-19 minutes in the rats exposed to 20000 ppm and within 65-90 minutes in those exposed to 4000 ppm. The body temperature of rats exposed to 4000 ppm decreased linearly 7ºC starting after exposure for 5 minutes. The animals were cold and had pale extremities. After 1 hour of exposure, there was a sharp increase in blood pressure. Heart rate and respiration decreased until death. The lungs of the animals were pale and white. The authors found that all physiological parameters stopped functioning around the same time, and no one parameter could be said to cause death.

Nitschke et al. (1986) exposed male Fischer 344 rats (5/group) to 4000, 10000, 20000, or 40000 ppm 99% pure sulfuryl fluoride. The chamber concentration was measured by an infrared spectrophotometer. During the first 10 minutes of exposure, each rat had to walk on a rotating activity wheel, followed by an alternating 2-5 minute rest period and 1 minute walk period. Incapacitation was defined as the time when the rats could no longer walk on the wheel, and the exposure ended. Surviving rats were allowed 150 minutes to recover before necropsy. Exposure to the two highest concentrations caused incapacitation within 12 minutes and death within 10 minutes post exposure. Rats exposed to 10000 ppm died 60 minutes post exposure, and rats exposed to 4000 ppm died up to 148 minutes post exposure. At the beginning of the exposure, the rats walked normally upon the activity wheel, but 3-4 minutes into the exposure, they began to cling to the wheel rather than walk. Cyanosis was observed at the 3 highest concentrations, and most rats (18/20) experienced tonic convulsions lasting 10 seconds in duration. Serum fluoride concentrations in exposed rats were significantly higher than concentrations in control rats.

3.1.2. Mice

Nitschke and Lomax (1989) exposed male and female B6C3F1 mice (5/sex/group) to 404, 603, or 1003 ppm 99.6% pure sulfuryl fluoride for 4 hours. The 1000 L stainless steel and glass chamber concentrations were analyzed by infrared spectrophotometer. Exposure to 1003 ppm caused death in all mice within 90 minutes post exposure, 3 of each sex during exposure. At 603 ppm, 100% mortality occurred within 5 days post exposure. Three males and one female died during exposure. The animals had tremors and were lethargic prior to death. None of the mice exposed to 404 ppm died. No treatment-related pathologic effects were observed in any of the mice.

Nitschke and Quast (1990) exposed male and female CD-1 mice (5/sex/group) to 596, 692, or 806 ppm 99.6% pure sulfuryl fluoride for 4 hours in a 1000 L stainless steel and glass chamber. The chamber concentrations were analyzed by infrared spectrophotometer. Death occurred at the 2 highest concentrations; 9/10 at 692 ppm and 7/10 at 806 ppm. At 692 ppm, 1 male and 1 female died during exposure. One female survived until necropsy on day 14. At 806 ppm, 3 males and 2 females died during exposure. By day 4, 1 male and 2 females remained in

the higher dose groups. None of the mice exposed to 596 ppm died during exposure. The mice were observed having tremors and acting lethargic during the exposure period. Visceral congestion was found in animals that died. The LC_{50} values, 660 ppm for male mice and 642 ppm for female mice, were determined by non-linear interpolation.

3.2. Nonlethal Toxicity

3.2.1. Rats

Torkelson (1959) reported exposures of male and females rats to 1000, 2000, 4000, 8000, or 15000 ppm sulfuryl fluoride. Exposure duration ranged from 6 min to 6 hr. The males (18-20/group) and females (10/group) were placed in a 160 L glass and Monel chamber. Chamber atmosphere was monitored as described in 3.1.1. No female rats died from exposure to 15,000 ppm for 6 min, but they were slow moving upon removal from the chamber. No female rats died from exposure to 2000 ppm for 1 hr. They were only slightly affected and lost a slight amount of weight. All male rats survived exposure to 1000 ppm for 2-3 hr. They exhibited slight tremors after exposure and slight weight loss.

Miller et al. (1980) exposed male and female Fischer 344 rats (10/sex/group) to 99.7% pure Vikane vapors for 4 hr. Males were exposed to 450, 1000, 1250, 1425, or 2025 ppm and females were exposed to 320, 450, 700, 790, 1020, 1000, 1200, 1425, or 2025 ppm Vikane (analytical concentration). Exposures were conducted described in 3.1.1. No deaths occurred at below 1000 ppm, but lethargy was observed. The eyes of the animals exposed to 790 ppm became dark and they had bluish tails. The animals recovered within 8 hr post exposure. The surviving rats had reduced body weight gain the first three days post exposure and recovered shortly after. Treatment-related effects were not observed following the 14 day recovery period.

Landry and Streeter (1983) exposed male Fischer 344 rats (4/ group) to 4000 or 10000 ppm 99.8% pure sulfuryl fluoride for 20 minutes. Respiratory frequency, tidal volume, and minute volume were measured before and during the head-only exposure using a flow type plethysmography technique. During the first two minutes of exposure, respiratory frequency increased and tidal volume and minute volume decreased. After 10 minutes of exposure, frequency and tidal volume returned to base line levels. None of the rats died from treatment, but rats exposed to 10000 ppm sulfuryl fluoride appeared very ill.

3.2.2. Mice

Nitschke and Lomax (1989) exposed male and female B6C3F1 mice (5/sex/group) to 404, 603, or 1003 ppm sulfuryl fluoride for 4 hours. No deaths occurred at 400 ppm and no treatment-related pathological effects were observed in these animals.

Nitschke and Quast (1990) exposed male and female CD-1 mice (5/sex/group) to 596, 692, or 806 ppm sulfuryl fluoride for 4 hours. At 596 ppm, no animals died and no clinical signs were noted.

TABLE 4. Summary of Acute Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Mortality (%)	Effect	Reference
Rat	2025 B 1425 B 1250 M 1200 F 1020 F 1000 M 1000 F 790 F 700 F 450 B 320 F 1122 M 991 F	4 hr	100 B 100 B 60 M 90 F 10 F 10 M 100 F 0 0 0 0 LC_{50} LC_{50}	Central nervous system depression; convulsions; ocular irritation; lesions of the respiratory tract, kidneys, and liver Some reduced body weight gain	Miller et al. 1980
Rat	10000 4000	20 min	0 0	↓ Tidal volume and minute volume, ↑ respiratory frequency during 1st 2 min of exposure with return to baseline by 10 min	Landry and Streeter 1983
Rat	20000 4000	20 min	100 100	↓ Body temperature; ↓ heart rate; ↓ respiration; pale extremities	Gorzinski and Streeter 1985
Rat	40000 20000 10000 4000	~ 6 min ~10 min ~17 min ~42 min	100 100 100 100	Tonic convulsions; incapacitation; ↑ serum fluoride; cyanosis at ≥ 10000 ppm,	Nitschke et al. 1986
Mouse	1003 603 404	4 hr	100 100 0	Tremors; lethargy No effects	Nitschke and Lomax 1989
Mouse	806 692 596	4 hr	70 90 0	Tremors; lethargy; visceral congestion No effects	Nitschke and Quast 1990

B = Male and female; M = Male, F = Female

3.3. Repeat-Dose Studies

3.3.1. Dogs

Nitschke et al. (1992) exposed beagle dogs (4/sex/group) to 0, 30, 100, or 200 ppm sulfuryl fluoride 6 hr/d, 5 d/wk for 13 weeks. The purity ranged from 96% to 99%. An infrared spectrophotometer was used to determine analytical chamber concentrations. Tremors and tetany were exhibited by one male dog on day 19, and one male and female dog had focal inflammatory and degenerative changes in the brain. These studies were followed by a 1 yr study in beagle dogs (Quast et al. 1993b). The dogs (4/sex/group) were exposed to 0, 20, 80, or 200 ppm sulfuryl fluoride 6 hr/d, 5 d/wk for one year. The dogs exposed to 200 ppm had significantly decreased weight gain and were removed from the study after 9 months of exposure due to pulmonary toxicity. Two male and three female dogs exposed to 200 ppm had bilateral focal malacia in the caudate nucleus. Dental fluorosis was present in all dogs exposed to 200 ppm and in some exposed to 80 ppm. No effects were noted in dogs exposed to 20 ppm sulfuryl fluoride.

3.3.2. Rats

Eisenbrandt et al. (1985) exposed male and female Fischer 344 rats (5/sex/group) to 100, 300, or 600 ppm sulfuryl fluoride 6 hr/day, 5 d/wk, for nine exposures over 2 weeks. A second

group of rats (10/sex/group) were exposed to 30, 100, or 300 ppm sulfuryl fluoride for 13 weeks (Eisenbrandt and Nitschke 1989). Stainless steel and glass chambers (4.1 m^3) were used for exposure. Chamber concentration was measured at least once per hour by infrared spectrophotometer. In the 2 week study, 9/10 rats exposed to 600 ppm died between the 2nd and 6th exposure. The animals became increasingly lethargic following each exposure. Severe kidney lesions including hyperplastic papillary epithelium, inflammation, and necrosis were found in the rats that died at 600 ppm. Some rats (4/9) had pulmonary edema and hemorrhage. Their body weight was reduced due to decreased food consumption. The surviving female rat had significantly elevated urea nitrogen, glucosuria, hyperglycemia, and decreased body weight. No rats died at any other concentration. At 300 ppm, half of all rats had minimal hyperplasia of the renal collecting ducts. In the 13 week study, exposure to 100 ppm or greater caused mottled teeth, and 300 ppm resulted in decreased body weight. Minimal brain vacuolation in the caudate putamen was found in rats exposed to 300 ppm, and pale foci (subpleural histiocytosis) were found on the lungs.

3.3.3. Mice

Nitschke and Quast (1993, 2002) exposed male and female CD-1 mice (5/sex/group) to 30, 100, or 300 ppm sulfuryl fluoride 6 hr/day, 5 d/wk for nine exposures over 2 weeks or to 10, 30, or 100 ppm for 13 weeks (14/sex/group). Of the animals exposed to 300 ppm, 9/10 died. Males experienced body tremors and males and females were thin with body weight significantly decreased compared to control rats, and they had roughened hair. Slight or moderate cerebrum vacuolization in the caudate putamen was observed in 8/10 exposed to 300 ppm and in 6/10 mice exposed to 100 ppm. No signs of toxicity were noted in mice exposed to 30 ppm. In the 13 week study, mice exposed to 100 ppm had a 10% decrease in body weight, hypertrophy of the follicular epithelium of the thyroid, and cerebrum vacuolization. No effects were observed in mice exposed to 30 or 10 ppm.

3.3.4. Rabbits

Eisenbrandt and Nitschke (1989) exposed male and female New Zealand White rabbits (3/sex/group) to 100, 300, or 600 ppm sulfuryl fluoride 6 hr/day, 5 d/wk, for nine exposures over 2 weeks. A second group of rabbits (7/sex/group) were exposed to 30, 100, or 600 ppm sulfuryl fluoride 6 hr/d, 5 d/wk, for 13 weeks. After the ninth exposure in the 13 week study, the highest concentration was lowered to 300 ppm because of clinical effects. Stainless steel and glass chambers (4.1 m^3) were used for exposure. Chamber concentration was measured at least once per hour by infrared spectrophotometer. In the 2 week study, two rabbits exposed to 600 ppm had a fractured vertebra; one resulting from a convulsion suffered after the 5th exposure, the other of unknown origin. Both animals were terminated. All other animals survived. At 300 and 600 ppm, brain vacuolation was observed in all rabbits in the globus pallidus, putamen, and myelinated tracts. Subacute to chronic nasal mucosa inflammation was seen at concentrations higher than 300 ppm. In the 13 week study, convulsions in 2 rabbits and a fractured vertebra in another following the 9th exposure necessitated the reduction from 600 ppm to 300 ppm. Brain lesions were similar to those seen in the rabbits exposed to 300 ppm in the 2 week study. Nasal mucosa inflammation, goblet cell hypertrophy, and hyperplasia of the pseudostratified epithelial cells of the nasal turbinates were observed at the higher concentration. Serum fluoride concentrations of all treated rabbits were significantly increased.

TABLE 5. Summary of Repeat-Dose Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Dog	200 100 30	6 hr/d, 5 d/wk for 13 weeks	200 ppm- Inflammatory and degenerative changes in the brain	Nitschke et al. 1992
Dog	200 80 20	6 hr/d, 5 d/wk for 1 year	200 ppm- Pulmonary toxicity, ↓ body weight gain	Quast et al. 1993b
Rat	600 300 100	6 hr/d, 5 d/wk for 2 weeks	600 ppm- 90% mortality; renal hyperplasia, inflammation, and necrosis; 300 ppm- minimal collecting duct hyperplasia	Eisenbrandt et al. 1985
Rat	300 100 30	6 hr/d, 5 d/wk for 13 weeks	300 ppm- minimal brain vacuolation, pale foci of lungs; ≥ 100 ppm- dental fluorosis	Eisenbrandt and Nitschke 1989
Mouse	300 100 30	6 hr/d, 5 d/wk for 2 weeks	300 ppm- 90% mortality; tremors; ↓ body weight; ≥ 100 ppm- moderate cerebrum vacuolization	Nitschke and Quast 2002
Mouse	100 30 10	6 hr/d, 5 d/wk for 13 weeks	100 ppm- cerebrum vacuolization, 10% ↓ body weight, thyroid hypertrophy	Nitschke and Quast 1993
Rabbit	600 300 100	6 hr/d, 5 d/wk for 2 weeks	≥ 300 ppm- brain vacuolation	Eisenbrandt and Nitschke 1989
Rabbit	600, 300 100 30	6 hr/d, 5 d/wk for 13 weeks	300 ppm- brain vacuolation, nasal mucosa lesions	Eisenbrandt and Nitschke 1989

3.4. Developmental/Reproductive Toxicity

Hanley et al. (1989) investigated the effects of sulfuryl fluoride inhalation on fetal development in Fischer 344 rats (35-36/group) and New Zealand white rabbits (28-29/group). Both species were exposed to 25, 75, or 225 ppm 99.8% pure sulfuryl fluoride for 6 hr/d on days 6 through 15(rats)/18(rabbits). The air concentration of the 4.3 m^3 stainless steel and glass chambers was measured using an infrared spectrophotometer. There were no treatment related effects of maternal or fetal toxicity in any exposed rats. In rabbits, maternal weight gain was significantly decreased in the 225 ppm group on gestation days 12-15 and remained low during the post exposure period (gestation days 19-29). Reduced fetal body weight was associated with reduced maternal weight gain. Sulfuryl fluoride exposure did not adversely affect fetal morphological development. The authors concluded that up to 225 ppm sulfuryl fluoride was not teratogenic in rats or rabbits, but was maternally toxic in rabbits.

Breslin et al. (1992, 1993) exposed male and female Sprague-Dawley rats (30/sex/group) for two generations via inhalation to 93.6-98.8% pure sulfuryl fluoride. Rats were exposed to 5, 20, or 150 ppm in a 14.5 m^3 chamber for 6 hr/d, 5 d/wk during premating (10 wk F0, 12 wk F1), mating (1-3 wk), gestation and lactation. Females were not exposed from gestation 21 through postnatal day 4. F1 rats were exposed via the dam (*in utero* and lactation). Their direct exposures began at approximately 6 weeks old during the premating period and continued until necropsy. Chamber concentration was determined by an infrared spectrophotometer. The highest concentration caused a 10% decrease in body weight of the adults of both generations. Dental fluorosis and tooth malformations were also noted in both generations exposed to 150 ppm. Chronic inflammation in the lungs was increased in both generations but had a higher

incidence of moderate severity in the F1 parents. Incidences of brain vacuolation were higher in F0 parents compared to F1 parents, and females had a higher incidence and higher severity of vacuolization than males. At 20 and 150 ppm there was an increase in aggregates of alveolar macrophages in the lungs. Offspring body weight of the 150 ppm group was reduced in both generations through lactation day 21. A parental NOEL for lesions in the lungs was 5 ppm. The neonatal growth NOEL was 20 ppm because of reduced offspring body weight at 150 ppm. The NOEL for reproductive toxicity and fertility was 150 ppm.

3.5. Genotoxicity

Gollapudi et al. (1990a) used the Ames test to evaluate sulfuryl fluoride. Four strains of Salmonella typhimurium (TA98, TA100, TA1535, and TA1537 with and without S-9) were exposed to 300, 1000, 3000, 10000, or 30000 ppm of 96.5% pure sulfuryl fluoride for four hours in 10 L glass desiccators. The plates were allowed to incubate for 2 days following exposure. Slight toxicity in the form of decreased background lawn was observed at 30000 ppm in all strains. The frequency of revertants in the exposed cultures (TA98, TA100, and TA1537) did not increase to greater than three to four times the frequency of revertants in untreated controls. Non-reproducible and non-dose dependent increased revertant rates were observed in strain TA1535 and sham-treated controls. From the results, sulfuryl fluoride was regarded as negative in the Ames test.

Gollapudi et al. (1990b) used the mouse bone marrow micronucleus test to evaluate sulfuryl fluoride. Male and female CD-1 mice (5/sex/group) were exposed for 4 hours to 99.6% pure sulfuryl fluoride at concentrations of 50, 175, or 520 ppm. Exposures occurred in 157 L stainless steel and glass chambers under dynamic air flow conditions. An infrared spectrophometer was used to determine chamber concentration. The analytical concentrations were 48, 180, and 520 ppm. The animals were observed for three days post exposure and bone marrow samples were removed from both femurs of the animals. Two females exposed to 520 ppm died after exposure, but no clinical signs were observed in those or any other animals. No difference was found in the ratio of polychromatic erythrocytes to normochromatic erythrocytes. Under the conditions tested, sulfuryl fluoride was regarded as negative for the bone marrow micronucleus test.

Gollapudi et al. (1991) used the unscheduled DNA synthesis assay to evaluate sulfuryl fluoride. Cultured hepatocytes from male Sprague-Dawley rats were exposed for 18-19 hours to 97.4% pure sulfuryl fluoride in three different trials. Exposures occurred in 16 x 93 mm Leighton tubes. The concentrations in the first trial were 612, 1020, 3060, 6120, 10000, 31000, and 61000 ppm. No cells survived exposure to 3060 ppm or higher. Slight toxicity was observed at 1020 ppm, and no toxicity at 612 ppm. Concentrations for trials two and three were 102, 204, 408, 612, 816, 1020, and 1530 ppm. Toxicity was observed only at 1530 ppm in the second and third trials. Autoradiograms were scored from 204, 408, 612, 816, and 1020 ppm exposed cells. A positive-response was not observed indicating that sulfuryl fluoride was negative in the rat hepatocyte unscheduled DNA synthesis assay.

Gollapudi et al. (2002a) used an *in vitro* chromosomal aberration assay to evaluate sulfuryl fluoride. Rat lymphocytes (with and without S-9) were exposed for 4 hours to 500, 1000, 2500, 5000, 10000, 15000, 25000, 38000, or 50000 ppm 99.8% pure sulfuryl fluoride. Exposures occurred in 15 mL centrifuge tubes and cells were harvested 20 hours post exposure. There was a reproducible clastogenic response in rat lymphocyte cultures exposed to 15000 ppm and higher

sulfuryl fluoride with and without S-9. No clastogenic effects were observed at 2500 ppm. Following exposure, the level of sulfuryl fluoride in the culture medium was analyzed. Very little was detected, but the concentrations of fluoride and fluorosulfate in the medium were increased. The authors report that the clastogenic activity was probably mediated via fluoride ion generation in the culture medium.

Gollapudi et al. (2002b) used the mouse lymphoma forward mutation assay to evaluate sulfuryl fluoride. Mouse lymphoma cells (L5178Y $TK^{+/-}$) with and without S-9 were exposed for four hours to 100-6000 ppm 99.8% pure sulfuryl fluoride. Exposures occurred in 40 mL glass vials and cells were harvested 48 hours post exposure. Concentrations higher than 4000 ppm were extremely toxic. There was a weak mutatgenic response at cytotoxic concentrations that the authors suggested may be due to the generation of fluoride ions in the culture medium.

3.6. Chronic Toxicity/Carcinogenicity

Quast et al. (1993a) exposed CD-1 mice (50/sex) to 5.1, 20.1, or 79.7 ppm 99.8% pure sulfuryl fluoride for 6 hr/d, 5 d/wk for 18 months. At 79.7 ppm, male and female body weight was decreased and minimal microvacuolation of the external capsule of the brain was observed. No in-life clinical effects of toxicity were observed at any concentration, no toxicologically significant effects were observed in the 5.1 or 20.1 ppm treated mice, and no evidence for oncogenicity was observed.

3.7. Summary

The effects of inhalation exposure of laboratory animals are noted in the above section along with reproductive/developmental toxicity and genotoxicity results. Effects frequently observed after death following a single exposure included pulmonary congestion and edema, renal tubular degeneration, and hepatocellular degeneration. Unsteadiness, weakness, tremors, and convulsions were observed prior to death. Some animals experienced death several days after exposure. Very few effects were observed in animals exposed to non-lethal concentrations of sulfuryl fluoride. Slight body tremors, slightly reduced body weight gain, and change in respiratory parameters the first few minutes of exposure were the main effects noted. Repeated exposures caused dental fluorosis, pulmonary toxicity, and brain vacuolization. The data were inconclusive as to whether or not sulfuryl fluoride is genotoxic.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Sulfuryl fluoride is absorbed from the lungs, skin and gastrointestinal tract. The non-ionized compound penetrates the respiratory system, skin, or gastrointestinal tract and forms a reservoir of fluoride ions that bind calcium and magnesium, forming insoluble salts (Bertolini 1992). Fumigated termites excreted inorganic sulfate, indicating the release of fluoride. The termites had metabolic changes characteristic of fluoride toxicity (HSBD, 2005). The fluoride ion is readily absorbed into the bloodstream and is carried to all organs of the body in proportion to their vascularity and the concentration in the blood; equilibrium across biological membranes is rapid (Perry et al. 1994). Significant deposition occurs in the bone, where the fluoride ion substitutes for the hydroxyl group of hydroxyapatite, the principal mineral component of bone.

The fluoride ion also binds to calcium and magnesium. The Krebs cycle is disrupted by increased fluoride resulting in ventricular fibrillations and cardiovascular collapse from extracellular release of potassium (Cordero et al., 2004). Elimination is primarily through the kidneys, but a small amount can be excreted in sweat, saliva, and milk. Mendrala et al. (2005) found that 28.4 and 274 ppm ^{35}S-labeled sulfuryl fluoride was rapidly absorbed via 4 hr nose-only inhalation exposure in male rats. The respiratory tract, spleen, and kidneys had higher levels of radioactivity due to its presence in the blood. It was primarily excreted in the urine. Fluorosulfate and sulfate were present in the blood and urine, and the authors suggested that sulfuryl fluoride is first hydrolyzed to fluorosulfate and then to sulfate with fluoride being released. Plasma fluoride levels increased during exposure and returned to normal approximately 2 hrs post exposure. Fluoride levels were also increased in urine, kidney, and brain during and after exposure.

4.2. Mechanism of Toxicity

The available studies indicate that sulfuryl fluoride is a severe irritant of the skin, eyes, and respiratory tract. It is also a central nervous system depressant. It is thought that the toxicity is due to the fluoride ion. Penetration into the lungs results in dyspnea, cough, pulmonary hemorrhage and edema and may result in death. Cardiopulmonary arrests have been seen in humans following inhalation exposure. Cardiac arrhythmias are the result of hypocalcemia- and hypomagnesemia-induced acidosis following fluoride uptake. The fluoride ions bind to calcium forming an insoluble salt which also prevents calcium from physiological action. Paresthesia, rhinorrhea, nausea, vomiting, hypoxemia, and diffuse pulmonary infiltration are also symptoms of exposure (HSDB 2005).

4.3. Structure Activity Relationships

No structure activity relationship data were located.

4.4. Other Relevant Information

4.4.1. Species Variability

Sulfuryl fluoride has been used to determine acute toxicity in rats and mice. In these studies, mice appeared to be more slightly more sensitive than rats and experienced death at concentrations which only caused reduced body weight gain in rats. Mortality occurred at 603 ppm in after a 4-hr exposure vs. 1000 pppm in rat for the same duration (Nitschke and Lomax 1989; Nitschke and Quast 1990; Miller et al. 1980). In longer studies rats and mice were exposed to the same concentrations 30, 100, or 300 ppm for 2 weeks (mice) and 13 weeks (rats), and 90% of the mice exposed to 300 ppm died, but no mortality was experienced by the rats. The rats had minimal brain vacuolation at 300 ppm and mice exposed to 100 ppm showed the same effect (Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002).

4.4.2. Susceptible Populations

The workers handling fumigation of buildings would be primarily exposed to sulfuryl fluoride. People entering the buildings following fumigation would also be at risk of exposure if the building has not been properly aerated. Fluoride residue remains on foods exposed to sulfuryl fluoride and may be ingested.

4.4.3. Concentration-Exposure Duration Relationship

The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, temporal scaling was performed, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

4.4.4. Concurrent Exposure Issues

Workers using Vikane as a fumigant may also be exposed to small amounts of chloropicrin, the warning material added to odorize sulfuryl fluoride.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values were identified.

5.2. Summary of Animal Data Relevant to AEGL-1

Acute toxicity data are available for rats and mice that report no clinical or treatment-related effects. Rats exposed to concentrations less than 1000 ppm (Miller et al. 1980) and mice exposed to concentrations less than 603 ppm (Nitschke and Quast 1990) did not experience any signs of toxicity. At or above 1000 ppm (rats) and 603 ppm (mice) mortality occurred.

5.3. Derivation of AEGL-1

The available human and animal data indicate that there is very little margin between exposures having no effects and lethal exposures, therefore AEGL-1 values were not derived.

TABLE 6. AEGL-1 Values for Sulfuryl Fluoride

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

NR= Not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values were identified.

6.2. Summary of Animal Data Relevant to AEGL-2

No animal data relevant to development of AEGL-2 values were identified. Acute exposures resulted in either no treatment-related effects or mortality (Miller et al. 1980; Nitschke and

Lomax 1989; Nitschke and Quast 1990).

6.3. Derivation of AEGL-2

In the absence of empirical data and the presence of a steep dose response relationship, the AEGL-2 values were derived by dividing the AEGL-3 values by 3 according to AEGL guidelines (NRC 2001). In 4-hr acute studies with the most sensitive species tested (mouse), no signs of toxicity were found at 404 or 596 ppm, but mortality occurred at 603 (100%) and 692 (90%), respectively, in two different strains of mouse (Nitschke and Lomax 1989; Nitschke and Quast 1990). Rats exposed for 4-hr to 790 ppm had cyanosis, and mortality occurred at the next highest concentration, 1000 ppm-10% male, 100% female (Miller et al. 1980).

TABLE 7. AEGL-2 Values for Sulfuryl Fluoride

10-minute	30-minute	1-hour	4-hour	8-hour
27 ppm (110 mg/m^3)	27 ppm (110 mg/m^3)	21 ppm (88 mg/m^3)	13 ppm (54 mg/m^3)	6.7 ppm (28 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

There were no human data relevant to deriving AEGL-3 values.

7.2. Summary of Animal Data Relevant to AEGL-3

Exposure to sulfuryl fluoride concentrations at or greater than 1000 ppm caused death in rats (Torkelson 1959; Miller et al. 1980; Nitschke et al. 1986). Prior to death, the rats experienced ocular irritation, central nervous system depression, tremors, and convulsions. Lesions of the respiratory tract, kidney, and liver were observed in rats. Mice appear to be more sensitive than rats to sulfuryl fluoride. Exposures to concentrations greater than 600 ppm caused death in two different strains of mice (Nitschke and Lomax 1989; Nitschke and Quast 1990). Lethargy and tremors were observed before death but no pathological changes were observed in the mice.

7.3. Derivation of AEGL-3

The data set used for deriving AEGL-3 values is from Nitschke and Lomax (1989), and provides exposure response data for mice exposed to sulfuryl fluoride for 4 hr at concentrations of 404, 603, and 1003 ppm. The 603 and 1003 ppm exposures resulted in 100% mortality in mice within 5 days following exposure. The highest concentration at which no mortality occurred (404 ppm) was used for AEGL-3 derivation. A total uncertainty factor of 10 was applied to account for interspecies extrapolation (1) and intraspecies variability (10). A 1 was applied for interspecies extrapolation because the most sensitive species was used (mouse) and sulfuryl fluoride has a steep concentration-response curve. The mouse was considered the most sensitive species because mortality occurred at 603 ppm in after a 4-hr exposure vs. 1000 pppm in rat for the same duration (Nitschke and Lomax 1989; Nitschke and Quast 1990; Miller et al. 1980). In longer studies rats and mice were exposed to the same concentrations 30, 100, or 300 ppm for 2 weeks (mice) and 13 weeks (rats), and 90% of the mice exposed to 300 ppm died, but

no mortality was experienced by the rats. The rats had minimal brain vacuolation at 300 ppm and mice exposed to 100 ppm showed the same effect (Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002). In acute studies, no signs of toxicity were found at 404 or 596 ppm, but mortality occurred at 603 (100%) and 692 (90%), respectively, in two different strains of mouse (Nitschke and Lomax 1989; Nitschke and Quast 1990). The use of a factor of 1 is also supported by the results of the acute and repeat-dose studies. Both rats and mice experienced tremors or convulsions after an acute exposure to sulfuryl fluoride (Miller et al. 1980, Nitschke et al. 1986; Nitschke and Lomax 1989; Nitschke and Quast 1990). Dogs, rats, mice, and rabbits exposed to 100-300 ppm sulfuryl fluoride from 2 weeks to 1 year showed central nervous system effects including tremors and lethargy and histological evaluation showed evidence of brain vacuolization in the same area of the brain of all the species (Nitschke et al. 1992; Quast et al. 1993b; Eisenbrandt et al. 1993; Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002; Nitschke and Quast 1993). A 10 was applied for intraspecies extrapolation because only qualitative human data were available, and it is unknown if sulfuryl fluoride would elicit the same response in humans as that observed in animals.

The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, temporal scaling was performed, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

TABLE 8. AEGL-3 Values for Sulfuryl Fluoride

10-minute	30-minute	1-hour	4-hour	8-hour
81 ppm (340 mg/m^3)	81 ppm (340 mg/m^3)	64 ppm (270 mg/m^3)	40 ppm (170 mg/m^3)	20 ppm (83 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

Due to insufficient data, AEGL-1 values were not derived. AEGL-2 values are a 3-fold reduction of AEGL-3 values because of the steep dose response relationship. In acute studies with the most sensitive species tested (mouse), no signs of toxicity were found at 404 or 596 ppm, but mortality occurred at 603 (100%) and 692 (80%), respectively, in two different strains of mouse (Nitschke and Lomax 1989; Nitschke and Quast 1990). Rats exposed for 4-hr to 790 ppm had cyanosis, and mortality occurred at the next highest concentration, 1000 ppm-10% male, 100% female (Miller et al. 1980). Irreversible effects were not observed. AEGL-3 values are based on the highest concentration that did not cause lethality in mice (404 ppm). All mice died at the next highest concentration (603 ppm) (Nitschke and Lomax 1989). The repeat-dose data supports the protective nature of the 10-min and 30-min AEGL-3 values. Dogs, rats, mice, and rabbits exposed to ≥100 ppm of sulfuryl fluoride from 2 weeks to 1 year showed central nervous system effects including tremors and lethargy and histological evaluation showed evidence of brain vacuolization in the same area of the brain of all the species. Dental fluorosis in some of the dogs exposed to 80 ppm for 1 year, and no effects in rats, mice, or rabbits were observed at concentrations less than 100 ppm (Nitschke et al. 1992; Quast et al. 1993b; Eisenbrandt et al. 1993; Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002; Nitschke and Quast 1993).

TABLE 9. Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Notable Discomfort)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	27 ppm (110 mg/m^3)	27 ppm (110 mg/m^3)	21 ppm (88 mg/m^3)	13 ppm (54 mg/m^3)	6.7 ppm (28 mg/m^3)
AEGL-3 (Lethal)	81 ppm (340 mg/m^3)	81 ppm (340 mg/m^3)	64 ppm (270 mg/m^3)	40 ppm (170 mg/m^3)	20 ppm (83 mg/m^3)

NR= Not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

8.2. Comparison with Other Standards and Guidelines

Currently available standards and guidelines are shown in Table 10. The Occupational Safety and Health Administration (OSHA) time weighted average, National Institute of Occupational Safety and Health (NIOSH) immediately dangerous to life and health values, and time weighted average value, and Dutch maximum allowable concentration (MAC) values have been published. The American Conference of Governmental Industrial Hygienists, Threshold Limit Value (ACGIH) threshold limit value-time weighted average (TLV-TWA) is listed as well. No other standards and guidelines were located for sulfuryl fluoride. The AEGL values are consistent with currently established guidelines.

TABLE 10. Extant Standards and Guidelines for Sulfuryl Fluoride

Guideline	**Exposure Duration**				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	27 ppm	27 ppm	21 ppm	13 ppm	6.7 ppm
AEGL-3	81 ppm	81 ppm	64 ppm	40 ppm	20 ppm
PEL-TWA (OSHA)[a]					5 ppm
IDLH (NIOSH)[b]		200 ppm			
REL-TWA (NIOSH)[c]					5 ppm
REL-STEL (NIOSH)[d]					10 ppm
TLV-TWA (ACGIH)[e]					5 ppm
TLV-STEL (ACGIH)[f]	10 ppm				
MAC (The Netherlands)[g]					5 ppm

NR= Not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

[a] OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average) (OSHA 2004) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week. The PEL was set at a level to protect workers from significant risks of kidney and lung injury and fluorosis.

[b] IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects. The IDLH is based on acute inhalation toxicity data in animals.

[c]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH 2005) is defined as the time-weighted average concentration for up to a 10-hour workday during a 40-hr workweek.

[d] NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit) (NIOSH 2005) is defined as a 15-minute time weighted average exposure that should not be exceeded at any time during the workday.

[e] ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 1991) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[f] ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit) (ACGIH 1991) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[g] MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration]) Nationale MAC List (2000). (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000 is defined analogous to the ACGIH-TLV-TWA.

8.3. Data Adequacy and Research

The data reported for human exposure to sulfuryl fluoride contain actual concentrations and duration parameters that workers were exposed to while using the fumigant. The levels are generally less than occupational standards. In cases of human lethality, the concentrations are unknown. Quantitative animal data that are available support human lethality data. The acute exposure animal data are sufficient for showing lethality and non-response. Data on mechanism of action, especially in the mouse where no pathological effects were observed in cases of mortality, would be helpful.

9. REFERENCES

ACGIH (American Conference of Government and Industrial Hygienists). 1991. Documentation of the Threshold Limit Values and Biological Exposure Indices: Sulfuryl Fluoride. Sixth ed., ACGIH, Cincinnati, OH.

Bertolini, J.C. 1992. Hydrofluoric acid: A review of toxicity. J. Emerg. Med. 10:163-168.

Breslin, W.J., A.B. Liberacki, H.D. Kirk, G.J. Bradley, and J.W. Crissman. 1992. Sulfuryl fluoride: Two generation reproduction study in Sprague-Dawley rats. The Dow Chemical Company. Midland, MI (January 7, 1992).

Breslin, W.J., A.B. Liberacki, H.D. Kirk, G.J. Bradley, and J.W. Crissman. 1993. Sulfuryl fluoride: Two generation reproduction study in Sprague-Dawley rats. #1439 The Toxicologist 13: 368.

Calvert, G.M., C.A. Mueller, J.M. Fajen, D.W. Chrislip, J. Russo, T. Briggle, L.E. Fleming, A.J. Suruda, and K. Steenland. 1998. Health effects associated with sulfuryl fluoride and methyl bromide exposure among structural fumigation workers. Am. J. Public Health 88:1774-1780.

Contardi, J.S., and D.A. Lambesis. 1994. Evaluation of sulfuryl fluoride exposures to workers during structural fumigations when using Vikane gas fumigant. The Dow Chemical Company. Midland, MI (October 6, 1994).

Cordero, S.C., W.W. Goodhur, E.M Splichal, and V.F. Kalasinsky. 2004. A fatality due to ingestion of hydrofluoric acid. J Anal. Toxicol. 28:211-213.

Eisenbrandt, D.L., K.D. Nitschke, C.M. Streeter, and E.L. Wolfe. 1985. Nephrotoxicity associated with inhalation of sulfuryl fluoride: A two-week toxicologic study in Fischer 344 rats. Presentation. The Dow Chemical Company. Midland, MI (December 10, 1985).

Eisenbrandt, D.L. and K.D. Nitschke. 1989. Inhalation toxicity of sulfuryl fluoride in rats and rabbits. Fundam. Appl. Toxicol. 12: 540-557.

Gollapudi, B.B., Y.E. Samson, and J.A. Zempel. 1990a. Evaluation of sulfuryl fluoride in the Ames Salmonella/mammalian-microsome bacterial mutagenicity assay. The Dow Chemical Company. Midland, MI (August 19, 1990).

Gollapudi, B.B., M.L. McClintock, and K.D. Nitschke. 1990b. Evaluation of sulfuryl fluoride in the mouse bone marrow micronucleus test. The Dow Chemical Company. Midland, MI (February 16, 1990).

Gollapudi, B.B., M.L. McClintock, and J.A. Zempel. 1991. Evaluation of sulfuryl fluoride in the rat hepatocyte unscheduled DNA synthesis (UDS) assay. The Dow Chemical Company. Midland, MI (October 7, 1991).

Gollapudi, B.B, M.R. Schisler, K.M. Jackson, T.H. DeLisle, S.M. Krieger, and D.L. Rick. 2002a. Revised report for: evaluation of sulfuryl fluoride in an *in vitro* chromosomal aberration assay utilizing rat lymphocytes. The Dow Chemical Company. Midland, MI (May 20, 2002, revised report issued July 29, 2005).

Gollapudi, B.B., V.A. Linscombe, M.R. Schisler, T.H. DeLisle, S.M. Krieger, and D.L. Rick. 2002b. Evaluation of sulfuryl fluoride in the mouse lymphoma (L5178Y $TK^{+/-}$) forward mutation assay. The Dow Chemical Company. Midland, MI (May 16, 2002).

Gorzinski, S.J., and C.M. Streeter. 1985. Effect of acute Vikane exposure on selected physiological parameters in rats. The Dow Chemical Company. Midland, MI (November 6, 1985).

Hanley, T.R., L.L. Calhoun, R.J. Kociba, and J.A. Greene. 1989. The effects of inhalation exposure to sulfuryl fluoride on fetal development in rats and rabbits. Fundam. Appl. Toxicol. 13: 79-86.

HSDB (Hazardous Substances Data Bank). 2005. Sulfuryl Fluoride. [Online] Available. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB [06/04/2005]. TOXNET, Toxicology Data Network. US. Natl. Library of Medicine.

Landry, T.D., and C.M. Streeter. 1983. Sulfuryl fluoride: effects of acute exposure on respiration in rats. The Dow Chemical Company. Midland, MI (December 19, 1983).

MAC (Ministry of Social Affairs and Employment SDU Uitgevers). 2000. Nationale MAC (Maximum Allowable Concentration) List, 2000. The Hague, The Netherlands.

Mendrala, A.L., D.A. Markham, and D.L. Eisenbrandt. 2005. Rapid uptake, metabolism, and elimination of inhaled sulfuryl fluoride fumigant by rats. Toxicol. Sci. 86: 239-247.

Miller, R.R., L.L. Calhoun, D.G. Keyes, and R.J. Kociba. 1980. Sulfuryl fluoride (Vikane fumigant): An LC_{50} determination. The Dow Chemical Company. Midland, MI (August 25, 1980).

NIOSH (National Institute for Occupational Safety and Health). 2005. Sulfuryl Fluoride. NIOSH Pocket Guide to Chemical Hazards. NIOSH, Cincinnati, OH.

Nitschke, K.D. and J.F. Quast. 1990. Sulfuryl fluoride: Acute LC_{50} study with CD-1 mice. The Dow Chemical Company. Midland, MI (December 21, 1990).

Nitschke, K.D. and J.F. Quast. 1993. Sulfuryl fluoride: Thirteen-week inhalation toxicity study in CD-1 mice. The Dow Chemical Company. Midland, MI (December 28, 1993).

Nitschke, K.D. and J.F. Quast. 2002. Sulfuryl fluoride: Two-week inhalation toxicity study in CD-1 mice. The Dow Chemical Company. Midland, MI (February 11, 2002).

Nitschke, K.D. and L.G. Lomax. 1989. Sulfuryl fluoride: Acute LC_{50} study with B6C3F1 mice. The Dow Chemical Company. Midland, MI (March 22, 1989).

Nitschke, K.D., R.R. Albee, J.L. Mattsson, and R.R. Miller. 1986. Incapacitation and treatment of rats exposed to a lethal dose of sulfuryl fluoride. Fundam. Appl. Toxicol. 7: 664-670.

Nitschke, K.D., M.J. Beekman, and J.F. Quast. 1992. Sulfuryl fluoride: 13-week inhalation toxicity study in beagle dogs. The Dow Chemical Company. Midland, MI (April 30, 1991).

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. The National Academies Press, Washington, DC.

Nuckolls, J.G., D.C. Galax, and D.C. Smith. 1987. Leads From the MMWR. Fatalities resulting from sulfuryl fluoride exposure after home fumigation-Virginia. JAMA 258: 2041-2044.

OSHA (Occupational Safety and Health Administration). 2004. Part 1910- Occupational Safety and Health Standards: Subpart Z- Toxic and Hazardous Substances: Table Z-1. [Online] Available. http://www.osha.gov [07/10/2007].

Perry, W.G., F.A. Smith, and M.B. Kent. 1994. Chapter Forty-three: The Halogens, In: Patty's Industrial Hygiene and Toxicology, Volume II, Part F, G.F. Clayton and F.E. Clayton (eds). John Wiley & Sons, Inc., New York.

Quast, J.F., G.J. Bradley, and K.D. Nitschke. 1993a. Sulfuryl fluoride: 18-month inhalation oncogenicity study in CD-1 mice. The Dow Chemical Company. Midland, MI (August 19, 1993).

Quast, J.F., M.J. Beekman, and K.D. Nitschke. 1993b. Sulfuryl fluoride: One year inhalation toxicity study in beagle dogs. The Dow Chemical Company. Midland, MI (October 21, 1993).

Scheuerman, E.H. 1986. Suicide by exposure to sulfuryl fluoride. J. Forensic Sci. 31: 1154-1158.

Taxay, E.P. 1966. Vikane inhalation. J. Occup. Med. 56: 425-426.

ten Berge, W.F., Zwart, A., Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Materials: 13: 301-309.

Torkelson, T.R. 1959. Summary report of toxicological studies with Vikane (sulfuryl fluoride, SO2F2). Single exposures of rats to Vikane. The Dow Chemical Company. Midland, MI. pp 27-31 (November 11, 1959).

APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 values for Sulfuryl Fluoride
AEGL-1 values were not derived due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

Key Study: None

Toxicity endpoint: None

Time scaling: None

Uncertainty factors: None

Modifying factor: None

Calculations: None

10-minute AEGL-1 NR
30-minute AEGL-1 NR
1-hour AEGL-1 NR
4-hour AEGL-1 NR
8-hour AEGL-1 NR

Derivation of AEGL-2 for Sulfuryl Fluoride

Key Studies: Nitschke and Lomax (1989). Sulfuryl fluoride: Acute LC_{50} study with B6C3F1 mice. The Dow Chemical Company. Midland, MI (March 22, 1989).

Toxicity endpoints: In the absence of empirical data and the presence of a steep dose response relationship, the AEGL-2 values were derived by dividing the AEGL-3 values by 3 according to AEGL guidelines (NRC 2001). In 4-hr acute studies with the most sensitive species tested (mouse), no signs of toxicity were found at 404 or 596 ppm, but mortality occurred at 603 (100%) and 692 (90%), respectively, in two different strains of mouse (Nitschke and Lomax 1989; Nitschke and Quast 1990). Rats exposed for 4-hr to 790 ppm had cyanosis, and mortality occurred at the next highest concentration, 1000 ppm-10% male, 100% female (Miller et al. 1980).

Time scaling: Not directly applicable; AEGL-2 values derived from 3-fold downward adjustment of AEGL-3 values

Uncertainty factors: See discussion in the AEGL-3 section; AEGL-2 is 1/3 of the AEGL-3.

Modifying factor: None

Calculations:

10-minute AEGL-2	AEGL-3 (81 ppm) /3 = 27 ppm
30-minute AEGL-2	AEGL-3 (81 ppm) /3 = 27 ppm
1-hour AEGL-2	AEGL-3 (64 ppm) /3 = 21 ppm
4-hour AEGL-2	AEGL-3 (40 ppm) /3 = 13 ppm
8-hour AEGL-2	AEGL-3 (20 ppm) /3 = 6.7 ppm

Derivation of AEGL-3 for Sulfuryl Fluoride

Key Studies: Nitschke and Lomax (1989). Sulfuryl fluoride: Acute LC_{50} study with B6C3F1 mice. The Dow Chemical Company. Midland, MI (March 22, 1989).

Toxicity endpoint: The AEGL-3 was based upon the highest concentration causing no lethality after a 4-hr exposure period.

Time scaling: $C^n \times t = k$, temporal scaling, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points due to lack of data to derive a value of n (NRC 2001). The 30-minute AEGL value was adopted for the 10-minute value according to the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001).

Uncertainty factors: A total uncertainty factor of 10 was applied to account for interspecies extrapolation (1) and intraspecies variability (10). A 1 was applied for interspecies extrapolation because the most sensitive species was used (mouse) and sulfuryl fluoride has a steep concentration-response curve. The mouse was considered the most sensitive species because mortality occurred at 603 ppm in after a 4-hr exposure vs. 1000 pppm in rat for the same duration (Nitschke and Lomax 1989; Nitschke and Quast 1990; Miller et al. 1980). In longer studies rats and mice were exposed to the same concentrations 30, 100, or 300 ppm for 2 weeks (mice) and 13 weeks (rats), and 90% of the mice exposed to 300 ppm died, but no mortality was experienced by the rats. The rats had minimal brain vacuolation at 300 ppm and mice exposed to 100 ppm showed the same effect (Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002). In acute studies, no signs of toxicity were found at 404 or 596 ppm, but mortality occurred at 603 (100%) and 692 (90%), respectively, in two different strains of mouse (Nitschke and Lomax 1989; Nitschke and Quast 1990). The use of a factor of 1 is also supported by the results of the acute and repeat-dose studies. Both rats and mice experienced tremors or convulsions after an acute exposure to sulfuryl fluoride (Miller et al. 1980, Nitschke et al. 1986; Nitschke and Lomax 1989; Nitschke and Quast 1990). Dogs, rats, mice, and rabbits exposed to 100-300 ppm sulfuryl fluoride from 2 weeks to 1 year showed central nervous system effects including tremors and lethargy and histological evaluation showed evidence of brain vacuolization in the same area of the brain of all the species (Nitschke et al. 1992; Quast et al. 1993b; Eisenbrandt et al. 1993; Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002; Nitschke and Quast 1993). A 10 was applied for intraspecies extrapolation because only qualitative human data were available, and it is unknown if sulfuryl fluoride would elicit the same response in humans as that observed in animals.

Modifying factor: None

Calculations: 404 ppm/10 = 40.4 ppm

$C^3 \times t = k$

$(40.4\ ppm)^3 \times 240\ min = 15825423.36\ ppm^3 \cdot min$

$C \times t = k$

$40.4\ ppm \times 240\ min = 9696\ ppm \cdot min$

10-minute AEGL-3 $C^3 \times 10\ min = 15825423.36\ ppm^3 \cdot min$

$C = 81\ ppm$

30-minute AEGL-3	C^3 x 30 min = 15825423.36 $ppm^3 \cdot min$
	C = 81 ppm
1-hour AEGL-3	C^3 x 60 min = 15825423.36 $ppm^3 \cdot min$
	C = 64 ppm
4-hour AEGL-3	C x 240 min = 9696 ppm·min
	C = 40 ppm
8-hour AEGL-3	C x 480 min = 9696 ppm·min
	C = 20 ppm

APPENDIX B: Time-Scaling Calculations

The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, temporal scaling was performed, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

APPENDIX C: Derivation Summary for Sulfuryl Fluoride AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR
SULFURYL FLUORIDE (CAS Reg. No. 2699-79-8)
DERIVATION SUMMARY

AEGL-1 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
NR	**NR**	**NR**	**NR**	**NR**
Key Reference:				
Test Species/Strain/Number:				
Exposure Route/Concentrations/Durations:				
Effects: ppm ppm ppm ppm ppm ppm				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: Total uncertainty factor: Interspecies: Intraspecies:				
Modifying Factor:				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				
Data Adequacy:				

AEGL-1 values were not derived due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

AEGL-2 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
27 ppm	**27 ppm**	**21 ppm**	**13 ppm**	**6.7 ppm**

Key Reference: Nitschke, K.D. and L.G. Lomax. 1989. Sulfuryl fluoride: Acute LC_{50} study with B6C3F1 mice. The Dow Chemical Company. Midland, MI (March 22, 1989).

Test Species/Strain/Number: Mouse/ B6C3F1/ 5/sex/group

Exposure Route/Concentrations/Durations: Inhalation/ 404, 603, 1003 ppm for 4 hours

Effects:
404 ppm: No treatment-related clinical or pathologic effects observed
603 ppm: 100% mortality within 5 days post exposure
1003 ppm: 100% mortality within 90 minutes post exposure

Endpoint/Concentration/Rationale: In the absence of empirical data and the presence of a steep dose response relationship, the AEGL-2 values were derived by dividing the AEGL-3 values by 3 according to AEGL guidelines (NRC 2001). In 4-hr acute studies with the most sensitive species tested (mouse), no signs of toxicity were found at 404 or 596 ppm, but mortality occurred at 603 (100%) and 692 (90%), respectively, in two different strains of mouse (Nitschke and Lomax 1989; Nitschke and Quast 1990). Rats exposed for 4-hr to 790 ppm had cyanosis, and mortality occurred at the next highest concentration, 1000 ppm-10% male, 100% female (Miller et al. 1980).

Uncertainty Factors/Rationale: See AEGL-3, AEGL-2 values are 1/3 of AEGL-3 values

Modifying Factor: none

Animal to Human Dosimetric Adjustment: none

Time Scaling: none

Data Adequacy: SEE AEGL-3

AEGL-3. VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
81 ppm	81 ppm	64 ppm	40 ppm	20 ppm

Key Reference: Nitschke, K.D. and L.G. Lomax. 1989. Sulfuryl fluoride: Acute LC_{50} study with B6C3F1 mice. The Dow Chemical Company. Midland, MI (March 22, 1989).

Test Species/Strain/Number: Mouse/ B6C3F1/ 5/sex/group

Exposure Route/Concentrations/Durations: Inhalation/ 404, 603, 1003 ppm for 4 hours

Effects:
404 ppm: No treatment-related clinical or pathologic effects observed
603 ppm: 100% mortality within 5 days post exposure
1003 ppm: 100% mortality within 90 minutes post exposure

Endpoint/Concentration/Rationale: Highest concentration with no mortality after exposure to 404 ppm

Uncertainty Factors/Rationale:
A total uncertainty factor of 10 was applied to account for interspecies extrapolation (1) and intraspecies variability (10). A 1 was applied for interspecies extrapolation because the most sensitive species was used (mouse) and sulfuryl fluoride has a steep concentration-response curve. The mouse was considered the most sensitive species because mortality occurred at 603 ppm in after a 4-hr exposure vs. 1000 pppm in rat for the same duration (Nitschke and Lomax 1989; Nitschke and Quast 1990; Miller et al. 1980). In longer studies rats and mice were exposed to the same concentrations 30, 100, or 300 ppm for 2 weeks (mice) and 13 weeks (rats), and 90% of the mice exposed to 300 ppm died, but no mortality was experienced by the rats. The rats had minimal brain vacuolation at 300 ppm and mice exposed to 100 ppm showed the same effect (Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002). In acute studies, no signs of toxicity were found at 404 or 596 ppm, but mortality occurred at 603 (100%) and 692 (90%), respectively, in two different strains of mouse (Nitschke and Lomax 1989; Nitschke and Quast 1990). The use of a factor of 1 is also supported by the results of the acute and repeat-dose studies. Both rats and mice experienced tremors or convulsions after an acute exposure to sulfuryl fluoride (Miller et al. 1980, Nitschke et al. 1986; Nitschke and Lomax 1989; Nitschke and Quast 1990). Dogs, rats, mice, and rabbits exposed to 100-300 ppm sulfuryl fluoride from 2 weeks to 1 year showed central nervous system effects including tremors and lethargy and histological evaluation showed evidence of brain vacuolization in the same area of the brain of all the species (Nitschke et al. 1992; Quast et al. 1993b; Eisenbrandt et al. 1993; Eisenbrandt and Nitschke 1989; Nitschke and Quast 2002; Nitschke and Quast 1993). A 10 was applied for intraspecies extrapolation because only qualitative human data were available, and it is unknown if sulfuryl fluoride would elicit the same response in humans as that observed in animals.

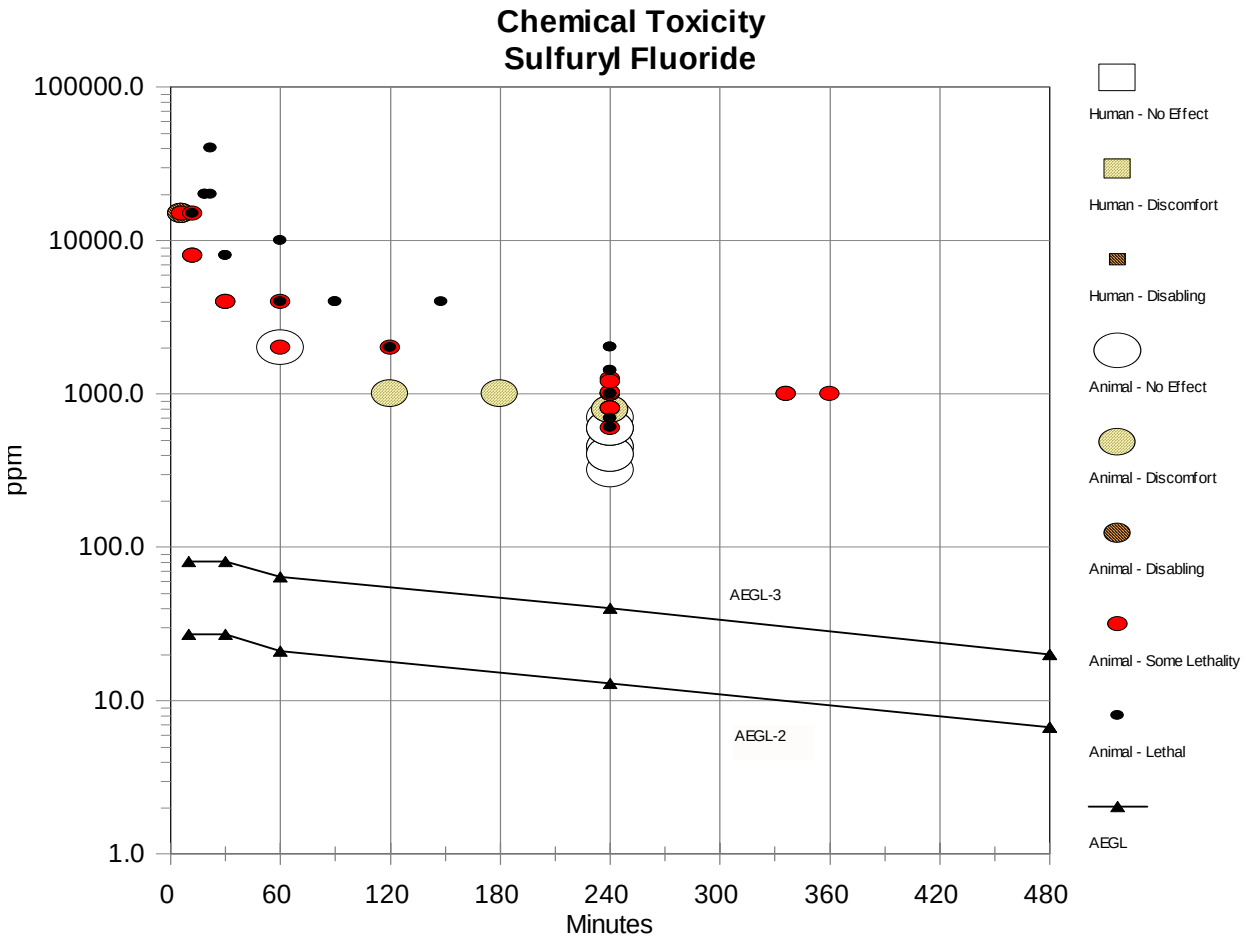
Modifying Factor: none

Animal to Human Dosimetric Adjustment: none

Time Scaling: The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, temporal scaling was performed, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

Data Adequacy: The study was considered adequate for AEGL-3 derivation. It was a well-designed and performed study, adequate numbers of animals were used, and an endpoint consistent with AEGL-3 definition and toxicity of sulfuryl fluoride was observed.

APPENDIX E: Category Plot for Sulfuryl Fluoride


Chemical Toxicity
Sulfuryl Fluoride
100000.0
10000.0
1000.0
100.0
10.0
1.0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

Category Plot Data

							For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal
Source	Species	Sex	Exposures #	ppm	Time (min)	Category	Comments
NAC/AEGL-1					10	AEGL	
NAC/AEGL-1					30	AEGL	
NAC/AEGL-1					60	AEGL	
NAC/AEGL-1					240	AEGL	
NAC/AEGL-1					480	AEGL	
NAC/AEGL-2				27	10	AEGL	
NAC/AEGL-2				27	30	AEGL	
NAC/AEGL-2				21	60	AEGL	
NAC/AEGL-2				13	240	AEGL	
NAC/AEGL-2				6.7	480	AEGL	
NAC/AEGL-3				81	10	AEGL	
NAC/AEGL-3				81	30	AEGL	
NAC/AEGL-3				64	60	AEGL	
NAC/AEGL-3				40	240	AEGL	
NAC/AEGL-3				20	480	AEGL	
Torkelson 1959	rat	f	1	1000	120	sl	10% mortality; slight tremors
Torkelson 1959	rat	m	1	1000	120	1	Slight tremors
Torkelson 1959	rat	m	1	1000	180	1	Slight tremors
Torkelson 1959	rat	f	1	1000	240	sl	20% mortality; convulsions
Torkelson 1959	rat	m	1	1000	240	sl	40% mortality; convulsions
Torkelson 1959	rat	f	1	1000	336	sl	20% mortality; convulsions
Torkelson 1959	rat	m	1	1000	336	sl	20% mortality; convulsions
Torkelson 1959	rat	m	1	1000	360	sl	50% mortality; convulsions
Torkelson 1959	rat	f	1	2000	60	0	Slight weight loss
Torkelson 1959	rat	m	1	2000	60	sl	5% mortality
Torkelson 1959	rat	f	1	2000	120	3	100% mortality
Torkelson 1959	rat	m	1	2000	120	sl	66% mortality
Torkelson 1959	rat	f	1	4000	30	sl	70% mortality
Torkelson 1959	rat	m	1	4000	30	sl	25% mortality
Torkelson 1959	rat	f	1	4000	60	3	100% mortality
Torkelson 1959	rat	m	1	4000	60	sl	95% mortality
Torkelson 1959	rat	f	1	8000	12	sl	10% mortality
Torkelson 1959	rat	m	1	8000	12	sl	5.5% mortality
Torkelson 1959	rat	f	1	8000	30	3	100% mortality
Torkelson 1959	rat	m	1	8000	30	3	100% mortality
Torkelson 1959	rat	f	1	15000	6	2	Slow moving post-exposure
Torkelson 1959	rat	m	1	15000	6	sl	5.5% mortality
Torkelson 1959	rat	f	1	15000	12	sl	90% mortality
Torkelson 1959	rat	m	1	15000	12	3	100% mortality

Miller et al. 1980	rat	m	1	450	240	0	No effects
Miller et al. 1980	rat	m	1	1000	240	sl	10% mortality
Miller et al. 1980	rat	m	1	1250	240	sl	60% mortality
Miller et al. 1980	rat	m	1	1425	240	3	100% mortality; convulsions
Miller et al. 1980	rat	m	1	2025	240	3	100% mortality; convulsions
Miller et al. 1980	rat	f	1	320	240	0	No effects
Miller et al. 1980	rat	f	1	450	240	0	No effects
Miller et al. 1980	rat	f	1	700	240	0	No effects
Miller et al. 1980	rat	f	1	790	240	1	Cyanosis
Miller et al. 1980	rat	f	1	1020	240	sl	10% mortality
Miller et al. 1980	rat	f	1	1000	240	3	100% mortality
Miller et al. 1980	rat	f	1	1200	240	sl	90% mortality
Miller et al. 1980	rat	f	1	1425	240	3	100% mortality; convulsions
Miller et al. 1980	rat	f	1	2025	240	3	100% mortality; convulsions
Gorzinski and Streeter 1985	rat	m	1	20000	19	3	100% mortality
Gorzinski and Streeter 1985	rat	m	1	4000	90	3	100% mortality
Gorzinski and Streeter 1985	rat	f	1	20000	19	3	100% mortality
Gorzinski and Streeter 1985	rat	f	1	4000	90	3	100% mortality
Nitschke et al. 1986	rat	m	1	4000	148	3	100% mortality
Nitschke et al. 1986	rat	m	1	10000	60	3	100% mortality
Nitschke et al. 1986	rat	m	1	20000	22	3	100% mortality
Nitschke et al. 1986	rat	m	1	40000	22	3	100% mortality
Nitschke and Lomax 1989	mouse	m	1	404	240	0	No effects
Nitschke and Lomax 1989	mouse	m	1	603	240	3	100% mortality
Nitschke and Lomax 1989	mouse	m	1	1003	240	3	100% mortality
Nitschke and Lomax 1989	mouse	f	1	404	240	0	No effects
Nitschke and Lomax 1989	mouse	f	1	603	240	3	100% mortality
Nitschke and Lomax 1989	mouse	f	1	1003	240	3	100% mortality
Nitschke and Quast 1990	mouse	m	1	596	240	0	No effects
Nitschke and Quast 1990	mouse	m	1	692	240	3	100% mortality
Nitschke and Quast 1990	mouse	m	1	806	240	sl	80% mortality
Nitschke and Quast 1990	mouse	f	1	596	240	0	No effects
Nitschke and Quast 1990	mouse	f	1	602	240	SL	80% mortality
Nitschke and Quast 1990	mouse	f	1	806	240	SL	60% mortality