

SULFURYL FLUORIDE (Vikane[®])
RISK CHARACTERIZATION DOCUMENT
Volume I
Health Risk Assessment

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I. TECHNICAL SUMMARY

This section describes the risk assessment process used and provides a summary of the Health Assessment for sulfuryl fluoride. The terms used in this summary are defined in **Appendix A. Glossary and Abbreviations**.

I.A. Risk Characterization Process For Sulfuryl Fluoride

I.A.1. General Step-wise Procedure

1. The pharmacokinetic and toxicology studies were reviewed and presented in the Toxicology Profile section. The toxicity studies can be categorized as acute (one day), subchronic (13-week), and chronic (1 or more years) in duration. From the treatment-related effects identified in the studies, the highest dose, which did not cause any toxicological effect, known as No-Observed-Effect Level (NOEL), or No-Observed-Adverse-Effect Level (NOAEL), was established for each study.
2. These NOELs and effects from the database were then evaluated to determine what would be the most appropriate NOEL, referred to as a critical NOEL, to evaluate particular duration or effects of concern. This is presented in the Hazard identification section. For sulfuryl fluoride, critical NOELs were identified for acute (1 to 2 days), 1 to 2 weeks, subchronic (13-weeks), chronic and lifetime exposures. In this section, the critical NOELs were adjusted to absorbed doses because human exposures were expressed as absorbed doses. The inhalation absorption factor for sulfuryl fluoride was 18%, derived from a pharmacokinetic study in rats. Since there was no clear evidence of sulfuryl fluoride oncogenicity, cancer potency factors were not calculated for lifetime exposure. These critical NOELs were also expressed in terms of reference concentrations for direct comparison with air concentrations. The reference concentration considered age-related inhalation rate differences and uncertainties in the use of NOELs from animal studies for risk assessment (see **Appendix D** for equations). These critical NOELs and reference concentrations were used to estimate the risk of exposure in the Risk Characterization step.
3. The product label and available studies on human exposure were evaluated to establish the exposure scenarios and to estimate the human exposure levels. For the uses of sulfuryl fluoride in structural and non-food fumigation, exposure scenarios for workers, residents, and bystanders were identified. Bystander is defined as any person not directly involved with the fumigation process, but is in the vicinity of the fumigation site. Estimates of exposure were based on limited monitoring data. The duration of exposure is defined as acute (24 hours or less), short-term (7 days or less), intermediate (more than 7 days to less than 1 year), annual (any exposure during the year), and lifetime.
4. In Risk Characterization, the risk associated with the estimated human exposures (Step 3) was evaluated using critical NOELs (Step 2). For all exposure scenarios in sulfuryl fluoride, the risk was expressed as a margin of exposure (MOE) with $MOE = \text{Critical NOEL} / \text{Estimated Human Exposure}$. The calculated MOE for each scenario was compared to a benchmark MOE, which

determined the acceptable risk level. Exposures with MOEs lower than this benchmark would be considered to pose health concerns. This benchmark was based on considerations of interspecies extrapolation, intraspecies variations, and other uncertainties. The benchmark MOEs were 100 and 1000 for occupational, and residential/bystander exposures, respectively. The 100-fold factor included the default uncertainty factors of 10-fold each for interspecies extrapolation and intraspecies variations. For residential/bystander exposures, an additional 10-fold uncertainty factor was included to address the lack of a developmental neurotoxicity study.

The ambient exposures for infant bystanders, the highest exposed group, were also compared with the acute reference concentration. Listing as a Toxic Air Contaminant would be recommended if the exposure level exceeded 1/10 of the reference concentration.

5. The uncertainties associated with the risk estimates were discussed in Risk Appraisal. These were generally due to limitations in the toxicology and human exposure data.

I.A.2. Specific Example

The following illustrates the risk evaluation for the acute exposure of infant bystanders during submaximal rate application of sulfuryl fluoride to a structure using the steps outlined above.

1. The database showed a range of NOELs and various toxicological effects in laboratory animals after acute exposure.
2. The critical acute NOEL was 300 ppm (calculated absorbed dose of 54 mg/kg/day) for lack of neurotoxicity in rats after exposure to sulfuryl fluoride for 6 hours/day for two days (Summary Table 1). Other terms in the calculations are: 4.17 mg/m³ (conversion factor of ppm to mg/m³ for sulfuryl fluoride), 0.96 m³/kg/day (default rat inhalation rate, Zielhuis and van der Kreek, 1979), 6 hours exposed/24 hours (amortization factor to extrapolate the 6 hours of exposure by rats in the study to a daily dose term), and 0.18 (the absorption factor based on a rat pharmacokinetic study, Mendrala *et al.*, (2002).

$$300 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 \times 0.96 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hours exposed}}{24 \text{ hours}} = 300 \text{ mg} / \text{kg} / \text{day}$$

$$\text{Absorbed dosage} = 300 \text{ mg/kg/day} \times 0.18 = 54 \text{ mg/kg/day}$$

This NOEL of 300 ppm resulted in a reference concentration of 0.12 ppm using the following equations (**Appendix E**). Other terms in the equation are: inhalation rate ratio to account for the difference in the inhalation rate between adult rat and infant human (0.96 m³/kg/day as default rat inhalation rate from Zielhuis and van der Kreek, 1979; 0.59 m³/kg/day as default infant human from Andrews and Patterson, 2000), 6 hours exposed/24 hours (amortization factor to extrapolate the 6 hours of exposure by rats in the study to a daily dose term), and 1000 (three 10-fold uncertainty factors to account for the extrapolation of data from laboratory animals, potential variation in response between individuals in a population, and the absence of a study to determine potential for sulfuryl fluoride to cause developmental neurotoxicity).

$$300 \text{ ppm} \times \frac{0.96 \text{ m}^3 / \text{kg} / \text{day}}{0.59 \text{ m}^3 / \text{kg} / \text{day}} \times \frac{6 \text{ hours exposed}}{24 \text{ hours}} = 122 \text{ ppm}$$

$$\frac{122 \text{ ppm}}{1000} = 0.12 \text{ ppm or } 0.51 \text{ mg} / \text{m}^3$$

3. The exposure assessment showed that the 24-hour time-weighted air level was 1.12 ppm (or calculated absorbed dose of 0.5 mg/kg/day for this age group) near a fumigated house (Summary Table 3).
4. Based on this exposure level, the MOE was 108 (54 mg/kg/day / 0.5 mg/kg/day) (Summary Table 5), nearly 10-fold below the benchmark of 1000. Compared to the reference concentration of 0.12 ppm, this exposure was 933% of the reference concentration (1.12 ppm/ 0.12 ppm x 100%). The infant exposure far exceeded the listing criteria of 1/10 the reference concentration.
5. Both the determination of the NOEL and exposure estimates contributed to the uncertainty of the risk. The risk would be underestimated if the NOEL for 24 hours of continuous exposure were substantially lower than the value based on amortization of a 6-hour study. On the other hand, the risk would be overestimated if infants were found to have lower exposures, *i.e.*, fewer than 24 hours being outdoors.

I.B. Summary of Health Assessment

The specific section with detailed discussion for each of the following summary is indicated in parenthesis after the heading.

I.B.1. Introduction (see **II.**)

Sulfuryl fluoride (Vikane→) is a fumigant registered for structural and non-food commodity fumigations in California. This comprehensive risk assessment focused on the current registered uses of sulfuryl fluoride and was conducted under the mandates of the Birth Defect Prevention Act (SB 950) and Toxic Air Contaminant Act (AB 1807). Potential exposure

to sulfuryl fluoride and fluoride in the diet from the use of sulfuryl fluoride (ProFume→) in food commodity fumigation will be assessed when the food-use registration is evaluated in California.

I.B.2. Toxicology Profile (see III.A. to III.I.)

A pharmacokinetic study in rats given ³⁵S-sulfuryl fluoride by inhalation showed that about 18% of the administered dose was absorbed. Peak plasma level was measured immediately after exposure, with the alpha phase half-life of 1 to 2 hours. The respiratory tract contained the highest level of radioactivity (³⁵S); lower levels were detected in the kidneys, brain, spleen, and other tissues. The primary route of excretion was via the urine (about 80% of the absorbed dose).

For acute toxicity, the concentrations for 50% lethality (LC₅₀) in rats were 3020-3730 ppm for 1-hour exposure and 991-1500 ppm for 4-hour exposure. The 4-hour LC₅₀ in mice was >400 ppm to 660 ppm. At non-lethal concentrations, neurotoxicity was observed in rats, mice, rabbits, and dogs. With acute to 2 weeks of exposures, clinical signs observed in these species included tremors, lethargy, respiratory effects, incapacitation, tetany, and convulsion. At the lowest-observed effect level, animals treated with sulfuryl fluoride for two weeks showed tissue damage in the kidney (rats), brain (rabbits, mice), and respiratory tract (rabbits and dogs). After 13 weeks of inhalation exposure, the brain was the primary target for sulfuryl fluoride toxicity in all species studied (rats, mice, rabbits, and dogs). The most common lesion was vacuoles in the cerebrum. Other effects reported were nasal tissue inflammation (rats and rabbits), kidney hyperplasia (rats), lung histiocytosis (rats), thyroid hypertrophy (mice), and fluorosis (rats).

After chronic exposure, the primary target tissue for sulfuryl fluoride was the brain and the respiratory tract in rats, mice, and dogs. As with subchronic exposure, brain vacuoles were observed in the cerebrum. The sites of lesions in the respiratory tract included nasal tissues, trachea, larynx, and lungs. Dental fluorosis was observed in both rats and dogs. Progressive glomerulonephropathy was considered the cause of death in sulfuryl fluoride treated rats.

Sulfuryl fluoride was not oncogenic in rats, mice, and dogs. Sulfuryl fluoride was not genotoxic in either *in vitro* or *in vivo* studies. The significant finding from reproductive and developmental toxicity studies was reduced body weight of fetuses (rabbits), pups (rat), and dams (rats). There were no teratogenic effects in rats or rabbits exposed to sulfuryl fluoride during gestation.

In humans, acute inhalation exposure to high concentrations of sulfuryl fluoride resulted in respiratory irritation, lung damage, central nervous system depression, and death. These high exposures occurred when people entered into structures illegally during fumigation or after insufficient aeration. Epidemiological studies showed that fumigation workers who used sulfuryl fluoride showed neurological effects, which included reduced performance on cognitive tests and pattern memory tests, and reduced olfactory function. However, there were confounding factors in these studies in that some workers were also exposed to methyl bromide, and actual exposure levels and duration were not investigated. Reversibility of effects or nasal tissue damage in these human studies was not examined.

I.B.3. Risk Assessment

Hazard Identification (see IV.A.)

The primary target tissues for sulfuryl fluoride inhalation toxicity for both humans and laboratory animals were the brain and respiratory system. In laboratory animals, dental fluorosis was reported after repeated exposures. Fluoride had been proposed as the active metabolite in the toxicity of sulfuryl fluoride. The primary support was the detection of fluoride in the pharmacokinetic study in rats. While dental fluorosis could be attributed to fluoride, the mechanism of toxicity for the other endpoints from the exposure to sulfuryl fluoride could be assumed to be due to fluoride and other metabolites (fluorosulfate and sulfate). However, there is no toxicity data on fluorosulfate or sulfate as a result of exposure to sulfuryl fluoride.

No tumors were found in rats or mice after chronic exposure to sulfuryl fluoride. Both *in vitro* and *in vivo* genotoxicity assays showed negative results. However, there were indications of pre-neoplastic effect. Hyperplasia of kidneys and nasal tissues, and hypertrophy of the thyroid were reported in laboratory animals after repeated exposures. Further experimental work is needed to determine whether or not sulfuryl fluoride would be carcinogenic to humans.

While not conclusive, there is some evidence that suggests fluoride can cause cancer, in particular the bone tissue. Fluoride is known to concentrate in calcified tissues. Both positive and negative results were reported in genotoxicity studies with sodium fluoride. Chronic toxicity studies with sodium fluoride in the drinking water showed low incidence of osteosarcoma in male rats, but not in female rats or either genders of mice in one study. Another study with sodium fluoride in the diet showed increased incidences of osteomas (benign bone tumors) in mice, but not rats. U.S. EPA classified sulfuryl fluoride as a chemical “not likely to be carcinogenic to humans”.

Since human case reports for sulfuryl fluoride did not provide sufficient exposure data, critical NOELs for risk characterization were established based on laboratory animal studies. The critical NOELs and reference concentrations are presented in Summary Table 1. The exposure durations of concern were acute, 1 to 2 weeks, subchronic, and chronic (annual) exposures. A NOEL for non-oncogenic effect after lifetime exposure was not separately identified. The reason is that the risk for lifetime exposure is lower than that for chronic exposure since the same chronic NOEL would be used to calculate risk for a much lower lifetime exposure. The reference concentrations for residential and bystander exposures were represented by infants because they have the highest inhalation rate, resulting in the lowest reference concentration compared to other age groups in the general population.

Exposure Assessment (see IV.B.)

Human exposures to sulfuryl fluoride could occur during the application and aeration phases of structural and non-food use commodity fumigations (Summary Tables 2 and 3). Exposure estimates were based on the assumption that label instructions were followed such that the maximum exposure was 5 ppm. Specifically, they were derived on monitoring data for

structural fumigation, and on the label limit of 5 ppm for commodity fumigation. While workers could experience acute and repeated exposures, residents and bystanders experienced primarily acute exposures. Bystander is defined as any person not directly involved with the fumigation process, but may be exposed as a consequence of the fumigant use. The air concentrations in these areas vary depending on many factors including weather conditions and location of the structure. In this document, the highest monitored levels were included in the exposure estimates, with the assumption that all bystanders, including neighbors, would be exposed to this level.

Summary Table 1. Critical no-observed-effect levels (NOELs) and reference concentrations for the risk characterization of sulfuryl fluoride.^a

Duration	NOEL (ppm)	NOEL (mg/kg/day)	NOEL in absorbed dose (mg/kg/day)	Reference concentration		Critical Endpoint
				Workers (Adult) UF=100	Residents/ Bystanders (Infants) UF=1000	
Acute 1 day	300	300	54	2.57 ppm 10.7 mg/m ³	0.12 ppm 0.51 mg/m ³	No effect in FOB and electro-physiological tests in rats
1-2 weeks	100	40	7.2	0.48 ppm 2.01 mg/m ³	0.023 ppm 0.10 mg/m ³	Brain lesion (malacia and vacuoles) in rabbits
Sub-chronic (13-week)	30	12	2.2	0.14 ppm 0.60 mg/m ³	0.007 ppm 0.03 mg/m ³	Brain lesion (vacuoles) in rabbits
Chronic	5	4	0.72	0.04 ppm 0.18 mg/m ³	0.002 ppm 0.01 mg/m ³	Lung inflammation, alveolar macrophage aggregates in rats

^{a/} From Table 18 of this volume.

Summary Table 2. Sulfuryl fluoride exposures of workers.^a

Exposure Groups	Short-term	Intermediate	Annual	Lifetime
A. Structural Fumigation				
Exposure duration	0.17 to 3.73 hrs/day, 1- 7 days	7 days to < 1 year	49 weeks/year	40 years/ 75 years
1. Fumigators at Submaximal Rate		Absorbed Dose (mg/kg/day)		
Introducing fumigant	0.03	0.01	0.006	0.003
Opening structure	0.0001	0.00004	0.00002	0.000009
Closing	0.000006	0.000002	0.0000008	0.0000004
Testing for clearance ^b	0.009	0.009	0.005	0.003
Total activities	0.04	0.02	0.01	0.006
Fumigator +tent crew	1.17	0.31	0.15	0.08
2. Tent Crew at Submaximal Rate				
Ground seam opening	0.30	0.05	0.02	0.01
Roof seam opening	0.31	0.07	0.04	0.02
Ground snake removal	0.04	0.01	0.007	0.003
Tarpaulin folding	0.06	0.02	0.008	0.004
General detarping	1.13	0.29	0.14	0.08
3. Fumigators at Maximal Rate				
Introducing fumigant	0.42	0.16	0.09	0.05
Opening structure	0.002	0.0005	0.0002	0.0001
Closing	0.00009	0.00002	0.00001	0.000006
Testing for clearance	0.009	0.009	0.005	0.003
Total activities	0.43	0.17	0.09	0.05
Fumigator +tent crew	16.85	4.39	2.17	1.16
4. Tent Crew Maximal Rate				
Ground seam opening	4.42	0.73	0.36	0.19
Roof seam opening	4.45	1.04	0.51	0.27
Ground snake removal	0.59	0.19	0.09	0.05
Tarpaulin folding	0.80	0.23	0.11	0.06
General detarping	16.42	4.22	2.08	1.11
B. Non-food Commodity Fumigation				
Exposure duration	Acute 8 hours/day		Annual 1 day/ year	Lifetime 1 day for 40/75 years
Handler	0.43	NA	0.001	0.001

^{a/} Values are from Table 7a and 7b of **Volume II** and in Table 19 of this volume. NA= not available.

Summary Table 3. Acute sulfuryl fluoride exposures of residents and bystanders.^a

Resident/Bystander Exposures (mg/kg/day)		
Structural Fumigation	Acute 12-hour	Acute 24-hour
Residents following clearance of home		
<1 year old	NA	0.57
1 to 18 years old	NA	0.49 to 0.20
Adult	NA	0.24
Bystanders during submaximal rate application		
<1 year old	0.36	0.50
1 to 18 years old	0.31 to 0.14	0.43 to 0.20
Adult	0.17	0.24
Bystanders during maximal rate application		
<1 year to 18 years old	3.6 to 1.4	5.0 to 2.0
Adult	1.7	2.4
Acute 2-hour		
Bystanders at TRAP aeration after submaximal rate application		
<1 year old		0.90
1 to 18 years old		0.78 to 0.36
Adult		0.43
Bystanders at TRAP aeration after maximal rate application		
<1 year old		13.1
1 to 18 years old		11.3 to 5.2
Adult		6.2
	Acute 1-hour	Acute 4-hour
Bystanders at Stack aeration after submaximal rate application		
<1 year old	0.14	0.15
1 to 18 years old	0.12 to 0.05	0.13 to 0.06
Adult	0.07	0.07
Bystanders at Stack aeration after maximal rate application		
<1 year old	1.4	1.5
1 to 18 years old	1.2 to 0.5	1.3 to 0.6
Adult	0.7	0.7
Non-food Commodity Fumigation		
	Acute 24-hour	
Bystanders at or near site		
<1 year to 18 years old	2.3 to 0.9	
Adult	1.1	

^{a/} Actual values from Tables 13 to 17 of the Exposure Assessment (Volume II) and in Tables 20 to 24 of this Volume. For exposure values presented as a range, they corresponded to the age range. NA=not available.

Risk Characterization (see IV.C.)

The acute NOEL was used to address the daily exposures (short-term exposures) of the fumigators and tent crews and acute exposures of residents and bystanders of the structural fumigation, as well as handlers and bystanders to non-food commodity fumigation. The short-term exposures of fumigators and tent crews were also assessed using a 1-2 week NOEL. Intermediate and annual exposures (more than 7 days per year) for these workers were assessed using subchronic and chronic NOELs, respectively. The potential risk from exposure to sulfuryl fluoride was evaluated by comparing the margins of exposure to benchmarks. The benchmarks were 100 and 1000 for occupational and residential/bystander exposures, respectively. For AB 1807, bystander exposures exceeding 1/10 of the reference concentration would be considered for listing as a toxic air contaminant. This criterion is equivalent to a MOE of less than 10,000 for bystander exposures.

A summary of the MOEs for occupational exposure scenarios is presented in Summary Table 4. For worker exposures in structural fumigation under submaximal rate applications, most of the MOEs were greater than 100, the benchmark for acceptable exposure. There were several acute and repeated exposure scenarios showed MOEs of less than 100. For exposures from maximal rate applications, the majority of the MOEs were less than 100. This was particularly the case for the tent crew. For handlers of non-food commodity fumigation, the MOE was 126 for acute exposure to the label limit of 5 ppm.

For all residential and bystander exposure scenarios, the MOEs for infant and children exposures were all less than 1000, the benchmark for acceptable exposure (Summary Table 5). In comparison with the acute reference concentration, the 24-hour time-weighted average exposures for infants during application and aeration phases were much higher than the acute reference concentration. For structural fumigation, infant estimated exposure was as much as 1,667% (during aeration using TRAP method) of the acute reference concentration. The estimated exposure for infants at a non-food commodity fumigation site was over 4,000% of the acute reference concentration.

Summary Table 4. Margins of exposure (MOEs) for sulfuryl fluoride exposures of workers.^a

Scenarios	Acute MOE	1-2 weeks MOE	Subchronic MOE	Chronic MOE
Structural fumigation at submaximal rate application				
<i>Fumigators</i>				
Introducing fumigant	>100	>100	>100	>100
Opening structure	>100	>100	>100	>100
Closing	>100	>100	>100	>100
Testing for clearance	>100	>100	>100	>100
Total activities	>100	>100	>100	67
Fumigator +tent crew	46	6	7	5
<i>Tent Crew</i>				
Ground seam opening	>100	24	44	29
Roof seam opening	>100	23	31	20
Ground snake removal	>100	>100	>100	>100
Tarpaulin folding	>100	>100	>100	94
General detarping	48	6	8	5
Structural fumigation at maximal rate application				
<i>Fumigators</i>				
Introducing fumigant	>100	17	13	8
Opening structure	>100	>100	>100	>100
Closing structure	>100	>100	>100	>100
Testing for clearance	>100	>100	>100	>100
Total activities	>100	17	13	8
Fumigator +tent crew	3	0.4	1	0.3
<i>Tent Crew</i>				
Ground seam opening	12	2	3	2
Roof seam opening	12	2	2	1
Ground snake removal	92	12	12	8
Tarpaulin folding	68	9	10	6
General detarping	3	0.4	1	0.3
Non-food commodity fumigation				
Handlers	>100	NA	NA	NA

^{a/} From Table 26 of this volume. NA=not available.

Summary Table 5. Margins of exposure for sulfuryl fluoride exposures of residents and bystanders.

Margins of Exposure (% Reference Concentration)^a		
Structural Fumigation	Acute 12-hour	Acute 24-hour
Residents following clearance of home		
<1 years old	NA	95
1- 18 years old	NA	110 to 270
Adult	NA	225
Bystanders during submaximal rate application		
<1 year old	150 (667% RfC)	108 (933% RfC)
1- 18 years old	174 to 386	126 to 270
Adult	318	225
Bystanders during maximal rate application		
All ages	15 to 39	11 to 27
	Acute 2-hour	
Bystanders at TRAP aeration after submaximal rate application		
<1 year	60 (1,667% RfC)	
1-18 years	69 to 150	
Adult	126	
Bystanders at TRAP aeration after maximal rate application		
<1 year	4	
1-18 years	5 to 10	
Adult	9	
	Acute 1-hour	Acute 4-hour
Bystanders at Stack aeration after submaximal rate application		
<1 year	386 (255% RfC)	360 (274% RfC)
1-18 years	450 to 1080	415 to 900
Adult	771	771
Bystanders at Stack aeration after maximal rate application		
<1 year	39	36
1-18 years	45 to 108	42 to 90
Adult	77	77
Non-food Commodity Fumigation	Acute 24-hour	
Bystanders at or near site		
<1 year	24 (4,167% RfC)	
1- 18 years	23 to 60	
Adult	49	

^{a/} From Tables 27-30 of this volume. % of Reference concentration (RfC) in parenthesis are for infant bystander exposures at submaximal application rate. % RfC was calculated only for this group, which had the highest exposures. NA=not available.

I.B.4. Risk Appraisal (see V.B to V.D.)

The uncertainties associated with the inhalation absorption factor and selection of the endpoints and NOELs were due to the use of studies with laboratory animals, and insufficient information for human. In this volume, the human absorbed dose after inhalation exposure was calculated using an absorption factor of 18%, based on a pharmacokinetic study in rats, assuming similar absorption of sulfuryl fluoride in humans. This is a simplistic approach since the internal dose is determined by the physiochemical properties of the chemical and the physiological functions of the animals. The higher rat inhalation frequency (80-100 breathes/minute), compared to those for humans (10-12 breathes/minute), suggests that more residential time in the alveolar space for the transfer of sulfuryl fluoride from the air to the blood, and therefore, a higher absorbed dose may be expected for humans. However, the extent of the uptake of sulfuryl fluoride from the air to the blood could be limited by the relative chemical solubility between these two compartments. Studies with volatile compounds showed generally higher (1.5 to 2-fold) blood: air partition coefficients for rat than human. This finding suggested that the chemical level in the rat blood may be the same or higher than those for human, contrary to that expected by considering inhalation rate alone. Because of the uncertainty in the calculation of the absorbed dose and the use of toxicity studies conducted using laboratory animals, DPR applied a default interspecies uncertainty factor of 10 for both pharmacokinetic and pharmacodynamic factors to the reference concentration and margin of exposure benchmark for sulfuryl fluoride. The use of this factor effectively sets the human exposure limit lower than a level based on the rat data alone. For intraspecies (individual) variations in the response to the toxicity of sulfuryl fluoride due to physiological and environmental factors, a default factor of 10-fold is also applied.

There were also uncertainties associated with the exposure estimates. Sources of under- and over-estimation of exposures included monitoring sample analyses, assumptions regarding use of Self-Contained Breathing Apparatus, application rate, frequency of use, and durations of exposure.

There was a large range of MOEs for workers depending on work activities. The MOEs for opening and closing structures were greater than 10,000, while they were less than 100 for some fumigator and tent crew activities. For adult residential exposures to structural fumigation (reentry, application, and aeration) at submaximal application rates, the acute MOEs for peak sulfuryl fluoride periods were generally greater than 100. However, the MOEs for young children were about 100, much less than the benchmark level of 1000. For bystanders to non-food commodity fumigation, the MOEs were all less than 100. These were based on the assumption of 24 hours of continuous exposures at 5 ppm. Since the bystander exposures exceeded 1/10 of the reference concentrations, sulfuryl fluoride meets the listing criteria for AB 1807.

I.B.5. Issues Related to the Food Quality Protection Act (see V.E.)

The Food Quality Protection Act (FQPA) mandated the U.S. EPA to address several issues in their risk assessment: potential increased sensitivity of infants and children, aggregate exposure from multiple routes, cumulative exposure from multiple sources, and potential for

endocrine disruption. While the current database did not show sulfuryl fluoride to cause endocrine disruption, there are concerns for the other three issues.

A comparison of NOELs showed that the NOELs for prenatal and post-natal toxicity (reduced fetal or pup body weights) of sulfuryl fluoride were higher than those for maternal effects. Therefore, the use of the lower NOEL for maternal effects would protect the younger population from effects at higher doses. However, there was a concern for potential developmental neurotoxicity in humans exposed to sulfuryl fluoride, which caused vacuoles in the brains of adult laboratory animals after repeated exposures. In the absence of a developmental neurotoxicity study, an additional ten-fold factor was included in the reference concentration calculation for residents/bystanders, and margins of exposure considerations.

For Vikane→, the primary route of exposure is inhalation. There would be aggregate exposures of sulfuryl fluoride and fluoride when ProFume→ is used for post-harvest fumigation of food commodities in California.

There is a potential for cumulative toxicity of fluoride from sources such as drinking water; food from the uses of cryolite and sulfuryl fluoride; uptake from soil; fluoride-supplemented consumer products; and the air. A worst-case scenario with highest worker exposure value showed total fluoride exposure of 0.85 mg fluoride/kg/day, a level clearly much higher than existing reference concentrations for fluoride. When the worker exposure was based on exposure at the reference concentration, the total exposure was 0.062 mg fluoride/kg/day with drinking water (0.028 mg fluoride/kg/day) as the main source and the worker exposure (0.003 mg/kg/day), a fraction (0.5%) of the total.

I.B.6. Conclusion

The human health risk associated with the use of sulfuryl fluoride in structural and non-food commodity fumigation was evaluated in this Risk Characterization Document. The critical toxicity endpoints were derived from laboratory animals: neurotoxicity in rats and rabbits for acute, 1-2 week, and subchronic exposures; and lung pathology in rats for chronic exposure. The primary route of exposure was inhalation for workers, residents, and bystanders. Estimated risks of human exposures were evaluated in terms of margins of exposure, and comparisons with the reference concentrations. The estimated acute exposures for bystanders exceeded 1/10 of the reference concentrations, thus would meet the criteria established by DPR for listing under the AB 1807 Toxic Air Contaminant Act. The MOEs for the following scenarios and exposure duration posed health concern with MOEs of less than 100 for occupational (adult) exposure or 1000 for residential and bystander exposures:

1. Structural fumigation:

- a. Workers at submaximal application rate: total fumigator activities (chronic), fumigator and tent crew tasks (all durations), ground seam opening (1-2 weeks, subchronic and chronic), roof seam opening (1-2 weeks, subchronic and chronic), tarpaulin folding (chronic), general detarping (all durations).
- b. Workers at maximal application rate: introducing fumigant (1-2 weeks, subchronic, and chronic), total fumigator activities (1-2 weeks, subchronic, and chronic),

- fumigator and tent crew tasks (all durations), all tent crew activities (all durations).
- c. Residents following clearance: all age groups (acute).
 - d. Bystanders during application phase: all age groups (submaximal and maximal rate application, acute 12-hours and 24-hours).
 - e. Bystanders during TRAP method of aeration: all age groups (submaximal and maximal rate application, acute 2-hours).
 - f. Bystanders during Stack method of aeration: all age groups, except 15-18 years (submaximal rate application, acute 1-hours), all age groups (submaximal rate application, acute 4-hours; maximal rate application, acute 1-hour and 4-hours).
2. Non-food commodity fumigation: all bystanders (acute 24-hours).

The potential for health concerns in these scenarios should be viewed in the context of the limitations and uncertainties discussed in this RCD. The toxicology database, while complete with respect to registration requirements in California, did not include a developmental neurotoxicity study. This study would be helpful to determine the neurotoxicity potential of sulfuryl fluoride in infants and children. The assumption was that the NOEL would be 10-fold lower than the critical NOELs. Additional acute toxicology studies with shorter observation periods or declining doses could better characterize the potential toxicity associated with some exposure scenarios. Additional exposure data, in particular those with maximal application rate and for commodity fumigation, would provide better estimates of actual exposure. At the time of this risk assessment, no air monitoring data were available for the non-food commodity fumigation scenario. Therefore, the worker exposure was assumed at 5 ppm, the maximum air concentration allowed by the label for workers not wearing SCBA. For bystanders, 5 ppm was also assumed to be the highest potential acute exposure after considering use practices for this scenario and 3 ppm as the highest monitored air concentration during structural fumigations. Since the Use Report indicates few uses of sulfuryl fluoride for non-food commodity fumigation, repetitive bystander exposure was considered unlikely. However, an expansion of uses to include food commodity fumigation may lead to more frequent exposures to sulfuryl fluoride by both workers and bystanders. This could produce greater risks than those calculated in this document. This prospect should be considered in the regulation of current and futures uses of sulfuryl fluoride.

II. INTRODUCTION

A human health risk assessment on the current use of sulfuryl fluoride (Vikane→) in structural and non-food commodity fumigation was conducted because of adverse effects identified in chronic and oncogenicity studies submitted under The Birth Defect Prevention Act of 1984 (SB 950). This assessment was also conducted because sulfuryl fluoride is a candidate for consideration as a toxic air contaminant under the Toxic Air Contaminant Act (AB 1807). Potential exposure to sulfuryl fluoride and fluoride ion (referred to as fluoride) in the diet from the use of sulfuryl fluoride in food commodity fumigation will be assessed when the food-use registration is evaluated in California. This latter assessment will also take into consideration the findings of the National Academy of Sciences (NAS)¹, if available, which is currently reviewing the regulatory levels for fluoride, a metabolite of sulfuryl fluoride. A glossary of terms used in this assessment is in **Appendix A**. A brief review of fluoride uses and toxicity is presented in **Appendix B**.

II.A. CHEMICAL IDENTIFICATION

Sulfuryl fluoride (sulfuric oxyfluoride) is a fumigant used in structural and commodity fumigations. Its insecticidal activity for drywood termites and other insects was first reported in 1956 (Kenaga, 1957; Doty and Kenaga, 1962). It is a non-flammable, non-corrosive, and odorless gas (Stewart, 1957). As an insecticide, sulfuryl fluoride disrupts carbohydrate and lipid metabolism of termites (Meikle *et al.*, 1963). Fluoride ion is considered the active metabolite; it inhibits lipase and other enzymes in the glycolysis cycle and increases oxygen uptake in treated termites. The termite dies when protein and amino acids, as energy sources, are depleted. Sulfuryl fluoride also inhibits metabolic processes in locust and mealworm eggs (Outram, 1970).

In humans, acute inhalation exposure to high concentrations of sulfuryl fluoride results in respiratory irritation, pulmonary edema, nausea, abdominal pain, central nervous system depression, numbness in the extremities, muscle twitching, seizures, and death (U.S. Environmental Protection Agency; U.S. EPA, 1999a). Proteinuria and azotemia may be associated with renal injury (U.S. EPA, 1999a). Case reports are presented in **III. HUMAN EXPOSURE**. The mechanism of sulfuryl fluoride toxicity in mammals has been attributed to fluoride (more discussion in **IV.A.2. Mechanism of Toxicity**). At lethal concentrations, sulfuryl fluoride would be expected to disrupt carbohydrate and lipid metabolism of humans similar to its action in termites. In addition, fluoride ion may affect muscle activity (muscle twitching, seizures) by binding to calcium (Scheuerman, 1985). Other effects may be attributed to its binding to potassium and magnesium ions. Direct contact with concentrated sulfuryl fluoride as a liquid causes tissue damage to eyes, mucous membranes, or skin (U.S. EPA, 1985a).

¹ In 2003, the U.S. EPA Office of Water requested the National Academy of Sciences (NAS) to evaluate the scientific and technical basis of the fluoride levels in the drinking water. The NAS has completed the project and the final report is pending. In the preprint report, the NAS recommended that the fluoride Maximum Contaminant Level Goal (MCLG) of 4 mg/L should be lowered. The U.S. EPA was to perform a risk assessment to determine the appropriate level.

II.B. REGULATORY HISTORY

The preparation, application, and aeration procedures for the use of sulfuryl fluoride, as Vikane→, are indicated on the product label, which has been approved by the U.S. EPA and Department of Pesticide Regulation (DPR).² In the preparation of a building for fumigation, the structure is evacuated and edible items are placed in airtight sealed containers. With windows and doors opened, the unoccupied building is covered with a tarpaulin (tarp) and sealed at the base to contain the fumigant. Since Vikane→ is odorless and colorless, chloropicrin is required to be added as a warning agent at 1 oz/10,000-15,000 ft³ or 0.07-0.1 g/m³ of space to be fumigated. It is released into the building at least 5 to 10 minutes prior to the introduction of Vikane→ from the outside at a specified application rate. On the next day, after the tarpaulin is removed, the inside is actively aerated with fans for at least 1 hour, and later passively to disperse and release the fumigant into the atmosphere. After a minimum aeration of 8 hours, the sulfuryl fluoride air concentration at the breathing zone inside the building is measured. The building is approved or "cleared" when the concentration is 5 ppm or less, a level considered safe for residents and workers to reoccupy the buildings. In non-food commodity fumigation, sulfuryl fluoride is introduced into containers or chambers containing the commodity to be fumigated. These chambers are then aerated with the release of sulfuryl fluoride via a stack into the atmosphere. Posting of a sign with information on the fumigation is required from application until the treated site air concentration is 5 ppm or less. More detailed discussion of the procedures is in the exposure assessment (**Volume II**).

II.B.1. U.S. EPA and California Regulations

Sulfuryl fluoride as Vikane→ was first registered as a pesticide for structural fumigation in 1959 (U.S. EPA, 1993a and b). In 1985, the U.S. EPA issued a reregistration guidance document for sulfuryl fluoride (U.S. EPA, 1985b). For reregistration, residue studies for sulfuryl fluoride and degradation products in the air and representative food and non-food articles were required because of concerns about human exposure to residues on fumigated household articles. Label changes were required to include the removal or sealing of edible items prior to fumigation, classification as a restricted use pesticide, precautionary statements for humans and ecological effects, inclusion of chloropicrin use directions if applicable, and respiratory protection equipment for applicators. There was no requirement for environmental fate data because sulfuryl fluoride was determined to be "strictly" for indoor uses and it dissipated into the atmosphere after use. The requirement of additional toxicology data was contingent upon the determination of residues on household items.

In 1993, U.S. EPA issued the Reregistration Eligibility Document (RED) for sulfuryl fluoride (U.S. EPA, 1993b). The RED concluded that the existing reentry level of 5 ppm did not provide sufficient margin of exposure (MOE) and needed to be lowered to 2 ppm for adults and 1 ppm for children. The registrant was allowed to submit additional data on residue dissipation for further assessment of the reentry level. Workers were required to wear NIOSH-approved, self-contained breathing apparatus (SCBA) upon reentry regardless of the sulfuryl fluoride air

² Actual images of the label and amendments for sulfuryl fluoride (registration number 62719-4) are available at <http://oaspub.epa.gov/pestlabl/ppls.home>

concentration. The U.S. EPA also determined that the workers might have subchronic and chronic exposures to sulfuryl fluoride and required the submission of a 90-day inhalation neurotoxicity study in rats. Label changes were needed to include more directions on the use of chloropicrin, fact sheets for adult occupants, and incorporation of an environmental hazard statement. After the completion of the RED, the U.S. EPA reevaluated the toxicology database and determined that a developmental neurotoxicity study should be required (U.S. EPA, 2001a). Based on monitoring data submitted under the RED, the U.S. EPA also determined that the worker reentry level should be at 1 ppm, but the residential exposure would be negligible (U.S. EPA, 2001b). To date, the label has remained at 5 ppm for worker reentry level, and has no requirement for SCBA for reentry.

In 2002, U.S. EPA issued temporary tolerances for the use of sulfuryl fluoride (ProFume→) in post-harvest fumigation of walnuts and raisins (U.S. EPA, 2001c and 2002a). The temporary tolerances were needed to support a 3-year experimental use permit (EUP) effective from 2002 to 2005. However, this EUP was never used because DPR did not issue the necessary state authorization for the EUP to proceed. This EUP was withdrawn when Dow Chemical Company submitted a petition to the U.S. EPA for the establishment of tolerances of sulfuryl fluoride and fluoride residues on dried fruits, nuts, and grains (U.S. EPA, 2002b). U.S. EPA later granted permanent tolerances for these uses (U.S. EPA, 2004a). A new petition to expand the post-harvest uses to additional food commodities, and on grassland was submitted by the registrant (U.S. EPA, 2005a) and new tolerances were recently established (U.S. EPA, 2005b).

In the evaluation of the year 2002 ProFume→ petition for these food uses, the U.S. EPA considered the residue chemistry databases for sulfuryl fluoride and fluoride ion as “marginally adequate,” since the available studies focused on the effect of fumigation conditions and not on residues resulting from proposed label directions. No worker or residential exposure data for commodity (food) fumigation use were submitted; U.S. EPA assumed that bystander exposure from grain processing facilities would not be of concern based on the following assumptions: (1) fumigation of grains is infrequent and the facilities are distant from residential areas, and (2) methyl bromide buffer zones used currently by the facilities would be adequate for sulfuryl fluoride. The U.S. EPA did not explain how a methyl bromide buffer zone would be applicable, but did indicate concerns regarding bystander exposure from tree nut and dried fruit fumigation facilities. Since there was no worker monitoring data, occupational exposure to ProFume→ was assumed at 1 ppm, the maximum limit on the label.

Also, the U.S. EPA noted that the Food Quality Protection Act (FQPA) factor (also referred to as the Special FQPA safety factor) to address potential increased sensitivity of infants and children was not needed (U.S. EPA, 2004 b and c). However, the database showed that sulfuryl fluoride is a neurotoxicant and a developmental neurotoxicity study was necessary. In the absence of such a study, the U.S. EPA applied a 10-fold FQPA safety factor (also referred to as the default FQPA safety factor) for the reference concentrations for chronic dietary exposure and repeated residential exposures. This FQPA mandated factor was retained since available data did not provide a basis to support the reduction or removal of such a factor. The requirement for a developmental neurotoxicity was later waived and replaced by a 10-fold uncertainty factor (more discussion under **V.E. Issues Related to the Food Quality Protection Act**). Because of

above inadequacies in the database, the U.S. EPA set conditions for the registration of ProFume→. These included the revision of the assessment after the NAS review of the fluoride maximum contaminant levels (MCLG and SMCL) in the water, and the submission of studies on developmental neurotoxicity, residues on fumigated commodities, and worker and resident exposures.

In California, Vikane→ is registered for use in structural and non-food commodity fumigations. The use of ProFume→ on grains, nuts, and dried fruits was recently approved with the maximum exposure limit of 1 ppm, as determined by the U.S. EPA. This use is being evaluated in a separate risk characterization document to address both inhalation and dietary exposures to sulfuryl fluoride. With respect to other regulatory actions in California, sulfuryl fluoride is a candidate for consideration as a toxic air contaminant under AB 1807. Sulfuryl fluoride is not listed under Proposition 65, the Safe Drinking Water Act because it is not considered a developmental/reproductive toxicant or a carcinogen.

II.B.2. Regulatory Limits and Standards

In establishing permanent tolerances for the use of sulfuryl fluoride in food commodities (U.S. EPA, 2004a), current U.S. EPA established reference concentrations (RfC) for inhalation exposure to sulfuryl fluoride as listed below. Additional discussion on these reference concentrations is under **IV.D.1. Hazard Identification and Reference Concentrations**.

- Short-term (1-30 days) exposure: 0.30 mg/kg/day (workers), 0.03 mg/kg/day (residents)
- Intermediate-term (1-6 months) exposure: 0.085 mg/kg/day (workers), 0.0085 mg/kg/day (residents)
- Long-term exposure (> 6 months): 0.028 mg/kg/day (workers), 0.0028 mg/kg/day (residents)

The Occupational Safety and Health Administration permissible levels for sulfuryl fluoride are: Permissible Exposure Level (PEL) of 5 ppm (20 mg/m³) as an 8-hour time-weighted average, and a Short-Term Exposure Level (STEL) of 10 ppm. The National Institute for Occupational Safety and Health set the Recommended Exposure Limit (REL) at 5 ppm and STEL at 10 ppm. The Immediately Dangerous to Life or Health Concentration (IDLH) is 200 ppm. The American Conference of Government Industrial Hygienists (ACGIH) Threshold Limit Values (TLV→) and STEL are 5 ppm and 10 ppm, respectively.

For fluoride, the U.S. EPA maximum contaminant level goal (MCLG) and secondary maximum contaminant level (SMCL) are 4 mg/L and 2 mg/L, respectively, in the drinking water (U.S. EPA, 2004a). These are equivalent to 0.114 mg fluoride/kg/day and 0.2 mg fluoride/kg/day for adults (70 kg and 2 L water/day) and children (10 kg and 1 L water/day), respectively. The chronic RfC for fluoride is 0.06 mg/kg/day with 0.01 mg/kg/day from the diet and 0.05 mg/kg/day from the drinking water containing 1 ppm fluoride (U.S. EPA, 2004a).

The California MCL for fluoride is 1.4 to 2.4 mg/L, depending on the ambient temperature (California Health and Safety Code, Title 22 as cited in OEHHA, 1997). The Office

of Environmental Health Hazard Assessment established a public health goal (PHG) of 1 ppm or 1 mg/L for the protection from dental fluorosis in children (OEHHA, 1997). This is equivalent to 0.1 mg fluoride/kg/day for children (10 kg and 1 L water/day).

II.C. TECHNICAL AND PRODUCT FORMULATIONS

Vikane® is the registered product for use in structural fumigation and non-food commodity fumigation in California. It is used to control a variety of pests such as drywood termites, powder post beetles, old house borers, bedbugs, clothes moths, rodents, and cockroaches in dwellings, buildings, construction materials, furnishings, and vehicles. Chloropicrin is used as a warning agent in the application of sulfuryl fluoride. In March 2005, DPR approved the registration of ProFume® for use in food commodity fumigation (raisins, nuts, and grains).

II.D. USAGE

From 1993 to 2004, Vikane® use increased from 1.5 million pounds to almost 3.3 million pounds per year in California (DPR, 2006). The major use is for structural pest control (>99% of total use) and the increase is attributed to the decline in the use of methyl bromide for the same purpose. For 2004, non-food commodity fumigation use of Vikane® was only 1,100 pounds. Vikane® is used year-round throughout the state with the highest use in Los Angeles County. The yearly use and use by county in California are in **Volume III**. Final use values for 2005 and 2006, which will include ProFume®, are not yet available.

II.E. ILLNESS REPORTS

Between 2000 and 2004, there were 26 cases reported to the DPR's Pesticide Illness Surveillance Program and determined to be at least possibly related to sulfuryl fluoride exposure due to direct spray, spill, drift, residues, and other causes (**Volume II**). Individuals with short-term exposures to sulfuryl fluoride, some in the presence of chloropicrin, had complained of eye (burning, water), nose (irritated), throat (coughing, dry), and respiratory (difficulty in breathing, shortness of breath) problems. Some also reported nausea, dizziness/light headedness, numbness of hands, disorientation, headache, confusion, and memory loss. Since these cases are generally not followed-up, there is no information on the reversibility of these effects. When people entering or remained in the houses during fumigation, deaths have been reported. Published case reports of human exposures to sulfuryl fluoride are presented in section **III.I. HUMAN EXPOSURE**.

II.F. PHYSICAL AND CHEMICAL PROPERTIES

Chemical name:	Sulfuryl fluoride, sulfuric oxyfluoride
CAS Registry number:	2699-79-8
Common name:	Sulfuryl fluoride
Trade name:	Vikane®, ProFume→
Molecular formula:	F ₂ O ₂ S
Molecular weight:	102.1 g/mole
Chemical structure:	$\begin{array}{c} \text{O} \\ \\ \text{F}-\text{S}-\text{F} \end{array}$
Physical appearance:	Odorless, colorless gas at 25EC
Solubility:	0.075 g/100 g water (25°C), 0.78 g/100 ml Wesson oil (20°C), 1.74 g/100 ml acetone (22°C), 2.12 g/100 ml chloroform (22°C)
Boiling point:	-55EC at 760 mm Hg
Melting point:	-136EC at 760 mm Hg
Vapor pressure:	1.16 x 10 ⁴ mm Hg at 20EC
Specific gravity:	1.342 g/ml for liquid at 25EC
Octanol:Water partition coefficient:	2.57
Henry's Law constant (K _b):	3.28 x 10 ⁻² atm·m ³ /mol
Conversion factor:	1 ppm=4.17 mg/m ³

^{a/} References: Torkelson, *et al.*, 1966; U.S. EPA, 1985 a and b, 1993 a and b; Rick *et al.*, 2000; Farm Chemicals Handbook, 2001; The Merck Index, 1996; Kenaga, 1957; and **Volume III**.

II.G. ENVIRONMENTAL FATE

Summary: Sulfuryl fluoride is hydrolyzed in water with release of fluoride ion. During structural and commodity fumigation, it is released into the air and binds to food components when the food items are not sufficiently sealed.

II.G.1. Environment

Sulfuryl fluoride is released into the air after use in structural and commodity fumigation. There is, however, little information on the ecological effect and environmental fate of sulfuryl fluoride. The U.S. EPA waived studies on soil and biota because they are difficult to conduct when the test compound is a gas at ambient temperature (U.S. EPA, 1993b). A discussion of available information is discussed in **Volume III**. In summary, available modeling program predicted that sulfuryl fluoride would not react with atmospheric radicals such as OH and NO₃. The estimated atmospheric lifetimes with respect to dissolution and/or degradation are 22 years in seawater and 1.25×10^7 years in cloud water. For lack of any data to suggest otherwise, sulfuryl fluoride is likely a greenhouse gas due to its ability to absorb infrared radiation and, expected long atmospheric lifetime.

II.G.2. Residues from Structural Fumigation

Sulfuryl fluoride is adsorbed into structural and household commodities during fumigation and desorbed when the fumigated structure is aerated. In response to the U.S. EPA requirement for residue data as part of the reregistration process (U.S. EPA, 1985b), several studies were conducted to determine if sulfuryl fluoride residues remained on household items after structural fumigation. The current label has food and closure requirements to minimize food contamination with sulfuryl fluoride during structural fumigation. In a laboratory study, sulfuryl fluoride residues were found in food items after fumigation with sulfuryl fluoride (36 mg/L or 360 mg/L) as a gas for 20 hours (Osbrink *et al.*, 1988 and Scheffrahn *et al.*, 1987). The items were in cups (except for apples and wrapped snack cakes) and were either uncovered, wrapped in one-layer, or two-layers of polyethylene films during fumigation. The films offered at least 79% and 96% of protection for one- and two-layers, respectively. Of the food items tested, highest levels of sulfuryl fluoride were detected in cooking oil and lowest in powdered milk (Table 1). At 36 mg/L sulfuryl fluoride and after 2 hours of aeration³, 23720 ppb, 4619 ppb, and 746 ppb of sulfuryl fluoride were detected in cooking oil samples with none, 1-layer, and 2-layer of films, respectively. At the same sulfuryl fluoride application rate, 5.4 ppb, 0.4 ppb, and 0.1 ppb of sulfuryl fluoride were detected in powdered milk for none, 1-layer, and 2-layer of films, respectively. With aeration of 2 hours and up to 960 hours, desorption half-life depended on the food item, fumigation concentration, and layers of polyethylene film. The half-life was generally shorter for items with lower initial concentration and density. For example in the 36 mg/L sulfuryl fluoride samples, the half-lives were about 3 hours for dog food and 8.06 to 11.36 hours for cake, compared to 13.86 to 31.51 hours for cooking oil.

³ In this and other Scheffrahn studies, the aeration was simply moving the fumigated samples to an air conditioned room. No specific air flow rate or temperature was provided.

The potential for sulfuryl fluoride residues in food stored on shelves or in freezers housed inside fumigated homes were examined in several studies. Scheffrahn *et al* (1989a) showed fluoride residues in frozen foods stored in a freezer during fumigation with sulfuryl fluoride (36 mg/L or 360 mg/L) for 20 hours and aeration for 5 minutes. For the two rates of sulfuryl fluoride, the corresponding fluoride residues in the uncovered food items were: 2.5 ppm and 66.1 ppm for beef, trace and 17.8 ppm for French fries, trace and 19.2 ppm for peas, 0.9 and 25.7 ppm for ice cream, and 5.9 and 89.7 ppm for flour.

Table 1. Effect of polyethylene film and the dissipation of sulfuryl fluoride residues from food or medicine.^a

Item	Layers of polyethylene film	Concentration (ppb) after 2 hours of aeration		Half-life (hours)	
		36 mg/L SF	360 mg/L SF	36 mg/L SF	360 mg/L SF
Cooking Oil	0	23,720	256,446	31.51	57.77
	1	4,619	22,431	14.44	63.02
	2	746	4,371	13.86	38.51
Flour	0	174	6,672	22.36	57.77
	1	13	59	10.19	99.03
	2	1	10	7.62	36.48
Beef	0	134	ND	22.36	ND
	1	10		5.93	
	2	0.9		NA	
Acetaminophen	0	17	682	20.39	49.51
	1	3.5	29	13.08	36.48
	2	0.3	8.7	NA	28.88
Apple	0	4,092	69,629	12.60	11.95
	1	70	4,176	NA	13.59
	2	2	402	NA	3.03
Cake	0	218	ND	11.36	ND
	1	25		8.06	
	2	0.5		NA	
Dog food	0	750	ND	3.71	ND
	1	134		3.26	
	2	28		3.15	
Powdered milk	0	5.4	ND	NA	ND
	1	0.4			
	2	0.1			

^{a/} Data from Osbrink *et al.*, 1988. SF=sulfuryl fluoride, NA=not enough data points to calculate, and ND=not fumigated at this rate. The half-life was not determined for powdered milk because only two aeration times (2 and 8 hours) were studied due to the low residues. Aeration occurred in an air-conditioned room; no specific air flow rate or temperature was provided.

In a similar study with longer aeration time, fluoride and sulfate residues were measured in 8 food items left on shelves during fumigation and aerated for 1, 8, or 15 days (Scheffrahn *et al.*, 1989b and 1987). There was essentially no change in the residue levels with time indicating that these ions were bound to the commodities. Higher fluoride and sulfate levels were found in dried beef and dry milk than in apple, cake, dog food, flour, acetaminophen and cooking oil. No measurable fluoride and sulfate residues were found in the oil samples, which contained relatively high levels of sulfuryl fluoride detected in another study (Osbrink *et al.*, 1988).

To test the effectiveness of bags to block sulfuryl fluoride entry into food, samples of frozen food (ground beef, French fries, peas, ice cream, and flour) were either uncovered or sealed inside polyethylene Ziploc bags (Scheffrahn, 1990a). They were placed inside a freezer (-20°C) in a fumigation chamber and fumigated for 20 hours at 727 and 6,803 mg sulfuryl fluoride-h/liter. After fumigation, the samples were extracted and analyzed for fluoride (quantitation limit of 0.8 ppm). No fluoride residues were found in any of the bagged samples. Fluoride residues found in uncovered samples were trace (French fries and peas) to 5.9 ppm (flour), and 17.8 (French fries) to 89.7 ppm (flour) for sulfuryl fluoride treatments of 727 mg-h/liter and 6803 mg-h/liter, respectively.

In another study, bags of different films and closures were filled with sulfuryl fluoride (5.4, 36, or 360 mg/L) to determine the protectiveness of the bags (Scheffrahn, 1990b). The concentrations corresponded to ca. 1.5, 10, or 100 times the field rate for drywood termite control. The closures from highest to lowest protection of leakage were: twist tie, heat seal, knot, masking tape, and Ziploc. Of the different types of bags, those made with nylon and nylon-containing film provided greater protection against sulfuryl fluoride penetration through the bags than those with polyethylene only.

Additional studies by Scheffrahn *et al* (1994) confirmed that nylon film bags provided more protection than polyethylene bags from sulfuryl fluoride entering the food during fumigation. Thirteen food items were placed either in a cupboard (22°C) or in a refrigerator (3°C) in a fumigation chamber and exposed to either 780 (refrigerated)/742 (cupboard) or 6113 (refrigerated)/6582 (cupboard) mg·h/L sulfuryl fluoride for 20 hours. After 2 hours of aeration, sulfuryl fluoride residues in the nylon film bags were 0 to 5.6 ppb (refrigerated) and 0 to 1.0 ppb (cupboard). Those in the polyethylene bags were 7.7 to 23.1 ppb (refrigerated) and 1.1 to 20.3 ppb (cupboard). The residue levels were further lowered with 6 hours of aeration and the reduction was greater for cupboards (6-10 fold) than the refrigerator (2-fold) samples.

The effect of manufacturer-packaging was also studied with store-bought items (Scheffrahn *et al.*, 1992). Each item was fumigated with 8,810 ppm sulfuryl fluoride for 20 hours. Sulfuryl fluoride entered into the food via diffusion through air channels in closures (reclosed peanut butter jar) or porous packaging (Parmesan cheese), and polymer permeation (polyurethane bagged foods). Factory sealed polyethylene terephthalate (PETE) containers, Barex (an acrylonitrile and butadiene copolymer) packaging, and vacuum-packaging provided good protection with low (or zero) residues in the food items. High residues were found in food with un-sealed packaging such as reclosed peanut butter (7.6 ppm) and Parmesan cheese (0.237 ppm).

III. TOXICOLOGY PROFILE

The toxicology database of sulfuryl fluoride consists mainly of inhalation toxicity studies because inhalation is the primary route of exposure. U.S. EPA evaluated the acute toxicity database and assigned a Toxicity Category I for acute inhalation toxicity (Lewis, 1999). U.S. EPA considered the submitted acute oral study as unacceptable and a Toxicity Category II was assigned for this route. The U.S. EPA waived other acute toxicity studies based on considerations of the physical-chemical properties and acute inhalation toxicity of sulfuryl fluoride. The assigned toxicity categories and studies were Category I for primary eye irritation, Category IV for acute dermal toxicity, Category IV for primary dermal irritation, and non-sensitizer for skin sensitization.

When DPR reviews the toxicity studies, the acceptability of the toxicology studies (except genotoxicity studies) is based on the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies is based on the Toxic Substances Control Act guidelines (Federal Register, 1985 and 1987). A study was considered supplemental information if the data requirement under SB 950⁴ for a certain study type was fulfilled by an acceptable study or if the study was not part of the data requirement. The toxicology summary for the studies is included in **Appendix C**. Individual animal data on serum fluoride levels from the 13-week subchronic toxicity studies are provided in **Appendix D**. These data were pertinent for the mechanism of toxicity discussion in **IV.A. Hazard Identification**. The no-effect levels in these studies may be expressed as No-Observed-Effect Levels (NOELs) or No-Observed-Adverse-Effect Levels (NOAELs). For the purpose of this volume, endpoints under either designation were considered relevant for hazard identification. NOELs for acute, 1-2 weeks, subchronic (13 weeks), and chronic exposures were identified. Selected toxicity studies considered for critical NOELs and lowest-observed-effect levels (LOELs) for hazard identification are presented in Tables 4, 10, and 14 for acute, subchronic, and chronic exposures, respectively. When available, the NOAELs established by the U.S. EPA (U.S. EPA, 2004b) were also included in the study summaries.

For comparison of doses between studies using different protocols and species, the exposure levels in ppm are converted to mg/kg/day doses. The nominal concentrations in ppm were used since they were almost the same as the measured concentrations. The equation took into consideration the air concentration, duration of exposure, and inhalation rate of the animal species studied (see **Appendix E** for calculations). This approach followed the dose calculation methods outlined in the 1992 U.S. EPA Exposure Assessment guidelines, where the potential dose is a function of the concentration and intake rate (U.S. EPA, 1992). It has generally been used for dietary exposure studies where the exposure concentration is expressed as the dose (for example, mg/kg/day) to account for consumption rate and duration of exposure. The doses indicated in the toxicology studies were not corrected for absorption. The study NOELs, which were chosen as the critical NOELs for risk characterization, were adjusted with an 18% absorption factor since exposure estimates were expressed as absorbed doses (**IV.A.4. Critical NOELs and Reference Concentrations**).

⁴The required studies are: chronic toxicity (in two species), oncogenicity (in two species), reproductive toxicity (rats), developmental toxicity (in two species), genotoxicity, and neurotoxicity studies.

III.A. PHARMACOKINETICS

Fischer 344 male rats (4/dose with jugular vein cannulated, and 4/dose non-cannulated) received nose-only inhalation exposure (4 hours) to ^{35}S -sulfuryl fluoride at 30 and 300 ppm (Mendrala *et al.*, 2002). Additionally, non-cannulated males (8/group) were exposed (4 hours, nose-only inhalation) to vehicle only or non-radiolabelled sulfuryl fluoride at 30 and 300 ppm. Time-weighted actual exposure concentrations with ^{35}S -sulfuryl fluoride were 28.4 ppm and 274 ppm at the 30 ppm and 300 ppm nominal levels respectively. They were 31.2 ppm and 312 ppm, respectively, for non-radiolabelled sulfuryl fluoride exposures. The actual dose administered was unknown since the amount inhaled and inhalation rates of the rats were not determined. Using a default rat inhalation rate of $0.96 \text{ m}^3/\text{kg}/\text{day}$ and an average body weight of 0.2 kg (0.19 to 0.24 kg used in the study), the estimated doses given over the 4 hours were 37 μmoles and 358 μmoles , respectively, for 28.4 ppm and 274 ppm.⁵ Blood, tissues (brain and kidney), and urine samples were collected and analyzed for radioactivity and fluoride levels at various times before, during, and after exposure. Based on the results of this study, the authors proposed the following metabolic scheme for sulfuryl fluoride. The rapid hydrolysis of sulfuryl fluoride was used to support their hypothesis that toxicity observed was due to fluoride, and not sulfuryl fluoride (additional discussion of fluoride under **IV.A.2. Mechanism of Toxicity**).



Radioactivity in the expired air of the 300 ppm group animals was monitored at 24 hours post-exposure. Since no radioactivity was detected at this time point, no further monitoring was conducted. Plasma levels of radioactivity peaked at 5.2 and 37.7 μg -equivalents/g (μg -eq./g) for 30 and 300 ppm, respectively, at the end of exposure. From the end of exposure to 24 hours post-exposure (alpha phase), half-lives were 2.6 and 2.4 hours at 30 and 300 ppm respectively, and from 24 hours post-exposure on (beta phase), half-lives were 82.7 and 56.2 hours, respectively. Red blood cell radioactivity reached 4.7 and 40.3 μg -eq./g red blood cell at 30 and 300 ppm respectively at the end of exposure. The alpha phase half-lives were 2.5 and 1.1 hours and beta phase half-lives were 222 and 139 hours at 30 and 300 ppm respectively.

After the 4-hour exposure, the majority of the radioactivity was detected in the urine (82-85% of absorbed dose) with lower levels in the feces (14-10% of absorbed dose) and tissues (5% of absorbed dose) for the two exposure levels (Table 2). Based on the estimated exposure dose of 37 μmoles and 358 μmoles for 30 ppm and 300 ppm, respectively, the total uptake was 18% and 16% accounting for cumulative levels in the urine and feces, and level in the tissues 7 days after exposure (Table 2). Since human exposures are expected to be less than 30 ppm, the 18% value was used to calculate the absorbed doses in the exposure assessment (**Volume II**). The uncertainty associated with the derivation and use of this factor is discussed in the Risk Appraisal section (**V.D. RISK CHARACTERIZATION**).

⁵ $28.4 \text{ ppm} \times 4.17 \text{ mg}/\text{m}^3 \times 0.96 \text{ m}^3/\text{kg}/\text{day} \times 0.2 \text{ kg} \times \text{day}/24 \text{ hours} \times 4 \text{ hours} \times 1 \text{ mmole}/102.07 \text{ mg} = 37 \mu\text{moles}$.

At 7 days post-exposure, the lungs had the highest radioactivity level, 0.77 and 6.30 $\mu\text{g-eq./g}$ for 30 and 300 ppm groups, respectively. Sulfuryl fluoride equivalents (for 30 and 300 ppm doses) in other tissues were: 0.312 and 3.491 $\mu\text{g-eq./g}$ in respiratory turbinates, 0.285 and 3.233 $\mu\text{g-eq./g}$ in olfactory turbinates, 0.394 and 3.075 $\mu\text{g-eq./g}$ in spleen, 0.368 and 2.756 $\mu\text{g-eq./g}$ in kidneys, and 0.227 $\mu\text{g-eq./g}$ and 1.913 $\mu\text{g-eq./g}$ in brain. Low levels of radioactivity were also measured in other tissues.

Elevated levels of fluoride ion were detected in urine, plasma, kidneys, and brain during and after exposure to sulfuryl fluoride (Table 2). Fluoride levels in other tissues were not measured. Most fluoride levels in the measured tissues returned to background levels at varying times post-exposure. Two radiolabelled metabolites, sulfate and fluorosulfate, as hydrolysis products, were identified in whole blood and urine.

Table 2. Distribution of ³⁵S-radioactivity and metabolites in the rat exposed to sulfuryl fluoride by inhalation.^a

Compartments/Time	Sulfuryl fluoride Concentration					
	30 ppm			300 ppm		
³⁵S-sulfuryl fluoride levels as μmole-equivalents 7 days after exposure						
Compartments	Level	% absorbed	% dose	Level	% absorbed	% dose
Urine	5.69	85	15	45.24	82	13
Feces	0.71	10	2	7.61	14	2
Tissues	0.34	5	0.9	2.9	5	0.8
Total % estimated dose			18			16
Metabolite levels as μmole/ml						
Time	Sulfate	Fluorosulfate		Sulfate	Fluorosulfate	
Urine						
During exposure	0.15	0.44		2.34	8.24	
Post exposure 0 to 6 hrs	0.76	0.55		3.83	2.82	
6 to 12 hours	0.12	0.02		0.70	0.16	
12 to 24 hours	ND	ND		0.23	0.04	
Blood						
During exposure	9.7	27.3		50.3	118.7	
Post exposure 0 hour	21.0	34.4		62.2	134.5	
1 hour	9.0	19.5		32.4	74.8	
4 hour	ND	ND		18.7	4.5	
Fluoride levels as μmole fluoride/g						
Plasma						
Non-exposed	0.033			0.033		
End of exposure	0.040*			0.132*		
Post exposure 2 hours	0.03			0.046		
4 hours	0.028*			0.037*		
8 hours	0.02*			0.0029*		
Brain						
Non-exposed	0.024			0.024		
End of exposure	0.042			0.119		
Post exposure 2 hours	0.041			0.070		
4 hours	0.042			0.052		
Kidney						
Non-exposed	0.119			0.119		
End of exposure	0.283*			0.292*		
Post exposure 2 hours	0.283			0.257		
4 hours	0.300*			0.265*		
Urine						
Non-exposed	0.117			0.134		
During exposure	0.491			4.013		
Post exposure 0 to 6 hrs	0.485			1.679		
6 to 12 hours	0.143			0.333		
12 to 24 hours	ND			0.265		

^{a/} Data from Mendrala *et al.*, 2002. Mean values (n=3) are presented. For 30 ppm and 300 ppm, the respective total absorbed levels were 6.74 μ mole -eq. and 55.75 μ mole-eq., and the estimated total inhaled doses were 37 μ moles and 358 μ moles. ND=not determined. *= Significant difference from control (non-exposed) at the indicated sacrifice time at p<0.05.

III.B. ACUTE TOXICITY

Summary: The lethal concentrations for 50% mortality (LC₅₀) in rats were 3,020-3,730 ppm for 1-hour exposure and 991-1500 ppm for 4-hour exposure. The 4-hour LC₅₀ in mice was >400 ppm to 660 ppm. At non-lethal concentrations, neurotoxicity was observed in rats, mice, rabbits, and dogs. With acute to 2 weeks of exposures, clinical signs observed in these species included tremors, lethargy, respiratory effects, incapacitation, tetany, and convulsions. At the lowest-observed effect level, animals treated with sulfuryl fluoride for two weeks showed tissue damage in the kidney (rats), brain (rabbits, mice), and respiratory tract (rabbits and dogs). Available oral and dermal toxicity studies did not provide sufficient data for toxicity evaluation. A summary of effects from acute and 1-2 weeks of exposures is shown in Table 4.

III.B.1. Inhalation- Rat

In an acute neurotoxicity study of sulfuryl fluoride, non-pregnant female Fischer rats (12/group) were exposed to sulfuryl fluoride (purity 93.6-99.7%; 0, 100 or 300 ppm) by whole-body inhalation (6 hours/day) for 2 days (Albee *et al.*, 1993a and b). Only females were used because they were more affected than males as measured by evoked potentials in a 13-week study (Mattsson *et al.*, 1986). Mean measured concentrations were 0, 97 or 291 ppm. There was no treatment-related effect in Functional Observational Battery (FOB), grip performance, landing foot splay, motor activity and electrodiagnostic responses (flash evoked potential, auditory brainstem response to clicks, and somatosensory evoked potential) examined within 24 hours after the final exposure. The NOEL was 300 ppm (300 mg/kg/day), the highest dose tested. This study was considered supplemental information to DPR. U.S. EPA set a NOAEL of 300 ppm for lack of neurotoxicity and other effects at the highest dose tested (Hansen, 1993; U.S. EPA, 2004b).

In a 2-week study, Fischer 344 rats (5/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 100, 300, or 600 ppm) by whole-body inhalation for 6 hours per day and 5 days per week (Eisenbrandt *et al.*, 1985; Eisenbrandt and Nitschke, 1989). The average measured concentrations were 0, 100, 293, and 597 ppm. At 600 ppm, 9/10 treated rats died or were moribund between the 2nd and the 6th dose. They were noted to be lethargic after the second exposure and “less active” with each additional exposure. Details on these observations were not provided in the report. Kidney effects (papillary necrosis, degeneration and regeneration of collecting tubules and proximal tubules) were noted in these animals with more severe findings in those that died early. At 300 ppm, 5/10 rats showed minimal renal changes (hyperplasia of the collecting ducts, basophilic epithelial cells in the proximal tubules) and statistically increased relative kidney weights in the female rats. Histopathological examinations showed no treatment-related effects in other organs including the brain and respiratory system. The acute NOEL was 300 ppm (300 mg/kg/day) for lethargy, morbidity and mortality at 600 ppm (600 mg/kg/day) after the second dose. The NOEL was 100 ppm (71 mg/kg/day) for kidney lesions at 300 ppm (214 mg/kg/day) after a two-week exposure.

Male rats (species not specified) were exposed to sulfuryl fluoride (purity not stated; 1,000 to 15,000 ppm) by whole-body inhalation exposure for up to 6 hours (Dow Chemical Company, 1959). Measured concentrations were stated to be the same as the nominal

concentrations. Treated rats showed tremors, convulsions, excess salivation, urination and occasionally bloody tears during the exposure. Mortality was observed in all groups. After 2-3 hours of exposure, rats of the lowest dose (1,000 ppm) were noted to show slight tremors and slight weight loss. There was one death (1/10 females) in this group after 2 hours of exposure. The estimated (from graphed data) 4-hour LC₅₀ was 1,500 ppm. The NOEL was <1,000 ppm (<334 mg/kg/day) for tremors and death after 2-3 hours of exposure to 1,000 ppm.

Fischer 344 rats (10/sex/group) were exposed to sulfuryl fluoride (purity 99.7%; 0, 250 to 2,000 ppm) by whole-body inhalation for 4 hours and were observed twice daily for 14 days (Miller *et al.*, 1980). Average measured concentrations were 450; 1,000; 1,250; 1,425; or 2,025 ppm for the male groups. They were 0; 320; 450; 700; 790; 1,000; 1,020; 1,200; 1,425; or 2,025 ppm for the female groups. No effects were observed at 450 ppm or less after 4 hours of exposure. The 4-hr LC₅₀s were 1,122 ppm and 991 ppm for males and females, respectively. At 1,425 and 2,025 ppm, treated rats showed sedation (20 minutes of exposure), prostration (40 minutes), convulsions (1-2 hours), and all died after 4 hours of exposure. At 1,000-1,250 ppm, some animals did not eat or drink and were lethargic, and some died. At or below 1,000 ppm, no deaths occurred but some female animals in the "750" ppm group (the report did not specify whether it was the measured 700- or 790-ppm groups) showed lethargy. The body weight gain of the survivors was generally lower (some statistically significant at $p < 0.05$) than that for the control during the 2-4 days after exposure. After 14 days, most of the animals recovered with only the 1,000-ppm males showing significantly decreased body weight gain. There were no significant treatment-related effects on the organ weights of liver, kidney, brain, lung, and testes. Gross examination of the animals that died during exposure showed lesions primarily in the respiratory tract and included accumulation of secreted material near the nose and/or eyes, inflammation of the nasal cavity, and edema in the lungs. Histological examination was conducted only for the control, 1,250-ppm males and 1,200-ppm females. Treatment related effects observed in animals killed or died in these groups were: kidney (renal tubular degeneration 0/20 control *versus* 7/20 treated for both genders), lung (mineralization and inflammation of the pleura 0/20 control *versus* 1/20 treated), heart (multifocal myocardial degeneration 0/20 control *versus* 1/20 treated) and spleen (cellular depletion of the red pulp or atrophy 0/20 control *versus* 4/20 treated). No visible lesions were found in the brain. The acute NOEL was 450 ppm (300 mg/kg/day) for lethargy at 750 ppm (500 mg/kg/day) and mortality at 1,000 ppm.

Male Fischer 344 rats (4/group) were exposed to sulfuryl fluoride (purity 99.8%; 0; 4,000; or 10,000 ppm) by head-only inhalation exposure for 20 minutes (Landry and Streeter, 1983). Measured concentrations were not given in the report, and the data were presented in graphical form. At 4,000 ppm, rats showed an initial increase in the mean respiratory frequency (maximum of 39%), but a decrease in mean tidal volume (maximum of 40%) and mean minute volume (maximum of 23%), when compared to pre-exposure levels. At 10,000 ppm, rats were more affected with a maximum of 60% increase in the mean respiratory frequency, maximum of 59% decrease in mean tidal volume, and maximum 53% decrease in mean minute volume, when compared to pre-exposure levels. These changes were transient as the maximum values for the group were measured after 1-2 minutes of exposure and were at near pre-exposure levels at 10 minutes of exposure and for the rest of the exposure duration. The 10,000-ppm rats were noted as "very ill" at the end of the 20-minute exposure but no clinical signs were specified. The

authors considered these effects to be an indication of pulmonary irritation. The NOEL was <4,000 ppm (<200 mg/kg/day) for respiratory effects at 4,000 ppm during the 20 minutes of exposure. This study was considered supplemental information to DPR.

Fischer 344 rats were exposed to 4,000 ppm (3 male/2 female) or 20,000 ppm (3 male/1 female) sulfuryl fluoride (purity 99.8%) by whole-body inhalation until death (Gorzinski and Streeter, 1985). Measured concentrations were not given in the report. The mean survival times were 79±10 minutes and 14±4 minutes for 4,000 ppm and 20,000 ppm, respectively. In the 4,000-ppm group, the body temperature decreased 7°C over 80 minutes while the systolic blood pressure gradually increased from about 140 mm Hg to 185 mm Hg. The heart rate continued to decrease until death. Necropsy showed slight perivascular and alveolar edema. The NOEL was <4,000 ppm (<667 mg/kg/day) for effects on body temperature, blood pressure, and heart rate at 4,000 ppm. This study was considered supplemental information to DPR.

Male Fischer 344 rats (5/group) were exposed to sulfuryl fluoride (purity 99.8%; 4,000; 10,000; 20,000; 40,000 ppm) by whole-body inhalation for 20 minutes while alternating walking in a rotating motor-driven activity wheel and resting during the exposure (Albee *et al.*, 1983; Nitschke *et al.*, 1986). Measured concentrations were not given in the report. The times to incapacitation were: 41.5 minutes (4,000 ppm), 16.3 minutes (10,000 ppm), 10.3 minutes (20,000 ppm), and 6.4 minutes (40,000 ppm). Depending on the dose, the survival times were less than 10 minutes (20,000 and 40,000 ppm), 60 minutes (10,000 ppm), or 2.5 hours (4,000 ppm) after the end of exposure. Some rats showed tonic convulsions prior to death. Necropsy showed vascular congestion, pulmonary congestion, and alveolar and interstitial edema. Pretreatment of rats with calcium gluconate enhanced the survival of the 4,000-ppm group but had no effect on convulsions. Pretreatment of rats with an anticonvulsant (phenobarbital, diazepam, or diphenylhydantoin) prevented convulsions during sulfuryl fluoride exposure (Nitschke *et al.*, 1986). As a post-exposure anticonvulsant for sulfuryl fluoride, phenobarbital was more effective than diazepam. Diphenylhydantoin, however, accentuated the toxicity of sulfuryl fluoride. The NOEL was <4000 ppm (<454 mg/kg/day) for incapacitation after 41 minutes of exposure. This study was considered supplemental information to DPR.

In a screening report of about 110 chemicals and solutions, rats (species not specified, 5/dose) were exposed to sulfuryl fluoride in bell jars or large desiccators for the determination of 1 hour lethal dose (Vernot *et al.*, 1977). No details of the study were provided. The reported 1 hour LC₅₀ were 3,730 (3,090-4,510) ppm for males and 3,020 (2,830-3,220) ppm for females.

III.B.2. Inhalation - Mouse

CD-1 mice (5/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 600, 700, or 800 ppm) by whole-body inhalation for 4 hours (Nitschke and Quast, 1990; Nitschke, 1994a). Mean measured concentrations were 0, 596, 692, or 806 ppm. No treatment-related effects were noted for mice in the 600-ppm group. There were deaths in the other groups: 9/10 for 700 ppm and 7/10 for 800 ppm. Body tremors and lethargy were observed in several mice in these two groups shortly after exposure. The reported LC₅₀s were 642 ppm and 660 ppm for males and females, respectively. The acute NOEL was 600 ppm (751 mg/kg/day) based on tremors, lethargy, and death at 700 ppm (876 mg/kg/day) and 800 ppm. This study was considered

acceptable with toxicity in Toxicity Category III under FIFRA guidelines.

B6C3F1 mice (5/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 400; 600; or 1,000 ppm) by whole-body inhalation for 4 hours (Nitschke and Lomax, 1989). Mean measured concentrations were 0; 404; 603; or 1,003 ppm. All mice at 600 ppm (5 days post exposure) and 1000 ppm (within 90 minutes) died. Some 600-ppm mice showed tremors and lethargy before death. No effects were observed for the 400-ppm group. The LC₅₀ (male/female) was > 400 ppm (1.67 mg/L) but < 600 ppm (2.80 mg/L). The acute NOEL was 400 ppm (500 mg/kg/day) for tremor, lethargy, and death at 600 ppm (751 mg/kg/day). The study was considered acceptable with toxicity in Toxicity Category III under FIFRA guidelines.

CD-1 mice (5/sex/group) were exposed to sulfuryl fluoride (purity 99.6%: 0, 30, 100, and 300 ppm) by whole-body inhalation for 6 hours per day, 5 days per week, for 9 exposures (Nitschke and Quast, 2002). Mice were sacrificed 1 day after the last exposure and subjected to limited hematology and clinical chemistry studies, gross necropsy and histopathology. At 300 ppm, 9 of 10 mice died between day 7 and necropsy. Deaths were preceded by inanition (statistically significant body weight losses, decreased ingesta in digestive tract, decreased body fat), and associated pathology (stomach erosion/ulcers, hepatocellular atrophy). Most decedents had “roughened hair coat” and at least 3 of the males had whole body tremors. All high dose mice, except for 2 with tissue autolysis, showed cerebral vacuolation (7/8 moderate, 1/8 very slight). At 100 ppm, 4/5 males and 2/5 females showed very slight cerebral vacuolation. The high dose mice (4/5 males, 1/5 females) also had very slight vacuolation of the medulla. Also, nine high dose mice had lacrimal/Harderian gland atrophy. The NOEL was 30 ppm (40 mg/kg/day) based on cerebral vacuolation at 100 ppm (134 mg/kg/day). This study was considered acceptable to DPR under FIFRA guidelines.

III.B.3. Inhalation – Rabbit

New Zealand white rabbits (3/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 100, 300, or 600 ppm) by whole-body inhalation for 6 hours per day and 5 days per week for two weeks (Eisenbrandt *et al.*, 1985; Eisenbrandt and Nitschke, 1989). The average measured concentrations were 0, 100, 293, and 597 ppm. One 600-ppm female rabbit had convulsions following the fifth exposure (Table 3). Another female rabbit had fractured vertebra after the 6th dose but the cause was unknown as no convulsions were noted. Both rabbits were euthanized. Other rabbits were noted to be “slightly hyperactive” (time of onset and frequency were not given in the report). All rabbits in the 300-ppm and 600-ppm groups showed lesions in the cerebrum (Table 3). Vacuolation was found in the globus pallidus and putamen (basal nuclei) as well as the external and internal capsules (myelinated tracts). The cerebrum of all rabbits in the 600-ppm group and 2/6 of the 300-ppm group showed malacia⁶ with reactive gliosis and demyelination. Tissue inflammation in the nasal, trachea, and bronchi/bronchioles was observed in the 300 ppm and 600 ppm rabbits. The NOEL was 100 ppm (40 mg/kg/day) for brain and respiratory tract lesions at 300 ppm (121 mg/kg/day). The U.S. EPA established a

⁶ Malacia is defined as liquefaction necrosis (Quast *et al.*, 1993c). The severity of very slight involves minimal localized amount of the caudate nucleus evaluated in the multiple sections. Slight indicates a larger size of the focal malacia involving 5 to 10% of the caudate nucleus. Moderate reflects greater than 10% of the section affected.

NOAEL of 100 ppm for focal malacia and vacuolation in the cerebrum and inflammation of the nasal tissue and trachea (U.S. EPA, 2004b; MRID 148956).

Table 3. Effects of sulfuryl fluoride in rabbits after 2-week inhalation exposure.^a

Effects ppm mg/kg/day	Males				Females			
	0	100	300	600	0	100	300	600
	0	40	121	241	0	40	121	241
Clinical Observation								
Convulsion	0/3	0/3	0/3	0/3	0/3	0/3	0/3	1/3 ^b
Hyperactivity- slight	0/3	0/3	0/3	3/3*	0/3	0/3	0/3	1/3
Histopathological Examination								
Cerebrum								
Malacia, bilateral, focal								
slight	0/3	0/3	0/3	0/3	0/3	0/3	1/3	2/3
moderate	0/3	0/3	1/3	3/3*	0/3	0/3	0/3	1/3
Vacuolation, bilateral,								
focal very slight	0/3	0/3	0/3	0/3	0/3	0/3	0/3	2/3
slight	0/3	0/3	3/3*	3/3*	0/3	0/3	3/3*	1/3
Nasal tissue								
Inflammation, multifocal								
slight	2/3	1/3	0/3	0/3	3/3	3/3	1/3	0/3
moderate	0/3	0/3	3/3*	3/3*	0/3	0/3	1/3	3/3*

^{a/} Data from Eisenbrandt *et al.*, 1985. *=Significance at $p < 0.05$ by the Fisher's Exact Test.

^{b/} One rabbit was euthanized after found with fractured vertebra.

III.B.4. Inhalation - Dog

Beagle dogs (1/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 0, 30, 100, or 300 ppm) by whole-body inhalation (6 hours/day) for nine exposures over two weeks (Nitschke and Quast, 1991). Average measured concentrations were 0, 28.9, 96.3, or 298.2 ppm. No treatment-related effects were observed in the 30-ppm and 100-ppm groups. The clinical signs observed were intermittent tremors and tetany in both 300-ppm dogs from day 5 onward. Specific time of occurrence was not reported. These effects were so severe that exposure was terminated after 5.5 hours on day 9. Dogs were reported to show normal appearance and behavior within 30 minutes after exposure. Histopathologic examination of the cerebral cortex, brain stem, cerebellum and medulla oblongata did not show any tissue damage. Nasal turbinates and trachea of 300-ppm dogs showed inflammation and was considered slight. The NOEL was 100 ppm (29 mg/kg/day) based on clinical signs after 5 exposures and nasal tissue inflammation after two-weeks at 300 ppm (87 mg/kg/day).

III.B.5. Oral - Rat and Guinea Pig

In an overview, Quast (1988) summarized several acute studies but no details were provided. In the oral toxicity studies, rats (males and females) and guinea pigs (females) were given sulfuryl fluoride bubbled into 1% corn oil. The LD₅₀ was reported to be 100 mg/kg. In another study, rats were fed sulfuryl fluoride fumigated feed for 66 days. No treatment-related effects were noted in rats given feed fumigated with 2 lbs sulfuryl fluoride/1,000 cubic feet of feed. However, dental fluorosis and kidney damage (not specified) were observed in animals treated at 10, 100, or 200 lbs sulfuryl fluoride/1,000 cubic feet. The authors considered these findings to be consistent with those observed in inhalation toxicity studies.

III.B.6. Dermal - Rabbit

Quast (1988) also described a study with rabbits exposed to sulfuryl fluoride dermally for a total of 7 hours. A bag filled with sulfuryl fluoride was wrapped around the body but the report did not indicate any skin preparation or actual exposure concentration. No effects were reported.

Table 4. Acute and 1-2 week inhalation toxicity of sulfuryl fluoride.^a

Species/ duration	Lethal Concentrations (LC ₅₀)- assigned as Category I by U.S. EPA	Ref
Rat	4 hours: 1,500 ppm 1 hour: 3,730 ppm (male); 3,020 ppm (female)	1 2
Mouse	4 hours: 1,122 ppm (male); 991 ppm (female) 4 hours: 642 ppm (male), 660 ppm (female) 4 hours < 600 ppm (LC ₅₀) > 400 ppm	3 4*,5 6

Species /duration	NOEL		LOEL		Effects at the LOEL	Ref.
	ppm	mg/kg/day ^b	ppm	mg/kg/day ^b		
Acute exposures (1-2 days)						
Rat 6 hr/d x 2d	300 HDT	300	ND^c	ND^c	No effects (FOB, electrodiagnostic tests)	7
Rat up to 6 hr	ND ^c	ND ^c	1,000	334	Slight tremors after 2-3 hours of exposure and weight loss, 1 death	1
Rat 4 hr	450	300	750	500	Lethargy (females) at 750 ppm (mortality at 1000 ppm, tissue lesions at 1200-1250 ppm)	3
Rat 20 min (head-only)	ND ^c	ND ^c	4000	200	Transient ↑ respiratory frequency, ↓ mean tidal volume & mean minute volume	8
Rat 1 hr	ND ^c	ND ^c	4000	667	↓ Body temperature, ↑ blood pressure, ↓ heart rate, death	9
Rat 41 min	ND ^c	ND ^c	4000	454	Incapacitation	10
Rat 6 hr/dx5d/w	300	300	600	600	Moribund and death between 2 nd and 6 th dose	11
Mouse 4 hr	600	751	700	876	Tremors, lethargy, death	4*
Mouse 4 hr	400	500	600	751	Tremors, lethargy, death	6*
1-2 weeks of exposure						
Rat 6 hr/dx5d/wx2w	100	71	300	214	Kidney lesions	11
Rat 6 hr/d x gd 6-15 ^d	100	100	300	300	↓ Body weight; liver, kidney effects	12
Rat 6 hr/d x gd 6-15 ^d	225 HDT	225	ND ^c	ND ^c	No effects observed	13*
Mouse 6 hr/dx5d/wx2w	30	40	100	134	Cerebral vacuolation	14*
Rabbit 6 hr/d x 5d/w x2w	100	40	300	121	Brain & respiratory tract lesions; convulsion (after the 6th dose) & hyperactivity at 600 ppm	11
Rabbit 6 hr/d xgd 6-18 ^d	100	56	300	169	Maternal: ↓ body weight, ↓ liver weight	12
Rabbit 6 hr/d xgd 6-18 ^d	75	42	225	127	Maternal and fetal: ↓ body weight	13*
Dog 6 hr/d x5d/w x 2 w	100	29	300	87	Intermittent tremors and tetany (day 5 onward), nasal tissue inflammation (slight)	15

^{a/} Unless noted, all studies were conducted with whole-body exposures. Abbreviations: min=minutes, hr=hour, d=day, w=week, gd=gestation day, HDT=highest dose tested. * Indicates study acceptable to DPR under FIFRA guidelines. References: 1. Dow Chemical Company, 1959; 2. Vernot *et al.*, 1977; 3. Miller *et al.*, 1980; 4. Nitschke and Quast, 1990; 5. Nitschke, 1994a; 6. Nitschke and Lomax, 1989; 7. Albee *et al.*, 1993a; 8. Landry and Streeter, 1983; 9. Gorzinski and Streeter, 1985; 10. Albee *et al.*, 1983; 11. Eisenbrandt *et al.*, 1985; 12. Hanley *et al.*, 1980; 13. Hanley *et al.*, 1981; 14. Nitschke and Quast, 2002; 15. Nitschke and Quast, 1991. Bolded study is used for risk characterization.

^{b/} Equations for calculations are in **Appendix E**.

^{c/} ND=not determined, when either the NOEL or LOEL was not experimentally determined.

^{d/} Studies described under **III.G. DEVELOPMENTAL TOXICITY**.

III.C. SUBCHRONIC TOXICITY

Summary: After 13 weeks of inhalation exposure, the brain was the primary target for sulfuryl fluoride toxicity in all species studied (rats, mice, rabbits, and dogs). The most common lesion was vacuoles in the cerebrum. Other effects reported were nasal tissue inflammation (rats and rabbits), kidney hyperplasia (rats), lung histiocytosis (rats), thyroid hypertrophy (mice), and dental fluorosis (rats). A summary of the subchronic toxicity studies is presented in Table 10.

III.C.1. Inhalation - Rat

Fischer 344 rats (10/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 30, 100 or 300 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 13 weeks (Nitschke *et al.*, 1987a; Eisenbrandt and Nitschke, 1989). Average measured concentrations were 0, 29.8, 100 or 297 ppm. No clinical signs were observed. The mean serum fluoride levels appeared to show a dose-related increase with treatment (Table 5). However, they were not statistically significant from the control because of the wide range of values for all the groups. For the males, the ranges of serum fluoride were: 0.416 µg/ml to 2.95 µg/ml (control), 0.356 µg/ml to 1.156 µg/ml (30 ppm), 0.456 µg/ml to 2.626 µg/ml (100 ppm), and 0.63 µg/ml to 2.538 µg/ml (300 ppm). For the females, the ranges of serum fluoride were: 0.252 µg/ml to 1.57 µg/ml (control), 0.274 µg/ml to 2.374 µg/ml (30 ppm), 0.372 µg/ml to 0.969 µg/ml (100 ppm), and 0.69 µg/ml to 3.272 µg/ml (300 ppm). Mottled incisors were observed in all treated animals at 100 and 300 ppm.

At 300 ppm, the body weights were reduced ($p < 0.05$) after 24 and 45 days of exposure, for females and males respectively. At termination (day 87), the body weights were 83% (males) and 85% (females), respectively, of controls. Pathological examination of the 300-ppm tissues showed slight cerebral vacuolation, kidney hyperplasia and decreased protein droplets, pulmonary subpleural histiocytosis and nasal mucosal inflammation (Table 5). The vacuolation was limited to the caudate-putamen nuclei. Special stains on the tissues did not provide any information on the characteristics of the vacuoles. The NOEL was 30 ppm (21 mg/kg/day) for mottled incisors at 100 ppm (71 mg/kg/day) and 300 ppm. For other effects, the NOEL was 100 ppm (71 mg/kg/day) for reduced body weights and histological changes in the brain, kidneys, lungs and nasal tissues at 300 ppm (214 mg/kg/day). This study was considered acceptable to DPR. U.S. EPA established only a NOAEL of 30 ppm for fluorosis.

Table 5. Serum fluoride and histopathology in rats after inhalation exposure to sulfuryl fluoride for 13 weeks.^a

Effects ppm <i>mg/kg/day</i>	Males				Females			
	0 0	30 21	100 71	300 214	0 0	30 21	100 71	300 214
Serum fluoride (mean ± sd µg/ml)	0.996 ±0.788	0.715 ±0.288	0.881 ±0.661	1.154 ±0.574	0.607 ±0.449	0.738 ±0.63	0.575 ±0.198	1.366 ±0.959
Histopathology	Number of animals affected/Total in group							
Brain (cerebrum) Vacuolation, focal: slight	0/10	0/10	0/10	10/10*	0/10	0/10	0/10	10/10*
Kidney (collecting duct) Hyperplasia: very slight	0/10	0/10	0/10	0/10	0/10	0/10	0/10	9/10*
Kidney (cortex) Protein droplets:very slight	0/10	0/10	0/10	10/10*	0/10	0/10	0/10	0/10
Lungs (alveolar) Histiocytosis, subpleural, slight	0/10	0/10	0/10	10/10*	0/10	0/10	0/10	10/10*
Nasal Tissues Inflammation, mucosa diffuse:								
very slight/slight	0/10	0/10	0/10	7/10*	0/10	1/10	0/10	10/10*
moderate/severe	0/10	0/10	0/10	3/10	0/10	0/10	0/10	0/10

^{a/} Data from Nitschke *et al.*, 1987a. *=Significance at $p < 0.05$ by Fisher's Exact Test.

Fischer 344 rats (7/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 30, 100 or 300 ppm) by inhalation (6 hours/day, 5 days/week) for 13 weeks (Mattsson *et al.*, 1986). A recovery group (2/sex/group at 0 or 300 ppm) was also treated and evaluated 2 months after exposure. Average measured concentrations were 0, 30, 100, and 297 ppm. Rats were implanted with epidural electrodes to monitor visual evoked response (FEP), cortical flicker fusion (CFF), auditory brainstem responses (ABR), cerebellar evoked response, somatosensory evoked response (SER-C and SER-S), and caudal nerve action potential. They were also subjected to a battery of neurological tests: hindlimb grip strength and an observation battery after the last exposure, but no treatment-related effects were observed at any dose. FEP and SER-S evoked responses were noted as significantly ($p < 0.05$) slower in females at 100 ppm, and the ABR latency in the 100-ppm males appeared to be increased (Table 6). At 300 ppm, rats for both genders showed increased latencies of various evoked responses and decreased rates for CFF. The brain of all rats in this group showed vacuoles (mild) in the caudate-putamen nuclei (Table 6). Other pathological changes included inflammation of the nasal tissues and kidney changes (hyperplasia of collecting ducts, decrease in protein droplets in cortical tubules). The 300-ppm recovery group showed the normal auditory brainstem response and no brain vacuoles; these results suggested that the effects observed after the treatment were reversible. The NOEL was 30 ppm (21 mg/kg/day) based on changes in the electrophysiological tests at 100 ppm (71 mg/kg/day) and brain lesions at 300 ppm. In the published article, the authors reported mottled incisors, likely due to fluorosis, in all rats at 100 and 300 ppm with a NOEL of 30 ppm (21 mg/kg/day). This study was considered supplemental information to DPR. The U.S. EPA also established 30 ppm as the NOAEL for the study based on neurotoxicity, lung histopathology, and dental fluorosis (U.S. EPA, 2004b; MRID 40839902).

Table 6. Effects in rats exposed to sulfuryl fluoride for 13 weeks and 2 months post-exposure.^a

Duration ppm mg/kg/day	Males				Females			
	0	30	100	300	0	30	100	300
	0	21	71	214	0	21	71	214
Electrophysiological responses (mean values for the group)								
FEP latency (msec)	-0.18	-2.05	-2.38	5.91*	0.00	0.05	11.87*	10.90*
CFF (flashes/sec)	45.26	48.33	46.86	42.67*	47.71	48.57	45.14	42.67*
ABR latency (msec)	0.02	0.04	0.14	0.18*	0.00	0.04	-0.03	0.16*
SER-C latency (msec)	-0.54	0.67	1.20	2.75*	0.51	0.86	-1.11	4.05*
SER-S latency (msec)	-0.36	-0.65	0.60	3.90*	0.17	2.56	4.44*	5.19*
Vacuoles in the cerebrum (Affected/Total examined)								
13-weeks exposure	0/3	0/6	0/7	4/4*	0/5	0/7	0/7	5/5*
2-month post-exposure	0/2	NA	NA	0/2	0/2	NA	NA	0/2

^{a/} Data from Mattsson *et al.*, 1986. FEP=flash evoked response (visual), CFF=cortical flicker fusion (flash rate that elicits a synchronized cortical response), ABR=auditory brainstem response, SER-C=somatosensory evoked response in cortex, SER-S=somatosensory evoked response in cerebellum, and NA=dose groups not included in post-exposure phase of the study. *=Significance at $p < 0.05$ by the Fisher's Exact Test.

III.C.2. Inhalation – Mouse

CD-1 mice (14/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 0, 10, 30, or 100 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 13 weeks (Nitschke and Quast, 1993; Nitschke, 1994b). Average measured concentrations were 0, 10, 30 or 100 ppm. Three mice died (one each in 0, 10, and 100 ppm) and were not considered treatment-related. No effects were observed at 10 or 30 ppm. Serum fluoride was measured in 4 animals per group and showed a dose-related increase with statistical significance for the 100 ppm both genders, and 30 ppm females (Table 7). Dental fluorosis was not noted for any animals.

At 100 ppm, there were reduced body weight gain (10%) as well as reduced absolute brain, heart, kidney (male only), and liver weights. No effects were noted in Functional Observational Battery and hematology. Clinical chemistry showed increased triglycerides and alkaline phosphatase levels (male only). Histological examination showed multifocal vacuoles in cerebrum in almost all animals in the 100-ppm group (Table 7). The one mouse without brain vacuoles had died on day 63 of the study. In this group, there were also microvacuoles in the thalamus/hypothalamus region as well as very slight hypertrophy of follicular epithelial cells and decrease in colloid in thyroid gland. The NOEL was 30 ppm (40 mg/kg/day) based on brain and thalamus/hypothalamus vacuolation, and thyroid changes at 100 ppm (134 mg/kg/day). This study was considered acceptable to DPR.

Table 7. Serum fluoride and brain vacuolation in mice exposed to sulfuryl fluoride for 13 weeks.^a

Effects ppm mg/kg/day	Males				Females			
	0 0	10 13	30 40	100 134	0 0	10 13	30 40	100 134
Serum fluoride (mean ± sd µg/ml) n=4	0.107 ±0.017	0.112 ±0.027	0.156 ±0.019	0.259* ±0.073	0.09 ±0.015	0.088 ±0.019	0.132* ±0.02	0.233* ±0.022
Histopathology								
Cerebrum vacuolation								
Caudate putamen								
very slight	0/10	0/10	0/10	7/10*	0/10	0/10	0/10	3/10
slight	0/10	0/10	0/10	2/10	0/10	0/10	0/10	5/10*
External capsule								
very slight	0/10	0/10	0/10	7/10*	0/10	0/10	0/10	6/10*
slight	0/10	0/10	0/10	2/10	0/10	0/10	0/10	4/10*
Thalamus/hypothalamus vacuolation, external capsule very slight	0/10	0/10	0/10	9/10*	0/10	0/10	0/10	10/10*

^{a/} Data from Nitschke and Quast, 1993. Incidences indicated are affected/total in groups examined.

*=Significance at p<0.05 by Fisher's Exact Test.

III.C.3. Inhalation - Rabbit

New Zealand white rabbits (7/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 30, 100, or 600/300 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 13 weeks (Nitschke *et al.*, 1987b; Eisenbrandt and Nitschke, 1989). The highest dose group was initially exposed to 600 ppm but was reduced to 300 ppm after 9 exposures because two animals had convulsions. Average measured concentrations were 0, 29.8, 100, or 337 ppm. No treatment-related effects were observed at 30 ppm. Mean serum fluoride levels were significantly increased for all the treated groups (Table 8). While a dose-related increase in mean fluoride levels was demonstrated for both groups, the range of individual fluoride levels in the 100 ppm group (0.72 µg/ml to 0.99 µg/ml) overlapped with that for the 300 ppm group (0.9 µg/ml to 1.086 µg/ml) in the females. At the mid- and high dose groups, the males showed lower (about half) serum levels compared to those in the females. Dental fluorosis was not noted in this study.

At 300 ppm, there was a statistically significant ($p < 0.05$) decrement in body weight gain (about 10%) from day 11 to day 60 and in liver weight (ca. 26%). Nasal and brain lesions were observed in the 100 and 300-ppm groups (Table 8). At 100 ppm, vacuolation was observed in the cerebrum (putamen, internal and external capsules of globus pallidus) of one female, and nasal inflammation in one male. While there was only a single incidence of brain vacuoles, this finding was of toxicological significance since the severity was moderate. In addition, there were increased incidences at the next higher dose. At 300 ppm, brain and nasal tissue lesions were found in more animals and increased severity. The brain lesions included cerebral vacuolation, severe malacia, and gliosis as well as hypertrophy of vascular endothelial cells. Nasal tissues showed moderate to severe degeneration, inflammation, and hyperplasia/hypertrophy. The NOEL was 30 ppm (12 mg/kg/day) for brain and nasal lesions at 100 ppm (40 mg/kg/day) and 300 ppm. This study was considered acceptable to DPR. The U.S. EPA established a NOAEL of 30 ppm for the noted effects (U.S. EPA, 2004c; MRID 40890901).

Table 8. Serum fluoride and histopathology in rabbits after inhalation exposure to sulfuryl fluoride for 13 weeks.^a

Effects ppm mg/kg/day	Males				Females			
	0	30	100	300 ^b	0	30	100	300 ^b
	0	12	40	120	0	12	40	120
Number of animals affected/Total in group								
Serum fluoride (mean ± sd µg/ml)	0.065 ±0.014	0.17* ±0.069	0.408* ±0.035	0.621* ±0.06	0.56 ±0.026	0.697* ±0.07	0.829* ±0.088	1.003* ±0.045
Histopathology								
Brain (cerebrum)								
Vacuolation, focal:								
very slight/slight	0/7	0/7	0/7	3/7	0/7	0/7	0/7	5/7*
moderate	0/7	0/7	0/7	0/7	0/7	0/7	1/7	0/7
Malacia, focal: severe	0/7	0/7	0/7	3/7	0/7	0/7	0/7	1/7
Gliosis, focal: slight	0/7	0/7	0/7	0/7	0/7	0/7	0/7	2/7
Hypertrophy, endothelium:								
very slight	0/7	0/7	0/7	0/7	0/7	0/7	0/7	2/7
Nasal Tissues								
Epithelial Degeneration,								
multifocal: slight	0/7	0/7	0/7	1/7	0/7	0/7	0/7	2/7
diffuse: slight/moderate	0/7	0/7	0/7	1/7	0/7	0/7	0/7	1/7
Submucosal inflammation,								
diffuse: severe	0/7	0/7	0/7	2/7	0/7	0/7	0/7	0/7
multifocal: very slight/slight	0/7	0/7	1/7	0/7	0/7	0/7	0/7	2/7
moderate	0/7	0/7	0/7	2/7	0/7	0/7	0/7	0/7
Epithelial								
hyperplasia/hypertrophy								
diffuse: very slight/slight	0/7	0/7	0/7	3/7	0/7	0/7	0/7	3/7
moderate/severe	0/7	0/7	0/7	4/7*	0/7	0/7	0/7	3/7

^{a/} Data from Nitschke *et al.*, 1987b; Eisenbrandt and Nitschke, 1989. *=Significance at p<0.05 by Fisher's Exact Test (histopathology), by Dunnett's test (female fluoride levels), and by Wilcoxon's test (male fluoride levels).

^{b/} This group was exposed to 600 ppm for 9 exposures, the exposure level was reduced to 300 ppm for the rest of the experiment.

III.C.4. Inhalation - Dog

Beagle dogs (4/sex/group) were exposed to sulfuryl fluoride (purity 96.25%; 0, 30, 100, or 200 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 13 weeks (Nitschke and Quast, 1992). Average measured concentrations were 0, 29.9, 99.0, or 197.6 ppm. There were no effects at 30 and 100 ppm. In the 200-ppm group, there were decreased body weights of 88% and 96%, males and females, respectively, of control values by the end of the study ($p < 0.05$ for both genders combined) (Table 9). Clinical signs were noted in one 200-ppm male and only on day 19 of the study. The observed signs were lateral recumbency, tetany, tremors, salivation, and incoordination. Histopathological examination of the mid-brain showed gliosis and vacuolation of focal areas of the putamen in one male and one female at 200 ppm. Serum fluoride level was not measured in this study. The NOEL was 100 ppm (29 mg/kg/day) based on reduced body weight gain and brain lesions at 200 ppm (58 mg/kg/day). The U.S. EPA established the NOAEL at the same dose as DPR (U.S. EPA, 2004b).

Table 9. Effects of sulfuryl fluoride in the cerebrum of dogs exposed to sulfuryl fluoride for 13 weeks.^a

Effects ppm mg/kg/day	Males				Females			
	0 0	30 9	100 29	200 58	0 0	30 9	100 29	200 58
Mean body weight in kg at end of study	13.68	13.52	12.58	12.10	11.19	11.88	11.62	10.76
% of control ^b	100%	99%	92%	88%*	100%	106%	104%	96%*
Clinical signs ^c (affected/total in group)	0/4	0/4	0/4	1/4 ^c	0/4	0/4	0/4	0/4
Histopathology (Affected^d/Total examined)								
Gliosis, bilateral, focal, very slight	0/4	0/4	0/4	1/4	0/4	0/4	0/4	1/4
Vacuolation, bilateral, focal, very slight	0/4	0/4	0/4	1/4	0/4	0/4	0/4	1/4

^{a/} Data from Nitschke and Quast, 1992.

^{b/} Body weights for both gender were combined for statistical analysis (*=Significance at $p < 0.05$ by the Fisher's Exact Test) since there were too few animals in each group.

^{c/} Clinical signs were observed only on day 19 and included: lateral recumbency, tetany, tremors, salivation, and incoordination.

^{d/} Gliosis and vacuolation were found in the same animal.

Table 10. Subchronic inhalation toxicity of sulfuryl fluoride.^a

Species/ Exposure duration	NOEL		LOEL		Effects	Ref.
	ppm	mg/kg/day ^b	ppm	mg/kg/day ^b		
Rat 6 hr/d x 5 d/w x 13 w	30	21	100	71	Mottled incisors	1*
	100	71	300	214	Reduced body weight and effects in brain (vacuoles), kidney (hyperplasia), lungs (alveolar histiocytosis) and nasal (inflammation) tissues	
Rat 6 hr/d x 5 d/w x 13 w	30	21	100	71	Mottled incisors	2
	30	21	100	71	Electrophysiological effects (brain lesions at 300 ppm)	
Mouse 6 hr/d x 5 d/w x 13 w	30	40	100	134	Brain (cerebrum and thalamus/ hypothalamus) vacuoles, thyroid hypertrophy	3*
Rabbit 6 hr/d x 5 d/w x 13 w	30	12	100	40	Brain (vacuoles) and nasal (inflammation) lesions	4*
Dog 6 hr/d x 5 d/w x 13 w	100	29	200	58	Reduced body weight gain, brain lesion (gliosis and vacuoles)	5

a/ Abbreviations: hr=hour, d=day, w=week. * Study was acceptable to DPR under FIFRA guidelines. References: 1. Nitschke *et al.*, 1987a; 2. Mattsson *et al.*, 1986; 3. Nitschke and Quast, 1993; 4. Nitschke *et al.*, 1987b; 5. Nitschke and Quast, 1992. Bolded study is used as the critical study for risk characterization. Incidences for brain lesions were noted in parentheses.

b/ Equations for calculations are in **Appendix E**.

III.D. CHRONIC TOXICITY AND ONCOGENICITY

Summary: After chronic exposure, the primary target tissue for sulfuryl fluoride was the brain and the respiratory tract in rats, mice, and dogs. As with subchronic exposure, brain vacuoles were observed in the cerebrum. The lesions in the respiratory tract included nasal tissues, trachea, larynx, and lungs. Dental fluorosis was observed in both rats and dogs. Progressive glomerulonephropathy was considered the cause of death in sulfuryl fluoride treated rats. Sulfuryl fluoride was not oncogenic in rats, mice, and dogs. A summary of the chronic toxicity studies is presented in Table 14.

III.D.1. Inhalation - Rat

In the satellite group of a chronic toxicity study, Fischer 344 rats (15/sex/group) were exposed to sulfuryl fluoride (93.6-99.7% purity; 0, 5, 20, or 80 ppm) by whole-body inhalation exposure (6 hours/day, 5 days/week) for 1 year (Spencer *et al.*, 1994). This study was designed only to evaluate the neurotoxicity of sulfuryl fluoride and was part of a 2-year study (Quast *et al.*, 1993a). Measured concentrations were not reported. No treatment-related effects were observed in Functional Observational Battery, grip performance, landing foot splay and motor activity test. The NOEL for neurotoxicity was \$ 80 ppm (\$57 mg/kg/day). This study was considered supplemental information to DPR.

Fischer 344 rats (50/sex/group) were exposed to sulfuryl fluoride (99.8% purity; 0, 5, 20, or 80 ppm) for 24 months (6 hours/day, 5 days/week, except holidays) (Quast *et al.*, 1993a). The average measured concentrations were 0, 5.1, 20.2, or 79.6 ppm. There was increased mortality in the 80-ppm groups. By the end of the study, the mortality rates were 100% (the last animal died between day 701-707) for treated males and females, compared with 42% (males) and 50% (females) for controls. Decreased body weights were noted for the 80-ppm males (86% of control) and all treated female groups (84% of control for 80 ppm) (Table 11). Premature death in this group was caused by chronic progressive glomerulonephropathy and mineralization/atrophy in a variety of tissues (aorta, bone, eyes, heart, liver, mammary gland, mediastinal tissues, mesenteric tissues, parathyroid glands, pituitary glands, spleen, stomach, and tongue). Glomerulo-nephropathy (very slight or slight), was noted in all groups including the control with the highest incidence in the 20-ppm females (Table 11). At the next dose, the severity of glomerulo-nephropathy progressed to moderate and severe level. Mineralization/atrophy in tissues either did not appear or reach an advanced degree until well beyond the first year of the study, and were considered being secondary to renal toxicity. Clinical chemistry showed significant ($p < 0.05$) changes (male/females in % of control) in the 80-ppm groups and included: elevated blood urea nitrogen (488%/555%), creatinine (400%/371%), phosphorus (207%/231%), and cholesterol levels (244%/164%), and reduced blood albumin levels (77%/72%).

Very slight multifocal vacuolation in the cerebrum and thalamus/hypothalamus was observed only in the 80-ppm females (Table 11). The authors suggested that perivascular edema was the cause of the vacuolation, which surrounded vessels in the dorsolateral outer cortical region. This vacuolation was considered not related to those observed in other studies because of the difference in affected location (caudate putamen region identified in other studies) and only females were affected. The authors also suggested that it might be associated with the “advanced chronic renal disease for females”. However, glomerulonephropathy showed only a gender

difference at 20 ppm but similar incidences at 80 ppm for both genders.

Possible direct responses of respiratory tissues to sulfuryl fluoride included aggregates of alveolar macrophages in lungs, and inflammation of larynx and trachea (Table 11). Dental fluorosis, graded as slight or very slight, in the males and females was observed at 20 ppm (16 mg/kg/day) and 80 ppm, respectively, with a NOEL of 5 ppm (4 mg/kg/day) for males (Table 11). The NOEL for non-dental effects was 20 ppm (14 mg/kg/day) based on kidney, brain and respiratory tract lesions at 80 ppm (57 mg/kg/day). There was no evidence of oncogenicity. This study was considered acceptable to DPR. The U.S. EPA established a NOAEL of 5 ppm for fluorosis at 20 ppm in male rats and a NOEL of 20 ppm for tissue effects (effects in the kidneys, adrenal cortex, brain, eyes, liver, nasal tissues, respiratory tract) at 80 ppm for female rats (Hansen, 1998; U.S. EPA, 2004b; MRID 43216702). The NOAEL for neurotoxicity was 80 ppm, the highest dose tested.

Table 11. Effects of sulfuryl fluoride in rats after inhalation exposure for 2 years.^a

Effects ppm mg/kg/day	Males				Females			
	0 0	5 4	20 14	80 57	0 0	5 4	20 14	80 57
Body weights (g and % of control)								
Day 565	436	427 (98%)	428 (98%)	374* (86%)	259	240* (93%)	250* (96%)	218* (84%)
Day 734	402	389 (97%)	379 (94%)	NA	255	265 (104%)	258 (101%)	NA
Histopathology (Affected/Total examined)								
Dental fluorosis	0/50	0/50	10/50*	50/50**	0/50	0/50	2/50	50/50**
Glomerulonephropathy								
very slight/slight	21/50	25/50	25/50	2/50*	47/50	47/50	50/50	3/50*
moderate/severe	28/50	22/50	24/50	5/50*	0/50	0/50	0/50	7/50*
very severe	1/50	2/50	1/50	43/50*	1/50	0/50	0/50	40/50*
Brain vacuoles								
Cerebral cortex	2/50	0/50	1/50	1/50	1/50	3/50	3/50	22/50*
Thalamus/hypothalamus	2/50	0/50	1/50	1/50	1/50	3/50	2/50	22/50*
Larynx- Inflammation								
acute	6/49	2/49	5/49	11/49	3/49	0/49	1/49	18/49*
chronic	6/49	6/49	7/49	18/49*	0/49	1/49	1/49	0/49
Lungs- Aggregates of alveolar macrophages								
very slight/slight	4/50	1/50	2/50	15/50*	2/50	0/50	3/50	6/50
moderate	1/50	0/50	0/50	34/50*	0/50	0/50	0/50	42/50*
Nasal tissues								
Reactive hyperplasia	3/50	2/50	2/50	31/50*	4/50	1/50	2/50	26/50*
Inflammation	12/50	7/50	8/50	33/50*	22/50	20/50	17/50	32/50*
Trachea Inflammation	1/50	0/50	0/50	9/50*	1/50	0/50	0/50	1/50

^{a/} Data from Quast *et al.*, 1993a. Significantly different from control, *p <0.05 or **p <0.01, using either the Dunnett's or Wilcoxon's tests from the report. NA=all animals died between day 701 and 707.

III.D.2. Inhalation - Mouse

CD-1 mice (50/sex/group) were exposed to sulfuryl fluoride (99.8% purity; 0, 5, 20, or 80 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 18 months (Quast *et al.*, 1993b). Satellite groups (10/sex/group) were sacrificed at 12 months. Average measured concentrations were 0, 5.1, 20.1, or 79.7 ppm. There were no treatment-related effects in the satellite groups or in the 5 and 20- ppm groups in the 18-month study. In the 80-ppm/18 month group, the body weights were consistently lower ($p<0.05$) than the control throughout the experiment (Table 12). By day 551, they were 85% (female) and 86% (male) of control values. In this group, there was increased mortality in females mainly due to increased incidence of systemic amyloidosis, noted by the investigators for CD-1 mice as having a genetic predisposition for this lesion (Table 12). By day 555, 64% (males) and 72% (females; $p<0.05$) of the 80-ppm group died compared to 46% (males) and 36% (females) in the controls. Other treatment-related effects included food impaction in the esophagus (12/50 males versus 3/50 in control) and inflammation and/or abscesses in the head and/or oral cavity at 80 ppm. Pathological examinations showed very slight vacuolation in both caudate putamen and external capsule of the cerebrum of 80-ppm groups at 12 months (Table 12). At 18 months, vacuolation was observed only in the external capsule with no increase in severity. The 80-ppm groups also showed increased incidences of thyroid epithelial cell hypertrophy (20/49 treated *versus* 0/49 control males, $p<0.05$), heart thrombus (14/50 treated *versus* 4/50 control females), and lung congestion (19/50 treated *versus* 6/50 control females, $p<0.05$). The NOEL was 20 ppm (27 mg/kg/day) based on systemic amyloidosis, brain, thyroid, heart, and lung effects at 80 ppm (107 mg/kg/day). There was no evidence of oncogenicity. This study was considered acceptable to DPR. The U.S. EPA also determined a NOAEL of 20 ppm (20 mg/kg/day)⁷ with a LOAEL of 80 ppm for decreased survival, body weight gain, and tissue effects (Hansen, 1998; U.S. EPA, 2004b; MRID 43354903).

Table 12. Effects of sulfuryl fluoride in mice after inhalation exposure for 18 months.^a

Effects	Male				Female			
	0 0	5 7	20 27	80 107	0 0	5 7	20 27	80 107
Body weight on day 551 (mean, g; % control)	41.0	41.6 (101%)	40.8 (100%)	35.3 (86%)	34.9	34.1 (98%)	35.0 (100%)	29.8 (85%)
Mortality (# mice dead)	23/50	20/50	25/50	25/50	18/50	12/50	20/50	36/50*
Systemic amyloidosis ^b	11/50	12/50	15/50	10/50	6/50	5/50	13/50	26/50*
Brain, vacuoles, v. slight								
Caudate putamen 12 months	0/10	0/10	0/10	1/10	0/10	0/10	0/10	0/10
External capsule								
12 months	0/10	0/10	0/10	10/10*	0/10	0/10	0/10	9/10*
18 months	0/50	0/50	0/50	13/50*	0/50	0/50	0/50	12/50*

^{a/} Data from Quast *et al.*, 1993b. * =Significance at $p<0.05$. v.=very

^{b/} Affected /total animals in the group. Affected = those died with amyloidosis as cause of death.

⁷ 20 ppm x 4.17 x 0.01m³/6 hrs x 1/0.03 kg x 5/7=19.84 mg/kg/day.

III.D.3. Inhalation - Dog

Beagle dogs (4/sex/group) were exposed to sulfuryl fluoride (99.8% purity; 0, 20, 80, or 200 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 1 year (Quast *et al.*, 1993c). Average measured concentrations were 0, 21, 79 or 198 ppm. The 200-ppm group was sacrificed at 9 months due to severe toxicity (breathing difficulties, decreased activity, and pale skin and mucous membranes). This group also had lower weight gain than the control within the first two weeks of exposure (Table 13). By day 278, the females lost 526 grams, compared to gains of 1462 grams for the males and 3100 grams for the controls. Body weights of other treated groups were not affected. At 80 ppm, there were chronic active inflammation in the lung alveoli, multifocal aggregates of alveolar macrophages, and dental fluorosis (Table 13). At 200 ppm, the incidence and severity were increased for those effects (except for alveolar macrophages). The effects on the alveoli could account for the breathing difficulties reported; edema was not reported.

In the brain, the malacia was considered slight/moderate and involved only the head of the caudate nucleus. Neutrophils and macrophages were found within the malacia foci but normal appearing cells were adjacent to the foci. The authors suggested ischemic tissue damage as the cause of the malacia. Additional effects in the thyroid (hypertrophy), lymph node (atrophy), thymus (atrophy), tonsil (atrophy), and liver (atrophy) were found in this group. The NOEL was 20 ppm (6 mg/kg/day) based on dental fluorosis and lung lesions at 80 ppm (23 mg/kg/day). There was no evidence of oncogenicity. This study was considered acceptable to DPR. U.S. EPA selected a NOAEL of 20 ppm with a LOEL of 80 ppm for decreased body weight gain, lung histopathological changes, and dental effects (Hansen, 1998; U.S. EPA, 2004b; MRID 43354901).

Table 13. Effects of sulfuryl fluoride in dogs after inhalation exposure for 9-12 months.^a

Effects	Male				Female				
	ppm mg/kg/day	0	20	80	200	0	20	80	200
		0	6	23	58	0	6	23	58
Mean Body Weight Gain (g)									
12 days		493	587	602	201	367	268	465	284
278 days		3184	4554	3225	1462	3175	2875	2788	-526*
Tissue Effects- (Affected/ Total examined)									
Lungs-inflammation									
very slight		0/4	0/4	0/4	2/4	0/4	0/4	2/4	1/4
moderate/severe		0/4	0/4	0/4	2/4	0/4	0/4	0/4	3/4
Alveolar									
-macrophages aggregates		0/4	0/4	3/4	0/4	0/4	0/4	1/4	0/4
Brain-malacia, caudate nucleus									
very slight, slight		0/4	0/4	0/4	2/4	0/4	0/4	0/4	2/4
moderate		0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
Tooth- fluorosis-									
very slight, slight		0/4	0/4	3/4	4/4*	0/4	0/4	1/4	4/4*

^{a/} Data from Quast *et al.*, 1993c. The 200-ppm group was exposed to sulfuryl fluoride for only 9 months.

*=Significance at $p < 0.05$ by Fisher's Exact Test.

Table 14. Chronic inhalation toxicity of sulfuryl fluoride.

Species/ Exposure duration	NOEL		LOEL		Effects	Ref ^a
	ppm	mg/kg/day ^b	ppm	mg/kg/day ^b		
Rat 6 hr/d x 5 d/w x 1 y	80	60	ND	ND	No neurotoxicity	1
Rat 6 hr/d x 5 d/w x 2 y	5 20	4 14	20 80	14 57	Dental fluorosis (males) Brain vacuoles, glomerulonephropathy, and respiratory tract macrophages and inflammation (females)	2*
Rat 6 hr/d x 5 d/w x 2-generation study^c	5 20 20	4 14 14	20 150 150	14 107 107	Maternal- lung inflammation and alveolar macrophage aggregates Maternal-brain vacuoles Reproductive- reduced pup body weight	3*
Mouse 6 hr/d x 5 d/w x 2 y	20	27	80	107	Decreased body weight, decreased survival, systemic amyloidosis, brain vacuoles, thyroid hypertrophy, heart thrombus, and lung congestion	4*
Dog 6 hr/d x 5 d/w x 1 y	20 20 80	6 6 23	80 80 200	23 23 58	Dental fluorosis Lung inflammation and alveolar macrophage aggregates Brain malacia	5*

^{a/} Abbreviations: hr=hour, d=day, w=week, y=year, ND=not determined. *Study was considered acceptable to DPR according to FIFRA guidelines. References: 1. Spencer *et al.*, 1994; 2. Quast *et al.*, 1993a; 3. Breslin *et al.*, 1992; 4. Quast *et al.*, 1993b; 5. Quast *et al.*, 1993c. Bolded study is used as the critical study for risk characterization.

^{b/} Equations for calculations are in **Appendix E**.

^{c/} Study described in **IIIF. REPRODUCTIVE TOXICITY**. The exposure was 5 days/week during pre-mating, but 7 days/week during gestation and lactation.

III.E. GENOTOXICITY

Summary: Sulfuryl fluoride was not genotoxic in either *in vitro* or *in vivo* studies.

III.E.1. Gene Mutation

Salmonella typhimurium strains (TA1535, TA1537, TA98 and TA100) were exposed to sulfuryl fluoride (purity 99.6%; 0; 300; 1,000; 3,000; 10,000 and 30,000 ppm) for 4 hours with and without rat liver S9 fraction (Gollapudi *et al.*, 1990a). The exposure was conducted with plates (without covers) inside glass dessicators. After exposure, the plates were incubated for 2 days before the colonies were counted. There was no increase in the reversion rate for any strains. The number of revertants was actually lower at 30,000 ppm than that for the control, suggesting cytotoxicity at this dose. This study was considered acceptable to DPR. U.S. EPA also concluded that there were no significant treatment-related effects in this study (U.S. EPA, 2004b; MRID 41603001).

III.E.2. Structural Chromosomal Effects

CD-1 mice (15/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 0, 50, 175, or 520 ppm) by whole-body inhalation for 4 hours (Gollapudi *et al.*, 1990b; Nitschke and Gollapudi, 1991). Average measured concentrations were 0, 48, 180, or 520 ppm. Bone marrow samples from the femurs were examined at 24, 48, or 72 hours after exposure. There was no increase in the number of micronucleated cells. No clinical signs were reported. This study was considered acceptable to DPR. U.S. EPA also concluded that there were no significant treatment-related effects in these studies (U.S. EPA, 2004b; MRID 41769102, 41448601).

III.E.3. Other Genotoxic Effects

Isolated hepatocytes from male rats (Sprague-Dawley outbred CrI:CD BR) were plated in tubes and exposed to sulfuryl fluoride (purity 97.4%; 0, 204, 408, 612, 816, 1020, or 1530 ppm) (Gollapudi *et al.*, 1991). While the period of treatment was 18-19 hours, cells in the tubes (Leighton tubes with septum caps) were rocked so that half of them were exposed to sulfuryl fluoride in the air at a time. There was no induction of unscheduled DNA synthesis as measured by autoradiography. This study was considered acceptable to DPR. U.S. EPA also concluded that there was no increase in unscheduled DNA synthesis in this study (U.S. EPA, 2004b; MRID 42179802).

III.F. REPRODUCTIVE TOXICITY

Sprague-Dawley rats (30/sex/group) were exposed to sulfuryl fluoride (purity 97.32%; 0, 5, 20, or 150 ppm) by inhalation (6 hours/day) in a 2-generation study (Breslin *et al.*, 1992; Kirk *et al.*, 1992). The rats were exposed for 5 days/week during pre-mating (for 10 weeks for F0 and 12 weeks for F1, excluding holidays); and 7 days/week during mating (1 to 3 weeks), gestation (3 weeks), and lactation (3 weeks). The females were not exposed to sulfuryl fluoride from gestation day 21 to postpartum day 4 (about 10 days). The pups (F1 generation) from F0 parents were exposed *in utero* during gestation and via the maternal milk from birth to postnatal day 21, but no direct exposure until pre-mating at about 6 weeks old. The average measured concentrations during F0 and F1 generations were 0, 5.0, 20.9 and 149.1 ppm, and 0, 5.2, 20.4, and 150.1 ppm, respectively. DPR calculated daily dosages were based on the longer continuous period, which was during pre-mating at 5 days per week for 10 weeks. In comparison, the 7 days per week period included 10 no exposure days. The daily dosages were: 0, 4, 14, and 107 mg/kg/day, respectively, for 0, 5, 20, and 150 ppm.

No parental effects were noted at 5 ppm. At 150 ppm, adults of both generations had body weight decrements of about 10%. These reductions were generally statistically significant at $p < 0.05$ during various measured periods. The teeth of these groups also showed various treatment-related effects (discoloration of lower incisors, overgrown incisors, broken upper incisors, malformation) (Table 15). At > 5 ppm, there were increased incidences of pathological findings in the lung and brain for both generations (Table 15). At 20 ppm and 150 ppm, the lungs showed increased incidences of aggregates of alveolar macrophages as multiple, round, pale, or gray foci. The aggregates were most commonly found in the subpleural or peribronchial locations. At 150 ppm, there were also increased incidences of chronic inflammation in the lungs. The incidences for moderate severity for these endpoints were higher in the F1 parents than those in the F0 parents. The authors of the report considered these indications of lung injury. In comparison, the incidences for brain vacuolation at the 150 ppm group were higher in the F0 than F1 parents. The severity was described as “very slight to slight” vacuolation of myelinated fiber tracts in the cerebrum.

The only effect on the pups was reduced body weight. F1 litter body weights were significantly reduced from day 1 (female only) to day 21 of lactation (Table 15). By day 21, they were 84% of control values. For the F2 litters, the reduction in body weight was also observed during lactation; however, the female pup weight reduction was statistically significant only on days 14 and 21. The parental systemic NOEL was 5 ppm (4 mg/kg/day) based on lesions in the lung at 20 ppm (14 mg/kg/day). The reproductive NOEL was 20 ppm (14 mg/kg/day) for reduced pup body weight in F1 and F2 generations at 150 ppm (107 mg/kg/day). This study was considered acceptable to DPR. The U.S. EPA established the NOAELs for the following endpoints: 5 ppm for parental toxicity (pathological changes in the lung), 150 ppm for reproductive toxicity (no effect at the highest dose tested), and 20 ppm for offspring toxicity (decreased pup body weight) (U.S. EPA, 2004b; MRID 42179801).

Table 15. Effects of sulfuryl fluoride in adult rats and pups in a 2-generation reproductive toxicity study.^a

Effects	ppm mg/kg/day	0 0	5 4	20 14	150 107
Gross pathology (Affected in both genders/Total examined)					
F0 parents					
Lungs-focus, gray, multifocal		0/60	0/60	5/60*	48/60*
Oral tissues- effects on incisors ^b		1/60	2/60	2/60	56/60*
F1 parents					
Lungs-focus, pale		1/60	0/60	10/60*	36/60*
Oral tissues- dark tooth		0/60	0/60	0/60	42/60*
Histopathology^c (Affected in both genders/Total examined)					
F0 parents					
Alveolar macrophage aggregates					
very slight to slight		10/60	15/59	30/60*	40/60*
moderate		0/60	0/59	0/60	20/60*
Lungs-chronic inflammation					
very slight to slight		4/60	5/59	2/60	39/60*
Brain vacuolation, cerebrum, bilateral					
very slight to slight		0/60	0/59	0/59	25/60*
F1 parents					
Alveolar macrophage aggregates					
very slight to slight		24/60	23/60	38/60*	36/60*
moderate		0/60	0/60	2/60	23/60*
Lungs-chronic inflammation					
very slight to slight		3/60	4/60	4/60	23/60*
moderate		0/60	0/60	0/60	2/60
Brain vacuolation, cerebrum, bilateral					
very slight to slight		0/60	0/60	0/60	9/60*
Pup body weight (mean, grams; % control)					
F1 litters					
Day 1 Male		7.2	7.1 (99%)	7.2 (100%)	7.0 (97%)
Female		7.1	6.6 (93%)	6.7 (94%)	6.6* (93%)
Day 21 Male		42.6	40.7 (96%)	43.0 (101%)	35.6* (84%)
Female		41.4	38.1 (92%)	41.0 (99%)	34.7* (84%)
F2 litters					
Day 1 Male		6.8	7.0 (103%)	7.2 (106%)	6.7 (99%)
Female		6.4	6.6 (103%)	6.8 (106%)	6.2 (97%)
Day 21 Male		41.5	43.8 (106%)	42.9 (103%)	38.3 (92%)
Female		39.8	42.4 (107%)	41.7 (105%)	35.6* (89%)

^{a/} Data from Breslin *et al.*, (1992). Thirty animals in each group were examined except 29 for histopathology of the 20 ppm F0 male group. *=Significance at p<0.05 by Fisher's Exact Test.

^{b/} Incisor effects include: dark, lower incisors; overgrown incisors; worn, broken upper incisors, and malformation, upper incisors. Some animals have more than one effect.

^{c/} Severity for alveolar macrophage aggregates: very slight=1 to 3 small aggregates, slight=3 to 6, usually larger aggregates, and moderate=> 6 large aggregates.

III.G. DEVELOPMENTAL TOXICITY

Summary: There were no teratogenic effects in rats or rabbits exposed to sulfuryl fluoride during gestation. The only fetal effect observed was reduced fetal body weight in rabbits, but not in rats. Maternal toxicity was limited to reduce body weights.

III.G.1. Inhalation - Rat

In a range-finding study, pregnant Fischer 344 rats (10/group) were exposed to sulfuryl fluoride (purity not stated; 0, 30, 100, or 300 ppm) by whole-body inhalation (6 hours/day) on gestation day 6 to 15 (Hanley *et al.*, 1980). The number of pregnant rats per group was 7, 8, 9, or 9 for 0, 30, 100, or 300 ppm, respectively. The respective average measured concentrations were 0, 30, 101, or 299 ppm. The 300-ppm dams showed a significant ($p < 0.05$) decrease in body weight (day 16, 92% of control), body weight gain (day 6-15, gain of 3.3 g compared to 24.6 g for control), and food consumption (73-79% of control throughout the study); increase in water consumption (168 to 212% of control throughout the study), as well as absolute (107% of control) and relative (118% of control) kidney weights. Gross pathological examination showed effects in the liver (diffuse paleness from equivocal to moderate, 7/9), kidney (subcapsular paleness in foci or areas, 8/9), and intestine (decreased contents, 2/9). There was no histological examination of the brain. No effects on the fetus were observed. The NOEL for maternal toxicity was 100 ppm (100 mg/kg/day) for effects on body weight, kidney weight, food consumption and water consumption at 300 ppm (300 mg/kg/day).

In the definitive study, pregnant Fischer 344 rats (35-36/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 25, 75, and 225 ppm) by whole-body inhalation (6 hours/day) on gestation day 6 to 15 (Hanley *et al.*, 1981 and 1989). The average measured concentrations were 0, 25, 76, or 225 ppm. There was neither maternal nor developmental toxicity. There was no histological examination of the brain. The maternal and developmental NOELs were > 225 ppm (> 225 mg/kg/day). This study was considered acceptable to DPR. The U.S. EPA established 225 ppm (the highest dose tested) as the NOAEL for maternal and developmental toxicity (U.S. EPA, 2004b; MRID 00090015).

III.G.2. Inhalation - Rabbit

In a range-finding study, pregnant New Zealand white rabbits (7/group) were exposed to sulfuryl fluoride (purity not stated; 0, 30, 100, or 300 ppm) by whole-body inhalation (6 hours/day) on gestation day 6 to 18 (Hanley *et al.*, 1980). The number of pregnant rabbits per group was 7, 6, 5, or 7 for 0, 30, 100, or 300 ppm. The respective average measured concentrations were 0, 30, 101, or 299 ppm. The 300-ppm does showed significant ($p < 0.05$) decreases in body weight (day 19, 87% of control), body weight gain (day 6-18, loss of 408.8 g compared to gain of 7.9 g in control), and absolute (65% of control) and relative (74% of control) liver weights. Gross pathological examination showed slight pale accentuation of the lobular pattern of the liver in 4 of 7 rabbits in the 300-ppm group. There was no histological examination of the brain. No effects on the fetus were observed. The maternal NOEL was 100 ppm (56 mg/kg/day) for body weight and liver weight effects at 300 ppm (169 mg/kg/day).

In the definitive study, pregnant New Zealand rabbits (28-29/group) were exposed to

sulfuryl fluoride (purity 99.8%; 0, 25, 75, or 225 ppm) by whole-body inhalation (6 hours/day) on gestation day 6 to 18 (Hanley *et al.*, 1981 and 1989). The average measured concentrations were 0, 25, 76, or 225 ppm. The significant ($p < 0.05$) effects observed were reduced (loss of 60 g compared to a gain of 240 g in control) overall maternal body weight gain and fetal body weight (86% of control) in the 225-ppm group. There was no histological examination of the brain. The maternal and fetal NOEL was 75 ppm (42 mg/kg/day) for reduced body weights at 225 ppm (127 mg/kg/day). This study was considered acceptable to DPR. The U.S. EPA established the NOAEL of 75 ppm for both maternal toxicity (decreased body weight and body weight gain) and developmental toxicity (decreased fetal body weight) (U.S. EPA, 2004b; MRID 00090015).

III.H. NEUROTOXICITY

Under FIFRA guidelines, a delayed neurotoxicity study is not required for sulfuryl fluoride. Acute neurotoxicity effects were described under **III.B. ACUTE TOXICITY**.

III.I. HUMAN EXPOSURE

III.I.1. Non-occupational Exposure

In the first case report, a man was exposed to both sulfuryl fluoride and chloropicrin for 4 hours with “limited ventilation” (Taxay, 1966). The initial symptoms were nausea, vomiting, crampy abdominal pain, and pruritus. Physical examination at the hospital showed reddened conjunctiva, pharyngeal and nasal mucosa; diffuse rhonchi; and paresthesia of the right leg. He was discharged 4 days later. The serum fluoride concentration was noted only as positive. The sulfuryl fluoride air concentration was not measured at the time of exposure but was reported to be 5 ppm “several hours” after the incident.

In a report of three cases, individuals were exposed to high concentrations of sulfuryl fluoride (Scheurman, 1985). The first case involved a man who died after entering a tarped and fumigated apartment before aeration. Postmortem examination of this man showed congestion in the mucosa of the larynx, trachea, bronchi, and lungs. The fluoride concentration was 50.42 mg/L, measured 24 to 36 hours postmortem. In the second case, a man was found dead next to an opened sulfuryl fluoride gas container. The postmortem examination showed congested respiratory and lung mucosa, and edematous brain tissues. In the third case, a woman was exposed to sulfuryl fluoride after entering a fumigated home not cleared for reentry. Her initial symptoms were coughing, chest discomfort, and hypotension. Approximately 6 hours after exposure, she showed hyperexcitability, hyperventilation, and tachycardia. She eventually died after developing severe pulmonary edema, carpal/pedal tetany, and cardiac dysrhythmias. The antemortem fluoride concentration was 20 mg/L.

An elderly couple was exposed to sulfuryl fluoride in their house already cleared for reentry (Dammann *et al.*, 1987). While the fumigation company opened windows and doors, and aerated the house with fans, sulfuryl fluoride level was not measured. It was not detected when the air was sampled 12 days after aeration. The couple experienced weakness, nausea and shortness of breath that evening. The man suffered a seizure and died the following day. His wife's condition got worse with pulmonary edema, and she died after a cardiovascular arrest 6 days later. Her serum fluoride level was 0.5 mg/L, 4 days after the exposure. For this case, the "expected" background fluoride level was reported to be 0.01 mg/L.

III.I.2. Occupational Exposure

Fumigators using methyl bromide and sulfuryl fluoride in California were evaluated using neurobehavioral tests (Anger *et al.*, 1986). The workers were divided into four groups: reference (29 workers on jobs related to the fumigation but were not exposed to fumigants), sulfuryl fluoride (24 workers who used sulfuryl fluoride 80% of the time), methyl bromide (32 workers who used methyl bromide 80% of the time), and combination (18 workers who used both fumigants 40-60% of the time).⁸ The number of days since last fumigation ranged from "hours" to 14-15 days for sulfuryl fluoride and combination groups, and ranged from "hours" to 61 days for the methyl bromide group. The methyl bromide group reported a higher prevalence of muscle aching and fatigue, and increased threshold for the two-point test for finger sensitivity, and a lower number of facts recalled in the Wechsler Memory Scale. This group also consistently showed lower performances on neurobehavioral test measures. Mild neurologic dysfunctions were observed in some subjects; they included increased tremors, unsteadiness on standing with eyes closed, ataxia, and poor grip strength. For the sulfuryl fluoride group, there was an increased prevalence of general symptoms and reduced performance on cognitive tests. The authors offered the following caveats for the results: (1) lack of information on participation rates and bias; (2) group differences in age, educational level, race, alcohol consumption, use of prescription drugs, and use of "illegal drugs"; and (3) the possibility of over-reporting of symptoms.

In a cross-sectional study of 123 structural fumigation workers in Florida, the majority (112/123) was exposed to both methyl bromide and sulfuryl fluoride, with the remaining workers exposed to sulfuryl fluoride only (Calvert *et al.*, 1998). The medians of years worked with methyl bromide and sulfuryl fluoride were 1.2 years (range 0-22.1 years) and 2.85 years (0.11 to 20.5 years), respectively. Neurological function tests included: nerve conduction, vibration testing, neurobehavioral tests (hand-eye coordination, simple reaction time, continuous performance test, symbol digit test, pattern memory for cognitive and visual memory, serial digit learning, mood scales), vocabulary test, Santa Ana Dexterity test, postural sway testing, contrast sensitivity (visual), olfactory, and urine analysis. The only significant findings were reduced performance on the pattern memory test and reduced olfactory function for workers with high sulfuryl fluoride exposure (used sulfuryl fluoride on 50% or more of jobs). There was no report of examination of the nasal tissue, which is a target tissue in laboratory animals exposed to sulfuryl fluoride.

⁸ Study groups were formed based on the proportion of the work week devoted to methyl bromide and sulfuryl fluoride fumigation activities as estimated by each worker and on his estimated length time in the occupation.

Reduction of dexterity and median nerve functions, and the prevalence of carpal tunnel syndrome were attributed to repetitive stress from the use of heavy-duty spring clamps. The authors found few health effects associated with methyl bromide but noted that the study had limited power to assess the exposures. The potential biases and limitations included: use of friends and neighbors as controls, study design (*e.g.* temporal sequence of cause and effect, and use of workers still employed in fumigation), and concomitant exposure to both fumigants.

IV. RISK ASSESSMENT

IV.A. HAZARD IDENTIFICATION

The most appropriate data for the hazard identification are those from human studies. However, human case reports of sulfuryl fluoride exposure (**III.I. HUMAN EXPOSURE**) did not provide sufficient data for evaluation. In the absence of human data, results from animal studies were extrapolated to humans assuming that the effects observed in laboratory animals would also be observed in humans. Toxicity endpoints and critical NOELs for risk characterization are discussed in this section. Only those endpoints considered of toxicological significance were used for hazard identification.

IV.A.1. Selection of Endpoints

The target tissues for sulfuryl fluoride inhalation toxicity in laboratory animals were the brain, respiratory system, and teeth. The NOELs for the effects in these tissues were generally lower or the same as those for other endpoints. Therefore, these are considered critical endpoints for risk assessment. The use of NOELs for these endpoints in risk characterization would protect against effects at higher doses such as those for kidney effects. After repeated dosing, the kidney effects included hyperplasia, decreased protein droplets, organ weights, and glomerulonephropathy in rats (Eisenbrandt *et al.*, 1985; Nitschke *et al.*, 1987a; Mattsson *et al.*, 1986; Quast *et al.*, 1993a; Hanley *et al.*, 1980), and reduced organ weights in mice (Nitschke and Quast, 1993; Nitschke, 1994b). Additional effects included thyroid epithelial hypertrophy in mice (Quast *et al.*, 1993b), reduced maternal and fetal/pup body weights in rats (Breslin *et al.*, 1992) and rabbits (Hanley *et al.*, 1981 and 1989), as well as adult body weight in dogs (Nitschke and Quast, 1992).

IV.A.1.a. Neurotoxicity – Brain Vacuolation and Malacia

Neurotoxicity was observed in both humans and laboratory animals exposed to sulfuryl fluoride. In humans, signs indicating neurotoxicity were described in the DPR's Pesticide Illness Surveillance Program reports (**II.E. ILLNESS REPORTS**) or case reports (**III.I. HUMAN EXPOSURE**). However, there was insufficient information to establish a cause-effect relationship. In addition, some workers were exposed to other chemicals, in particular methyl bromide, a fumigant with known neurotoxicity (Anger *et al.*, 1986; Calvert *et al.*, 1998).

In laboratory animals, clinical signs included tremors, lethargy, convulsion, hyperactivity, tetany, and incoordination (Table 4). Tetany may be due to hypocalcemia since fluoride has been shown to bind to calcium (Scheuerman, 1985). The most prominent pathological lesion was the vacuolation and/or malacia of the cerebrum in all species (rats, mice, rabbits, and dogs) tested (Table 16). Both lesions were described as focal in nature and were found primarily in the basal ganglia (caudate putamen nucleus, the external capsule and internal capsule of the globus pallidus). When the brain was examined, the incidence and severity of the vacuolation were dose-related (Tables 3, 5-9, 11-13, and 15). The incidences at the low and mid-doses generally involved none or few animals but involved disproportionately more animals at the high dose. At increasing doses, the severity progressed from very-slight to slight in most

studies, and to moderate in few studies.

Table 16. The lowest-observed-effect levels (LOELs) for brain lesions and clinical signs in sulfuryl fluoride-treated animals.

Duration/ Species (reference ^a)	Clinical Signs		Brain Lesions	
	LOEL mg/kg/day	Findings	LOEL mg/kg/day	Findings
2-Week Exposure				
Rat (1)	600	Moribund		(Not conducted)
Mouse (2)	402	Tremors	134	Vacuoles- very slight (6/10)
Rabbit (1)	241	Convulsion, hyperactivity	121	Vacuoles-slight, 6/6 Malacia-moderate, 2/6
Dog (3)	89	Tetany and tremors		(Not conducted)
13-Week Exposure				
Rat (4)	>200	No effect	214	Vacuoles-slight, 20/20
Rat (5)	71	No effects in hindlimb grip strength and FOB but changes in evoked potential responses.	214	Vacuoles-severity not reported, 9/9
Mouse (6)	>134	No effect on FOB	134	Vacuoles-very slight/slight, 17-19/20 in 3 regions
Rabbit (7)	>120	No effect	40	Vacuoles-moderate, 1/14, malacia/ gliosis at next dose at 120 mg/kg/day
Dog (8)	58	Clinical signs ^b (1/8) only on day 19	58	Vacuoles- very slight, 2/8, Gliosis- very slight, 2/8
Chronic Exposure				
Rat (9)	> 57	No effect on FOB	57	Vacuoles ^c -very slight, 23/100
Rat (10)	>107	No effect	107	Vacuoles- very slight/slight, 25/60 (F0), 9/60 (F1)
Mouse (11)	>107	No effect	107	Vacuoles-very slight, 25/100
Dog (12)	> 58	No effect	58	Malacia-very slight/moderate, 5/8

^{a/} References in parenthesis are: 1. Eisenbrandt *et al.*, 1985; 2. Nitschke and Quast, 2002; 3. Nitschke and Quast, 1991; 4. Nitschke *et al.*, 1987a; 5. Mattsson *et al.*, 1986; 6. Nitschke and Quast, 1993; 7. Nitschke *et al.*, 1987b; 8. Nitschke and Quast, 1992; 9. Quast *et al.*, 1993a; 10. Breslin *et al.*, 1992; 11. Quast *et al.*, 1993b; 12. Quast *et al.*, 1993c.

^{b/} Signs included lateral recumbency, tetany, tremors, salivation, and incoordination.

^{c/} Not considered the same effect as in other studies.

The brain lesions also were related to the duration of exposure with the LOEL at lower doses with longer exposure duration (Table 16). For rats, rabbits, and mice, the LOELs for 2-week or 13-weeks of exposure were higher than those for chronic studies. For example in rats, the LOELs were 214 mg/kg/day for vacuolation in two 13-week studies (Nitschke *et al.*, 1987a and Mattsson *et al.*, 1986) and 107 mg/kg/day in the chronic study (Breslin *et al.*, 1992). Similarly in mice, the LOELs were 134 mg/kg/day for the 13-week study (Nitschke and Quast, 1993) and 107 mg/kg/day for 18 months in the chronic toxicity study (Quast *et al.*, 1993b). The duration-effect relationship was less clear in dogs where the same dose of 58 mg/kg/day caused vacuolation and gliosis in the 13-week study (Nitschke and Quast, 1992), but malacia and not vacuolation in the 1-year study (Quast *et al.*, 1993c). Malacia is generally considered a more severe effect.

The cause of the vacuolation and malacia in the brain after sulfuryl fluoride exposure is unknown. There is no information on whether intact sulfuryl fluoride enters the brain. Pharmacokinetic studies showed ³⁵S radioactivity and fluoride in the brain tissue (Mendrala *et al.*, 2002). Vacuolation is a pathological term for a clear space (space) in the brain tissue; it may be part of the degenerative process such as that following ischemia (Gopinath *et al.*, 1987). With sulfuryl fluoride, some investigators hypothesized that the vacuolation was due to perivascular edema (Quast *et al.*, 1993a) and malacia was due to ischemic tissue damage (Quast *et al.*, 1993c). The regionality of the lesions suggested sulfuryl fluoride affected regional metabolism (Eisenbrandt and Nitschke, 1989). The use of conventional and special stains⁹ did not provide any indication of the cause of the lesions. Vacuolation in brain tissues has been observed with other pesticides. For example, chlorfenapyr, a pyrrole compound with insecticidal and mitocidal activities, caused vacuolation in the mouse brain white matter after chronic exposure (U.S. EPA, 1999b). The finding was thought to be associated with the edema between the myelin layers. In a 2-week toxicity study, permethrin caused vacuolation and swelling of unmyelinated fibers and Schwann cell hypertrophy in rats (Glaister *et al.*, 1977). In neural diseases, the formation of intracellular vacuoles in the brain is a marker for the diagnosis of a group of neural degenerative diseases called spongiform encephalopathies (De Girolami *et al.*, 1999). Vacuolation of the neurons in the cerebrum, cerebellum, and other nuclei is also a finding in aging rats (Solleveld and Boorman, 1990).

With sulfuryl fluoride exposure, the vacuolation in the brain tissue did not appear to be related to clinical signs or electrophysiological changes in the brain. As shown in Table 16, most of the studies did not show the presence of clinical signs. In the few studies with reported clinical signs, the LOELs were higher than those for the brain lesions. Mattsson *et al.* (1986) showed the vacuolation was not related to the changes in evoked potential responses after sulfuryl fluoride treatment. The LOEL for the evoked potential responses were also lower (71 mg/kg/day) than that for brain vacuolation (214 mg/kg/day) (Table 6). Furthermore, sulfuryl fluoride-treated rat brain tissues showed no vacuolation and normal evoked potentials 2 months after the last exposure (Mattsson *et al.*, 1986). While these findings suggested the effects were reversible, it should not lessen the concern about the brain lesion. This apparent reversibility was based on limited evaluation of the brain function, and histology data (only two animals per group from

⁹ Stains used were: hematoxylin-eosin, luxol fast blue-periodic acid Schiff (lipids/myelin, glycogen), and Sevier-Munger (neural tissues) stains.

control and high dose). There is no information on the reversibility of other neurotoxicity effects.

Therefore, the findings of vacuolation and malacia were considered toxicologically significant as indicators damage to the brain tissue. They were clearly related to sulfuryl fluoride treatment and were found in treated animals of multiple species. Since the long-term and functional consequence of such damage has not been studied, this type of damage should be considered adverse especially when the brain and nervous system is being developed. The potential involvement of fluoride in the mechanism of toxicity is under **IV.A.2.b.(2) Central Nervous System**, and the application of an additional uncertainty factor for this concern is under **V.E.1. Pre- and Post-natal Sensitivity**.

IV.A.1.b. Respiratory System Effects

The respiratory system was also a target for sulfuryl fluoride toxicity after inhalation exposure. DPR's Pesticide Illness Surveillance Program reported individuals complaining of respiratory problems after exposures to sulfuryl fluoride and chloropicrin (**Volume II**). It is not known if one or both compounds contributed to the symptoms. Respiratory tract effects were also reported in humans after accidental or intentional acute exposures (**III.I.1. Non-occupational Exposure**). Postmortem examination findings in humans included respiratory and lung congestion, and pulmonary edema after exposure to high concentration during application (Scheurman, 1985) and lower concentration in a house cleared for reentry (Dammann *et al.*, 1987). These effects were likely due to irritation and inflammation induced by sulfuryl fluoride. In the studies on structural fumigation workers with repeated exposures to sulfuryl fluoride, respiratory tract function evaluation was not included (Anger *et al.*, 1986; Calvert *et al.*, 1998). Additional studies on the cause of pulmonary edema are needed to elucidate the mechanism involved.

In laboratory animals, pharmacokinetic study in rats showed highest radioactivity in the lungs after inhalation exposure (Mendrala, 2002). At high concentrations during acute exposure, sulfuryl fluoride was a respiratory irritant resulting in increased respiratory frequency, and reduced mean tidal and minute volumes in rats (Landry and Streeter, 1983). Pulmonary edema, a finding in human exposure, was also reported in rats (Miller *et al.*, 1980; Gorzinski and Streeter, 1985; Albee *et al.*, 1983). At lower concentrations and short exposure durations (2 to 13 weeks), there was inflammation of the larynx, nasal tissue, and trachea in rats (Nitschke *et al.*, 1987a; Table 5), rabbits (Eisenbrandt *et al.*, 1985; Nitschke *et al.*, 1987b; Tables 3 and 8) and dogs (Nitschke and Quast, 1991). With chronic exposure, chronic inflammation (Quast *et al.*, 1993c; Breslin *et al.*, 1992; Tables 13 and 15) and alveolar macrophage aggregates (Quast *et al.*, 1993a; Quast *et al.*, 1993c; Breslin *et al.*, 1992; Tables 11, 13, and 15) were found in rats and dogs, and lung congestion was observed in mice (Quast *et al.*, 1993b). Epithelial hyperplasia/hypertrophy of the nasal tissues were noted in rats (chronic exposure; Quast *et al.*, 1993a) and rabbit (13-week exposure; Nitschke *et al.*, 1987b).

IV.A.1.c. Dental Fluorosis

In addition to neurotoxicity and respiratory effects, one prominent effect was dental fluorosis from repeated exposure to fluoride ion. Mottled tooth enamel or dental fluorosis was

reported in rats and dogs after repeated sulfuryl fluoride exposures (Tables 11, 13, and 15). No dental effects were reported in mice after chronic exposure (Quast *et al.*, 1993b) at dosages higher than those in the rat and dog chronic toxicity studies (Table 14). The U.S. EPA has stated that fluorosis was a cosmetic effect, and not an adverse effect (U.S. EPA, 2004b). The National Academy of Sciences is currently examining the issues related to the fluoride exposure and toxicity (see footnote 1). The toxicity of fluoride associated with sulfuryl fluoride uses and other sources will be addressed in the dietary risk assessment.

IV.A.2. Mechanism of Toxicity

The primary target tissues for sulfuryl fluoride inhalation toxicity are the brain, respiratory system, and teeth in laboratory animals. While dental fluorosis could be attributed to fluoride, the mechanism of toxicity for the other endpoints could be assumed to be due to fluoride and the other metabolites (fluorosulfate and sulfate). However, there is no toxicity data on fluorosulfate or sulfate as a result of exposure to sulfuryl fluoride.

IV.A.2.a. Proposed Mechanism of Toxicity

One hypothesis on the mechanism of toxicity for sulfuryl fluoride was that the toxicity observed in laboratory animals was due to fluoride (Dow AgroSciences, 2004 a and b). The primary support was the detection of only fluoride and fluorosulfate in the pharmacokinetic study in rats (Mendrala *et al.*, 2002). The authors considered fluorosulfate to be nontoxic, but did not provide any toxicity information. In addition, elevated serum fluoride levels and brain vacuolation were found in the same group of treated mice (Nitschke and Quast, 1993). The toxicity of sulfuryl fluoride and the role of fluoride were also discussed in a published article by Eisenbrandt and Nitschke (1989). This discussion emphasized the role of fluoride in the toxicity of sulfuryl fluoride, but lacked detailed analysis. Indirect effects (adrenal cortex hypertrophy, hyperglycemia, and lymphoid tissue necrosis) observed with sulfuryl fluoride were attributed to fluoride ion as well as stress. This conclusion was based on reports showing sodium fluoride elevated serum glucose in rats, enhanced glucose-6-phosphatase activity in the liver and kidney, and stimulated adrenocortical function. Lymphoid necrosis observed could have been caused by increased plasma glucocorticoids. While noting that nephrotoxicity was found in their sulfuryl fluoride studies and published fluoride studies, these authors did not provide any explanation as to why nephrotoxicity was noted in sulfuryl fluoride treated rats but not rabbits. This difference in response was inconsistent with significantly elevated mean serum fluoride levels in rabbits, not rats. As for neurotoxicity, the authors did not compare this endpoint with fluoride and speculated on the role of fluoride ion and regional differences in metabolism of sulfuryl fluoride in the brain. For respiratory inflammation by sulfuryl fluoride, the authors stated that it might have been due to irritation, but the mechanism was unknown.

IV.A.2.b. Role of Fluoride in Sulfuryl Fluoride Toxicity

The following is an analysis of the data to determine if there is evidence to support the role of fluoride as the active metabolite for sulfuryl fluoride. In this analysis, the dose-response relationship, temporal relationship, and species consistency in the toxicity for both fluoride and sulfuryl fluoride were considered. Ideally, this should be accomplished by comparing results

from studies conducted with the same protocols at the same time and laboratory with thorough clinical observations and histological examinations. Lacking such a study, the toxicology databases for fluorides (**Appendix B**) and sulfuryl fluoride showed that the chronic toxicity studies in rats and mice, and developmental and reproductive studies in rats for these two compounds provided adequate data for such a comparison (Table 17). These studies were conducted with similar protocols and included examination of major tissues. In these comparisons, the fluoride levels from the sulfuryl fluoride studies were corrected for absorption since the pharmacokinetic study (Mendrala *et al.*, 2002) showed only 18% of the given dose was absorbed. These were compared to the fluoride levels in the sodium fluoride study, which were not corrected for absorption since the absorption for sodium fluoride was 75 to 90%. There are, however, limitations to this comparison. The routes of exposure were different: drinking water for sodium fluoride and inhalation for sulfuryl fluoride. The fluoride contents in the diet and water were not controlled in the sulfuryl fluoride studies. Different strains of mice were used in the chronic toxicity study: B6C3F1 for sodium fluoride and CD-1 for sulfuryl fluoride. Other studies in the fluoride database showed that fluoride affected multiple organs including the brain and respiratory system (**Appendix B**). While the endpoints are not the same as those observed with sulfuryl fluoride studies, they showed that fluoride is inherently toxic and can contribute toward the overall toxicity of sulfuryl fluoride.

IV.A.2.b.(1) Dental Fluorosis

The comparison of chronic toxicity studies showed that the dental fluorosis was observed in rats for both sodium fluoride and sulfuryl fluoride at similar fluoride doses (Table 17). This endpoint was consistent with the detection of fluoride in the pharmacokinetic study with sulfuryl fluoride (Mendrala *et al.*, 2002), and was expected since fluoride is accumulated in the teeth. The lowest-observed-effect levels in the sulfuryl fluoride studies were similar to those for sodium fluoride in experiments conducted by the oral route after adjustment for absorption factor. In the sulfuryl fluoride chronic inhalation toxicity study, the lowest-observed-effect levels (LOELs) as absorbed fluoride¹⁰ were 1 mg/kg/day for F344 rats and 2 mg/kg/day for beagle dogs (Breslin *et al.*, 1992; Quast *et al.*, 1993c). The LOELs for fluorosis were >0.6 mg/kg/day in rats (F344) and mice (B6C3F1) given sodium fluoride in the drinking water (NTP, 1990). Therefore, fluorosis in sulfuryl fluoride treated rats after inhalation was likely caused by fluoride.

¹⁰ The absorbed (abs) fluoride dose was calculated from the sulfuryl fluoride dose using the following equation:

$$F \text{ abs} = \text{ppm SF} \times \frac{4.17 \text{ mg}}{\text{m}^3} \times \text{animal inhalation rate} \times \frac{5 \text{ days exposed/week}}{7 \text{ days}} \times \frac{6 \text{ hours exposed/day}}{24 \text{ hours}} \times 0.18 \times \frac{38}{102}$$

The default rat, mouse, and dog inhalation rates are 0.96 m³/kg/day, 1.8 m³/kg/day, and 0.39 m³/kg/day, respectively. The inhalation absorption factor was 18% determined in pharmacokinetic study in rats (Mendrala *et al.*, 2002). The factor of 38/102 is molecular weight ratio for 2 molecules of fluoride per each molecule of sulfuryl fluoride.

Table 17. Comparison of effects in laboratory animals exposed to sodium fluoride and sulfuryl fluoride.

Organ/tissue	Sodium Fluoride (in drinking water)	Sulfuryl Fluoride (inhalation exposure) ^a
Chronic Toxicity Studies^b		
Teeth	Dental fluorosis at >0.6 mg F/kg/day in rats and mice	Dental fluorosis at 20 ppm SF (1 mg F/kg/day abs) in rats, but not mice
Central Nervous System	None in rats or mice	Brain vacuoles at 80 ppm in rats (4 mg F/kg/day abs), and mice (7 mg F/kg/day abs).
Respiratory tract	None in rats or mice	Aggregates of alveolar macrophages at 80 ppm SF (4 mg F/kg/day abs) in rats Lung congestion at 80 ppm SF (7 mg F/kg/day abs) in mice.
Skeleton	No skeletal fluorosis reported, but bone osteosarcoma found in rats.	No skeletal fluorosis reported
Liver	None in rats or mice	Mineralization and atrophy at 80 ppm SF (4 mg F/kg/day abs) in rats (considered secondary to renal toxicity). No effect in mice.
Kidney	None in rats or mice	Glomerulonephropathy at 80 ppm (4 mg F/kg/day abs) in rats. No effect in mice.
Cardio-vascular	None in rats or mice	Mineralization and atrophy of heart at 80 ppm SF (4 mg F/kg/day abs) in rats (considered secondary to renal toxicity). Heart thrombus at 80 ppm (7 mg F/kg/day abs) in mice.
Developmental and Reproductive Toxicity Studies		
Develop-mental	Decrease in the ossification of the hyoid bone in 250 ppm (11.7 mg F/kg/day) F2 rat fetuses in a 3-generation study (Collins <i>et al.</i> , 2001a). Hyoid bone effect was not observed in single generation study (Collins <i>et al.</i> , 1995; Heindel <i>et al.</i> , 1996).	No developmental effects in rats (≥225 ppm, 15 mg F/kg/day abs) or rabbits (≥225 ppm, 8 mg F/kg/day abs) (Hanley <i>et al.</i> , 1981 and 1989)
Reproductive	No reproductive toxicity at 12.8 mg fluoride/kg/day in rats (Collins <i>et al.</i> , 2001b).	Reduced pup weight at 150 ppm SF (7 mg F/kg/day abs), but no effect on reproductive parameters in a 2-generation study in rats (Breslin <i>et al.</i> , 1992).

a/ The absorbed (abs) fluoride (F) dose was calculated from the sulfuryl fluoride (SF) dose using the following equation:

$$F \text{ abs} = \text{ppm SF} \times \frac{4.17 \text{ mg}}{\text{m}^3} \times \text{animal inhalation rate} \times \frac{5 \text{ days exposed/week}}{7 \text{ days}} \times \frac{6 \text{ hours exposed/day}}{24 \text{ hours}} \times 0.18 \times \frac{38}{102}$$

The default rats and mice inhalation rates were 0.96 m³/kg/day and 1.8 m³/kg/day, respectively. The inhalation absorption factor was 18% determined in pharmacokinetic study in rats (Mendrala *et al.*, 2002). The factor of 38/102 was molecular weight ratio for 2 molecules of fluoride per each molecule of sulfuryl fluoride.

b/ In the sodium fluoride study (NTP, 1990), the fluoride doses were: 0.2 to 4.5 mg F/kg/day in rats, 0.6 to 9.1 mg F/kg/day in mice. In the sulfuryl fluoride studies, the absorbed fluoride doses were: 0.2 to 4 mg F/kg/day in rats (Quast *et al.*, 1993a) and 0.4 to 7 mg F/kg/day in mice (Quast *et al.*, 1993c).

There was, however, a difference in response for the mouse. While the National Toxicology Program (NTP, 1990) study showed fluorosis in the mouse given sodium fluoride, this endpoint was not reported for the mouse (CD-1) given sulfuryl fluoride (Quast *et al.*, 1993b). In this latter mouse study, the estimated absorbed fluoride was 7 mg/kg/day for the high dose (80 ppm) group. This was much higher than the LOEL of >0.6 mg fluoride/kg/day in the NTP study. The difference in response might be due to the differences in the strain (CD-1 versus B6C3F1) disposition of fluoride. While bone fluoride level was measured in the NTP study, it was not measured in the sulfuryl fluoride study.

IV.A.2.b.(2) Central Nervous System

The most prominent pathological lesion after sulfuryl fluoride exposure was the vacuolation and/or malacia of the cerebrum in all species (rats, mice, rabbits, and dogs) treated with sulfuryl fluoride (Table 16). Both lesions were described as focal in nature and were found in the basal ganglia region (caudate putamen nucleus, the external capsule and internal capsule, of the globus pallidus). In all studies where the brain was examined, the incidence and severity of the vacuolation was dose-related with the lowest LOEL ranged from 40 to 214 mg sulfuryl fluoride/kg/day depending on duration of exposure and species. In the chronic toxicity study, brain vacuoles were observed at 80 ppm in rats (calculated absorbed fluoride of 4 mg/kg/day) and in mice (calculated absorbed fluoride of 7 mg/kg/day) (Quast *et al.*, 1993a; Quast *et al.*, 1993c). This specific lesion was not reported in rats (up to 4.5 mg fluoride/kg/day) or mice (up to 9.1 mg/kg/day) exposed to sodium fluoride at similar doses in the NTP study (NTP, 1990), or other studies with fluoride-containing compounds (**Appendix B**). This could be due to the completeness of the histological examination, which generally is not conducted or is limited in published studies.

The possible role of fluoride in brain tissue damage was further investigated by examining the tissue fluoride levels. The pharmacokinetic study with sulfuryl fluoride showed that brain fluoride level was relatively low compared to other tissues such as the lungs and kidneys, and was similar to that measured for the plasma (Table 2; Mendrala *et al.*, 2002). This suggested that the brain was a deposition site for fluoride, either from distribution or regional metabolism. However, the brain fluoride levels were not measured in any toxicity studies. An analysis of the serum fluoride levels measured in three 13-week subchronic toxicity studies conducted in rats, mice, and rabbits showed, in general, high fluoride levels and increased incidences of brain lesion at the high dose groups (**Appendix D**). Examination of the individual animal data showed most consistent association with the mouse data (Table D1; Nitschke and Quast, 1993). In this study, the serum fluoride levels were measured only in 4 animals (there were 10 animals per group).

In comparison, the results with rats and rabbits were not as consistent. In the rat study, there was no difference in the mean serum fluoride levels between the control and treated groups (Table D2; Nitschke *et al.*, 1987a). The individual data showed a wide-range of fluoride levels for the control and treated groups in both genders. However, brain vacuoles were observed only in the high dose groups. With rabbits, there was an association of high serum fluoride and brain vacuoles only for the high dose males (Table D3; Nitschke *et al.*, 1987b). In the females, vacuoles were noted in one mid-dose animal (#1) with fluoride level lower than those for the

high dose groups with vacuoles. On the other hand, animals with the same serum fluoride level in the high dose group showed different findings, one animal (#5) had normal brain histology while the others showed vacuoles and malacia.

Therefore, sulfuryl fluoride-induced brain vacuolation could be due to fluoride. Of the three species, which showed vacuolation after exposure to sulfuryl fluoride, the mouse data showed an association with increased serum fluoride level. The lack of correlation for rats and rabbits might be confounded by varying fluoride intake from drinking water and feed or individual variation in response. It also could be that the serum fluoride level was not a good indicator for actual tissue levels, especially after repeated exposures. Data on brain fluoride levels, especially in affected regions, would provide more definitive determination of whether and how fluoride was involved in the toxicity of sulfuryl fluoride.

IV.A.2.b.(3) Respiratory System

No effects to the respiratory system were detected in the oral chronic studies with sodium fluoride in rats or mice (NTP, 1990). However, the respiratory tract is a target organ for both sulfuryl fluoride and hydrogen fluorides after inhalation exposure. Sulfuryl fluoride is a respiratory irritant at high concentrations in both humans and laboratory animals (Scheuerman, 1985; U.S. EPA, 1999a; Miller *et al.*, 1980; Gorzinski and Streeter, 1985; Albee *et al.*, 1983). Sulfuryl fluoride caused increased respiratory frequency, and reduced mean tidal and minute volumes in rats during the 20-minute exposure to 4,000 ppm (Landry and Streeter, 1983). At lower concentrations and repeated exposures in experimental animals (rats, rabbits, mice, and dogs), effects included nasal inflammation, epithelial degeneration and hyperplasia/hypertrophy, lung inflammation and congestion, and alveolar macrophage aggregates (Eisenbrandt *et al.*, 1985; Nitschke *et al.*, 1987b; Nitschke *et al.*, 1987a; Quast *et al.*, 1993c; Breslin *et al.*, 1992; Quast *et al.*, 1993a, b and c). These lesions in the lung could be caused by a direct irritation by sulfuryl fluoride, and could explain the breathing difficulties experienced by dogs in the one-year study (Quast *et al.*, 1993c). The roles of the metabolites, fluorosulfate and sulfate, cannot be established at this time since their levels in the lungs were not measured in the pharmacokinetic study (Mendrala *et al.*, 2002). There is no toxicity information on fluorosulfate in the published literature. Published reports on the respiratory toxicity of sulfuric acid showed that the acid moiety (H⁺) was the causative agent, and not the sulfate moiety (OEHHA, 1999¹¹). Sulfate salts with near or at neutral pH have not been found to induce respiratory effects in humans or laboratory animals.

Hydrogen fluoride is also an irritant. Some of these effects from sulfuryl fluoride exposure were similar to those observed in laboratory animals (rats, rabbits, guinea pigs, dogs, and mice) exposed to hydrogen fluoride by inhalation (**Appendix B**). The severity of the toxicity was related to the concentration and duration of exposure, and site of deposition. Toxic effects included mild nasal irritation, pulmonary hemorrhage, respiratory distress, congestion, edema, and desquamation of the respiratory epithelium, and lung tissue necrosis (ATSDR, 2003). Pharmacokinetic studies with hydrogen fluoride showed absorption in the upper respiratory tract

¹¹ OEHHA, 1999. Chronic Toxicity Summary: Sulfuric Acid. Determination of noncancer chronic reference exposure levels. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.

after inhalation exposure. Therefore, the reported effects in the respiratory system after sulfuryl fluoride exposure could be due to *in situ* conversion to fluoride.

IV.A.2.b.(4) Other Organs/Tissues

After sulfuryl fluoride chronic exposure, glomerulonephropathy (at calculated absorbed dose of 4 mg fluoride/kg/day) was observed in rats, but not mice (Quast *et al.*, 1993a and c) (Table 17). In addition, these rats showed mineralization and atrophy in the liver and heart, secondary to glomerulonephropathy. In contrast, these findings had not been reported for sodium fluoride with neither rats nor mice at similar or higher fluoride levels (up to 4.5 mg fluoride/kg/day in rats and 9.1 mg fluoride/kg/day in mice) (NTP, 1990).

As for developmental and reproductive effects, no developmental effects were observed in fetuses from pregnant rats or rabbits exposed to sulfuryl fluoride during gestation (Hanley *et al.*, 1981 and 1989). In comparison, Collins *et al.* reported a decrease in the ossification of the hyoid bone of the F2 pups in a 3-generation study, but not in a single generation toxicity study (Collins *et al.*, 2001a, 1991; and Heindel *et al.*, 1996). Neither sodium fluoride nor sulfuryl fluoride affected reproduction of rats (Collins *et al.*, 2001b; Breslin *et al.*, 1992).

IV.A.3. Selection of No-Observed-Effect Levels

Critical NOELs were established for exposure durations: acute (1 day), 1-2 week, subchronic (13-weeks), and chronic exposures. These NOELs would be used to address the exposure scenarios of workers, bystanders, and residents described in **IV.B. EXPOSURE ASSESSMENT**.

IV.A.3.a. Acute Toxicity

For acute exposure, the critical NOEL was 300 mg/kg/day (300 ppm, the highest dose tested) for no effects in Functional Observational Battery or electrophysiological responses in rats after two days of exposure (Albee *et al.*, 1993a). This NOEL was supported by the same NOEL of 300 mg/kg/day from two studies (Eisenbrandt *et al.*, 1985; Miller *et al.*, 1980) (Table 4). In these latter studies, treatment-related effects (lethargy at 500 mg/kg/day and death at 600 mg/kg/day, respectively) were observed at the next dose. In comparison, a head-only exposure study by Landry and Streeter (1983) showed a lower LOEL of 200 mg/kg/day (4000 ppm for 20 minutes) for respiratory effects. However, the estimated NOEL (ENEL) from this study was not selected because of the quality of the study and the transient nature of the effect. The results were available only as graphs and sulfuryl fluoride concentrations were relatively high with actual measurements not given in the report. The effects were transient with peak effect after 2 minutes of exposure and gradually returned to pre-exposure level by 10 minutes of post-exposure. They were likely indication of pulmonary irritation. This ENEL may be appropriate for accidental exposures to relatively high concentrations but not for the lower exposures associated with label-use of sulfuryl fluoride. Higher NOELs (500 and 751 mg/kg/day) were found for mice where tremors, lethargy, and death were observed when exposed to 751 and 876 mg/kg/day (600-700 ppm) sulfuryl fluoride in two 4-hour studies (Nitschke and Quast, 1990; Nitschke and Lomax, 1989). These results in mice and the finding of one death in the rat study

between the 2nd and 6th dose (Eisenbrandt *et al.*, 1985) at about 2-fold of the NOEL suggested a steep dose-response relationship for sulfuryl fluoride neurotoxicity.

IV.A.3.b. 1-2 weeks Exposure Toxicity

For exposures of 1-2 week in duration, the critical NOEL was 40 mg/kg/day (100 ppm) for malacia and vacuoles in the cerebrum of rabbits exposed to 121 mg/kg/day (300 ppm) sulfuryl fluoride (Tables 3 and 4) for two weeks (Eisenbrandt *et al.*, 1985). The magnitude of the effect (and incidence) in rabbits at the LOEL were considered slight to moderate (2/6) for malacia and slight (6/6) for vacuolation. Neurotoxicity (convulsions after the 6th dose and slight hyperactivity) was observed at the higher dose of 600 ppm. This NOEL was supported by similar findings, though less severe, in mice with the same NOEL (Nitschke and Quast, 2002). In two developmental toxicity studies with rabbits at similar doses (NOELs of 56 mg/kg/day and 42 mg/kg/day) (Table 4), the only finding was reduced body weight at 169 and 127 mg/kg/day after the first week of exposure (Hanley *et al.*, 1980 and 1981). However, it was not known if there were any brain lesions since histopathological examination was not conducted in the maternal tissues. External, soft tissue, and skeletal examinations of the fetuses did not show any treatment-related effects in these studies.

In rats, no brain lesions were observed in the 1-2 week studies although the animals treated at 420 mg/kg/day (600 ppm) were either moribund or died early in the study (Eisenbrandt *et al.*, 1985). In this group, the primary histopathological effect was in the kidneys (hyperplasia of the collecting ducts and basophilic epithelial cells in the proximal tubules) with the NOEL at 71 mg/kg/day (100 ppm). Kidney effects (focal paleness), along with reduced body weight and liver effects with a NOEL of 100 mg/kg/day (100 ppm), were observed in pregnant rats in a range-finding developmental toxicity study (Hanley *et al.*, 1980). These effects, however, were not observed in the definitive developmental toxicity study (Hanley *et al.*, 1981).

In dogs, a lower NOEL of 29 mg/kg/day (100 ppm), compared to 40 mg/kg/day for rabbits (Eisenbrandt *et al.*, 1985), was determined for intermittent tremors and tetany on day 5 onward as well as nasal tissue inflammation at 87 mg/kg/day (300 ppm) (Nitschke and Quast, 1991). However, this study was not selected for the determination of the critical NOEL because of the quality of the study. The study had only one dog per group per gender. The specific times of occurrence and frequency for the tremors and tetany were not reported. While the effects were considered severe and the exposure was terminated on day 9, treated dogs were also reported to show normal appearance and behavior within 30 minutes afterward. Lesions were not observed in the histological examination of the brain. Since the LOEL for clinical signs was at 87 mg/kg/day, the use of the NOEL of 40 mg/kg/day as the critical NOEL should be adequate to address these clinical observations in dogs.

As for the inflammation effect on the dog nasal tissue, the severity was graded as slight at the LOEL (300 mg/kg/day; Nitschke and Quast, 1991) with the actual NOEL likely to be closer to the LOEL. This effect was also observed in rabbits at 121 mg/kg/day (300 ppm) after 2 weeks of exposure (Eisenbrandt *et al.*, 1985; Table 3).

IV.A.3.c. Subchronic Toxicity

With subchronic inhalation exposure (13-weeks) to sulfuryl fluoride, brain vacuoles were observed in rats, mice, rabbits, and dogs (Table 10). The most sensitive species for this endpoint was the rabbit with the critical NOEL at 12 mg/kg/day (30 ppm) (Nitschke *et al.*, 1987b). While the incidence was only 1/7 and affecting only females at the LOEL of 40 mg/kg/day (100 ppm), the lesion was considered toxicologically significant as it was graded moderate. In addition, a higher incidence of vacuolation and more severe lesions (malacia and gliosis) were observed at 300 ppm. The NOELs for brain effects were higher in other species. In rats, the NOELs were 71 mg/kg/day (100 ppm, Nitschke *et al.*, 1987a; Table 5) and 21 mg/kg/day (30 ppm, Mattsson *et al.*, 1986; Table 6). For mice and dogs, the NOELs were 40 mg/kg/day (30 ppm, Nitschke and Quast, 1993; Table 7) and 29 mg/kg/day (100 ppm, Nitschke and Quast, 1992; Table 9), respectively. The selection of 12 mg/kg/day (30 ppm) in rabbits for brain lesions as the critical NOEL would also protect against other effects such as nasal tissues, kidneys, lungs, and thyroid lesions as well as dental fluorosis with the same or higher NOELs (Table 10).

IV.A.3.d. Chronic Toxicity

With chronic exposure to sulfuryl fluoride, dental fluorosis and respiratory system effects were the more sensitive endpoints with lower NOELs than that for brain lesions (Table 14). The critical NOEL was 4 mg/kg/day (5 ppm) in rats for dental fluorosis in a chronic toxicity study (Quast *et al.*, 1993a; Table 11) and for lung inflammation and alveolar macrophage aggregates in a 2-generation reproductive toxicity study (Breslin *et al.*, 1992; Table 15). This critical NOEL was supported by a similar NOEL of 6 mg/kg/day (20 ppm) for similar pulmonary findings in dogs (Quast *et al.*, 1993c; Table 13). In comparison, brain vacuolation was observed at higher doses (LOELs at ≥ 57 mg/kg/day and NOELs at ≥ 14 mg/kg/day) in these studies (Table 14). For the purpose of this risk assessment, respiratory system effects were considered the critical effect for chronic inhalation exposure of sulfuryl fluoride.

IV.A.3.e. Oncogenicity of Sulfuryl Fluoride

No tumors were found in rats or mice after chronic exposure to sulfuryl fluoride (Quast *et al.*, 1993a and b). Both *in vitro* and *in vivo* genotoxicity assays showed negative results (**III.E. GENOTOXICITY**). However, there were indications of pre-neoplastic effect. Hyperplasia of kidneys and nasal tissues, and hypertrophy of the thyroid were reported in laboratory animals after repeated exposures (Nitschke *et al.*, 1987a and b; Quast *et al.*, 1993a and b). Further experimental work is needed to determine whether or not sulfuryl fluoride would be carcinogenic to humans.

While not conclusive, there is some evidence that suggests fluoride can cause cancer, in particular the bone tissue. Fluoride is known to concentrate in calcified tissues. Both positive and negative results were reported in genotoxicity studies with sodium fluoride. Chronic toxicity studies with sodium fluoride in the drinking water showed low incidence of osteosarcoma in male rats, but not in female rats or either genders of mice in one study (NTP, 1990). Another study with sodium fluoride in the diet showed increased incidences of osteomas (benign bone tumors) in mice, but not rats (Maurer *et al.*, 1990). Additional discussion on the oncogenicity of fluoride is provided in F. Additional Information in Appendix B. U.S. EPA classified sulfuryl

fluoride as a chemical “not likely to be carcinogenic to humans” (U.S. EPA, 2004b and c).

IV.A.4. Critical NOELs and Reference Concentrations

The critical NOELs and reference concentrations for risk characterization are presented in Table 18. The NOELs and LOELs were adjusted with an inhalation absorption factor of 18% (see **III.A. PHARMACOKINETICS**) since human exposures are expressed in absorbed dose terms (**Volume II**). The assumption was that the absorption in rats was the same as that in humans. The reference concentrations, as 24-hour time weighted averages, were based on uncertainty factors of 100 (10-fold each for intraspecies and interspecies extrapolation) for occupational and of 1000 (with an additional 10-fold factor for the lack of a developmental neurotoxicity study) for residential/bystander exposures. The higher inhalation rate (lower reference concentration) of infants, compared to older children and adult groups, was used to calculate the reference concentrations for residents/bystanders as a group. In comparison, the maximal reference concentrations would be those for adults whose inhalation rate (0.28 m³/kg/day) was about half of that for infants (0.59 m³/kg/day).

Since fluoride is inherently toxic and human exposure to fluoride was not assessed in this RCD, the additional contribution of fluoride from sulfuryl fluoride use, if regulated at the reference concentration levels, was calculated. The chronic reference concentration for infants was 0.01 mg sulfuryl fluoride/m³, which is equivalent to 0.0004 mg fluoride/kg/day¹². For adults, the chronic reference concentration was 0.18 mg/m³, or a fluoride level of 0.003 mg/kg/day¹³. Using the average fluoridation level of 1 ppm in the drinking water, the average exposures to fluoride are 0.1 mg/kg/day and 0.03 mg/kg/day for a 10-kg child and 70-kg adult drinking 1 liter and 2 liters of water/day, respectively. Based on these calculations, these fluoride levels from Vikane→ are estimated to represent 0.4% (0.0004/0.1 x 100%) and 10% (0.003/0.03 x 100%) of the average drinking water levels, for infants and adults, respectively. Calculation of fluoride exposure for additional scenarios is presented in the Risk Appraisal section (**V.E.3. Cumulative Toxicity**).

¹² Absorbed fluoride level in infants= mg sulfuryl fluoride/m³ x 38/102 x absorption factor x human inhalation rate. The absorption factor was 18% based on a pharmacokinetic study in rats (Mendrala *et al.*, 2002). The infant inhalation rate was 0.59 m³/kg/day.

¹³ Absorbed fluoride level in adults= mg sulfuryl fluoride/m³ x 38/102 x absorption factor x human inhalation rate. The absorption factor was 18% based on a pharmacokinetic study in rats (Mendrala *et al.*, 2002). The adult inhalation rate was 0.28 m³/kg/day.

Table 18. Critical no-observed-effect levels (NOEL) and reference concentrations for the risk characterization of sulfuryl fluoride.

Duration	NOEL (ppm)	NOEL (mg/kg/day)	NOEL in absorbed dose ^a (mg/kg/day)	Reference concentration ^b		Critical Endpoint	Ref. ^c
				Workers (Adult) UF=100	Residents/Bystanders (Infants) UF=1000		
Acute 1 day	300	300	54	2.57 ppm 10.7 mg/m ³	0.12 ppm 0.51 mg/m ³	No effect in FOB and electro-physiological tests in rats	1
1-2 weeks	100	40	7.2	0.48 ppm 2.01 mg/m ³	0.023 ppm 0.10 mg/m ³	Brain lesion (malacia and vacuoles) in rabbits	2
Sub-chronic (13-week)	30	12	2.2	0.14 ppm 0.60 mg/m ³	0.007 ppm 0.03 mg/m ³	Brain lesion (vacuoles) in rabbits	3*
Chronic	5	4	0.72	0.04 ppm 0.18 mg/m ³	0.002 ppm 0.01 mg/m ³	Lung inflammation, alveolar macrophage aggregates in rats	4*

^{a/} Equations for calculations are in **Appendix E**. The absorbed dose was calculated using a 18% inhalation absorption factor.

^{b/} The reference concentration as 24-hour time-weighted averages is the ratio of human equivalent NOEL to a default uncertainty factor (**Appendix E**). When the UF is 1000, an additional 10x database factor was included. The RfC for occupational exposure was based on human adult inhalation rate of 0.28 m³/kg/day, and for residential/bystander exposure was based on infant inhalation rate of 0.59 m³/kg/day.

^{c/} * indicates study acceptable to DPR under FIFRA guidelines. References: 1. Albee *et al.*, 1993a; 2. Eisenbrandt *et al.*, 1985; 3. Nitschke *et al.*, 1987b; 4. Breslin *et al.*, 1992.

IV.B. EXPOSURE ASSESSMENT

Workers, residents, and bystanders are exposed to sulfuryl fluoride from its use in structural and non-food commodity fumigations. The complete exposure assessment is in **Volume II**; a summary is presented in this section. The inhalation exposure estimates were based either on monitoring studies or when data were not available, an assumed maximum air level of 5 ppm allowed on the label. The latter case applied to tester of clearance in structural fumigation, as well as handlers and bystanders of non-food commodity fumigation. Their exposure estimates were based on the assumption that label instructions were followed and that the maximum exposure was 5 ppm. The actual exposure could be higher or lower than those values. For workers, the label requires the use of a NIOSH or Mine Safety and Health Administration approved positive pressure self-contained breathing apparatus (SCBA) or combination air supplied/SCBA respirator whenever the air concentration of sulfuryl fluoride exceeds 5 ppm. A bystander, including neighbors, is defined as any person not directly involved with the fumigation process, but may be exposed as a consequence of the fumigant use. The air concentrations for the bystanders vary depending on many factors including weather conditions and location of the structure. For bystanders in non-food commodity fumigation, 5 ppm was assumed to be the highest potential acute exposure. This assumption considered available air monitoring data collected during structural fumigations were the highest reported air concentration was 3 ppm, and the infrequent use of sulfuryl fluoride for this type of fumigation. More explanation of this use scenario is in **Volume II**.

The monitoring studies used application rates lower than that allowed on the label, referred to as the submaximal rate. For exposures at the maximal rate allowed on the label, they were extrapolated from data for the submaximal rate with the assumption that exposure was directly proportional to the application rate. The extrapolation factor was either 14.5-fold or 10-fold depending on the rates used in the monitoring studies. The exposure estimates¹⁴ were expressed as absorbed doses using an inhalation absorption factor of 18% based on a pharmacokinetic study in rats. The exposure durations were defined as acute (24 hours or less), short-term (7 days or less), intermediate (more than 7 days to less than 1 year), annual (any exposure during the year), and lifetime (Andrews, 2001). Some of these durations were different than those defined by the U.S. EPA (U.S. EPA, 2001d).¹⁵

IV.B.1. Occupational Exposure

Occupational exposures for fumigators and tent crews were based on personal air monitoring data. For handlers of non-food commodity fumigation, their exposures were assumed at 5 ppm, the maximum exposure limit according to the current Vikane® label.

¹⁴ The exposure values were rounded to no more than 2 significant figures in the discussion. Some of these values contained additional figures in the Tables, which came from Volume II. These values in the Tables were used in the margin of exposure calculations.

¹⁵ U.S. EPA definitions for worker/residential exposure duration are: short-term (1 day to 1 month), intermediate (1 to 6 months), and long-term (several months to lifetime) (U.S. EPA, 2001d).

IV.B.1.a. Structural Fumigation - Fumigators and Tent Crew

For structural fumigation, exposures were estimated for fumigators during phases of the application and aeration, and tent crew workers doing detarping activities (Table 19). The frequency of exposure per activity was 0.17 to 3.7 hours per day, about 4 days per week, and for 180 or 196 days per year depending on the activity. For the individual activities, the short-term exposures for the fumigators were calculated using the 95th percentile air concentrations from personal air monitoring studies of workers using submaximal application rate of sulfuryl fluoride. Their exposures ranged from 0.000006 mg/kg/day (closing of structure) to 0.03 mg/kg/day (introducing fumigant) (Table 19). Since the fumigator is not restricted to a single activity during the fumigation, the total exposure from doing all fumigator activities as well as the fumigator doing tent crew activities were also estimated. The combined short-term exposures were 0.04 mg/kg/day (all fumigator activities) and 1.17 mg/kg/day (fumigator and tent crew activities). The short-term exposures of the tent crew ranged from 0.04 mg/kg/day (ground snake removal) to 1.13 mg/kg/day (general detarping).

For repeated exposures at the submaximal application rate, the exposures were based on the mean air concentrations from the studies. The intermediate exposures ranged from 0.000002 mg/kg/day (closing structures) to 0.31 mg/kg/day (fumigator and tent crew activities) for fumigators, and from 0.01 mg/kg/day (ground snake removal) to 0.29 mg/kg/day (general detarping) for the tent crew (Table 19). The annual exposures ranged from 0.0000008 mg/kg/day (closing structures) to 0.15 mg/kg/day (fumigator and tent crew activities) for fumigators, and from 0.007 mg/kg/day (ground snake removal) to 0.14 mg/kg/day (general detarping) for the tent crew. The lifetime exposures ranged from 0.0000004 mg/kg/day (closing structures) to 0.08 mg/kg/day (fumigator and tent crew activities) for fumigators, and from 0.003 mg/kg/day (ground snake removal) to 0.08 mg/kg/day (general detarping) for the tent crew. At the maximal application rate, the exposures were 14.5 times that of the submaximal rate for all exposure groups.

IV.B.1.b. Non-food Commodity Fumigation - Handler

For non-food commodity fumigation, the handler exposures applied to all commodity workers (i.e. fumigators and commodity post-fumigation handlers) and were assumed at 5 ppm, since there were no monitoring studies at DPR. Furthermore, the worker exposure duration was assumed at 8 hours per day but only one application per year since this use is relatively rare as discussed in **Volume II**. The acute, annual, and lifetime exposures for these workers were 0.43 mg/kg/day, 0.001 mg/kg/day, and 0.001 mg/kg/day, respectively (Table 19).

IV.B.2. Residential and Bystander Exposures

The exposures of residents reentering fumigated homes were based on air monitoring studies for 7 homes. For bystander exposures during the application of sulfuryl fluoride, they were estimated from ambient air monitoring from actual fumigations. During aeration with

TRAP¹⁶ methods, the bystander exposures were estimated from monitoring data of workers doing general detarping activities. The bystander exposures for the Stack aeration, on the other hand, were based on monitoring data for the method. The bystander exposure at a non-food use commodity fumigation was based on the 5 ppm exposure limit. Under each scenario, exposures were determined for different age groups using age-dependent inhalation rates, hours of exposure, and body weight. For all scenarios, infants (less than 1 year old) had the highest exposure because of their higher inhalation rate (m³/hr/kg, Table 8 in **Volume II**).

IV.B.2.a. Structural Fumigation – Residents

Exposures were estimated for residents returning to homes after clearance for occupation using monitoring data collected following minimum clearance requirement (Table 20). The data showed continuous dissipation of sulfuryl fluoride over a 7-day period (Figure 5 in **Volume II**). The acute, short-term, and annual absorbed doses were estimated as an upper bound during sulfuryl fluoride dissipation following clearance. The lifetime absorbed dose was the mean air concentration of the interval of 0-7 days following clearance. For acute exposure, the range of exposures was 0.20 mg/kg/day (15-18 years old) to 0.57 mg/kg/day (<1 year old). The range of short-term exposures was 0.05 mg/kg/day (12-18 years) to 0.13 mg/kg/day (<1 year old). The range of annual exposures was 0.0009 mg/kg/day (15-18 years) to 0.0025 mg/kg/day (<1 year old). The lifetime exposure for adults was 0.0002 mg/kg/day.

IV.B.2.b. Structural Fumigation - Bystanders

Bystander exposures during fumigant application and aeration phases were estimated based on air monitoring studies (Tables 21-23). During the application phase, peak sulfuryl fluoride was detected in the ambient air after application and dissipated over a 24-hour period (Figure 6 in **Volume II**). The bystander exposures were estimated for the first 12-hour, and overall 24-hour period (Table 21). For all age groups and at submaximal application rate, the acute-12 hour exposures ranged from 0.14 mg/kg/day (15-18 years old) to 0.36 mg/kg/day (<1 year old). The 24-hour overall exposures were 0.2 mg/kg/day (15-18 years old) to 0.50 mg/kg/day (<1 year old). The annual exposures (1 day per year) ranged from 0.0006 mg/kg/day (12-18 years old, adult) to 0.0014 mg/kg/day (<1 year old). The lifetime exposure of adults was 0.0002 mg/kg/day. The exposures for maximal application rate were 10 times that of the submaximal rate (see **Volume II** for explanation).

On the first day of aeration, the bystanders were exposed primarily during the first few hours. The exposures were estimated based on monitoring studies for two aeration methods with the Stack method resulting in lower exposures (see Glossary of Terms). Using the TRAP method for aeration, the acute 2-hour exposures ranged from 0.36 mg/kg/day (15-18 years old) to 0.90 mg/kg/day (<1 year old) (Table 22). The annual exposures ranged from 0.001 mg/kg/day (12 years old to adult) to 0.003 mg/kg/day (<1 year old). The lifetime exposure of adults was 0.0002 mg/kg/day. The exposures for maximal application rate were 14.5 times that of the submaximal

¹⁶ TRAP=Tarpaulin Removal and Aeration Plan, a standard aeration practice in California. The Stack plan is an alternative aeration procedure. The main difference is the longer aeration time with the Stack plan. Details of these methods are in Appendix A.

rate.

Using the Stack method, the peak exposure was after 1 hour in a 4-hour period (Table 23). The overall exposures were lower than those for the TRAP method (Tables 22 and 23). It should be noted that the Stack method is not current practice in California. The acute 1-hour exposures ranged from 0.05 mg/kg/day (15-18 years old) to 0.14 mg/kg/day (<1 year old). For the 4-hour exposure period, the acute exposures ranged from 0.06 mg/kg/day (15-18 years old) to 0.15 mg/kg/day (<1 year old). The annual exposures ranged from 0.0002 mg/kg/day (9 years old to adults) to 0.0004 mg/kg/day (<1 year old). The lifetime exposure of adults was 0.00005 mg/kg/day. The exposures for maximal application rate were 10 times that of the submaximal rate.

IV.B.2.c. Non-food Commodity Fumigation – Bystanders

For non-food commodity fumigation, the bystander exposures were assumed to occur for only one day and at 5 ppm as assumed for the handlers. The acute 24-hour exposures ranged from 0.9 mg/kg/day (15-18 years old) to 2.3 mg/kg/day (<1 year old) (Table 24). The annual exposures ranged from 0.0025 mg/kg/day (15-18 years old) to 0.0063 mg/kg/day (<1 year old). The lifetime exposure of adults was 0.002 mg/kg/day.

Table 19. Sulfuryl fluoride exposure estimates of structural and non-food commodity fumigation workers.^a

Exposure Groups	Short-term	Intermediate	Annual	Lifetime
A. Structural Fumigation				
Exposure duration	0.17 to 3.73 hrs/day, 1 to 7 days	7 days to < 1 year	49 weeks/year	40 years/ 75 years
1. Fumigators at Submaximal Rate		Absorbed Dose (mg/kg/day)		
Introducing fumigant	0.03	0.01	0.006	0.003
Opening structure	0.0001	0.00004	0.00002	0.000009
Closing	0.000006	0.000002	0.0000008	0.0000004
Testing for clearance ^b	0.009	0.009	0.005	0.003
Total activities	0.04	0.02	0.01	0.006
Fumigator +tent crew	1.17	0.31	0.15	0.08
2. Tent Crew at Submaximal Rate				
Ground seam opening	0.30	0.05	0.03	0.01
Roof seam opening	0.31	0.07	0.04	0.02
Ground snake removal	0.04	0.01	0.007	0.003
Tarpaulin folding	0.06	0.02	0.008	0.004
General detarping	1.13	0.29	0.14	0.08
3. Fumigators at Maximal Rate				
Introducing fumigant	0.42	0.16	0.09	0.05
Opening structure	0.002	0.0005	0.0002	0.0001
Closing	0.00009	0.00002	0.00001	0.000006
Testing for clearance ^b	0.009	0.009	0.005	0.003
Total activities	0.43	0.17	0.09	0.05
Fumigator +tent crew	16.85	4.39	2.17	1.16
4. Tent Crew Maximal Rate				
Ground seam opening	4.42	0.73	0.36	0.19
Roof seam opening	4.45	1.04	0.51	0.27
Ground snake removal	0.59	0.19	0.09	0.05
Tarpaulin folding	0.80	0.23	0.11	0.06
General detarping	16.42	4.22	2.08	1.11
B. Non-food Commodity Fumigation				
Exposure duration	Acute 8 hours/day		Annual 1 day/ year	Lifetime 1 day for 40 years in 75 years
Handler^{b,c}	0.43	NA	0.001	0.001

a/ Values are from Table 7a and 7b of **Volume II**. NA=not applicable. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, respiratory protection factor (when applicable), and an absorption factor of 18% (Mendrala *et al.*, 2002 in **III.A. PHARMACOKINETICS**). Exposures at maximal application rate were assumed to be 14.5 times those from the submaximal rate.

b/ Based on the maximal air concentration of 5 ppm.

c/ Non-food Commodity Handler values would apply to all commodity workers (i.e. fumigators and commodity post-fumigation handlers) assuming on-site air levels did not exceed 5 ppm.

Table 20. Sulfuryl fluoride exposure estimates for residents following clearance of fumigated homes.^a

Resident	Acute absorbed dose (mg/kg/day)	Short-term absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	14-17 hours during the first 24 hours of reoccupation	1 to 7 days during reoccupation	≤ 7 days/year	≤ 7 days/year for 57 of 75 years
Age (years)				
<1	0.57	0.13	0.0025	NA
1-2	0.49	0.12	0.0023	NA
3-5	0.42	0.10	0.0019	NA
6-8	0.32	0.08	0.0015	NA
9-11	0.29	0.07	0.0014	NA
12-14	0.23	0.05	0.0010	NA
15-18	0.20	0.05	0.0009	NA
Adult	0.24	0.06	0.0011	0.0002

^{a/} Values are from Table 13 of **Volume II**. NA=not applicable. Exposure was based on air monitoring data collected during the first 48 hours following minimum clearance requirements. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, and an absorption factor of 18% (Mendrala *et al.*, 2002 in **III.A. PHARMACOKINETICS**).

Table 21. Sulfuryl fluoride exposure estimates for bystanders at a structural fumigation site during the application phase.^a

Bystander (Age in years)	Acute-12 hours absorbed dose (mg/kg/day)	Acute-24 hours absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	12 hours/day	24 hours/day	1 day/year	1 day/year for 57 of 75 years
Structural Fumigation at Submaximal Rate				
<1	0.36	0.50	0.0014	NA
1-2	0.31	0.43	0.0012	NA
3-5	0.28	0.39	0.0010	NA
6-8	0.23	0.33	0.0009	NA
9-11	0.22	0.32	0.0009	NA
12-14	0.17	0.23	0.0006	NA
15-18	0.14	0.20	0.0006	NA
Adult	0.17	0.24	0.0007	0.0002
Structural Fumigation at Maximal Rate				
<1	3.6	5.0	0.014	NA
1-2	3.1	4.3	0.012	NA
3-5	2.8	3.9	0.010	NA
6-8	2.3	3.3	0.009	NA
9-11	2.2	3.2	0.009	NA
12-14	1.7	2.3	0.006	NA
15-18	1.4	2.0	0.005	NA
Adult	1.7	2.4	0.007	0.002

^{a/} Values are from Tables 14a and 14b of **Volume II**. NA=not applicable. Exposure was based on air monitoring data from structural fumigation. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, and an absorption factor of 18% (Mendrala *et al.*, 2002 in **IIIA. PHARMACOKINETICS**). Exposures at maximal application rate were assumed to be 10 times those for the submaximal rate.

Table 22. Sulfuryl fluoride exposure estimates for bystanders at a structural fumigation site during the aeration phase using TRAP method.^a

Bystander (Age in years)	Acute- 2 hours absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	2 hours/day for 1 day	1 day per year	1 day/year for 75 years
Structural Fumigation at Submaximal Rate			
<1	0.90	0.003	NA
1-2	0.78	0.002	NA
3-5	0.70	0.002	NA
6-8	0.58	0.002	NA
9-11	0.56	0.001	NA
12-14	0.41	0.001	NA
15-18	0.36	0.001	NA
Adult	0.43	0.001	0.0002
Structural Fumigation at Maximal Rate			
<1	13.1	0.04	NA
1-2	11.3	0.03	NA
3-5	10.2	0.03	NA
6-8	8.4	0.02	NA
9-11	8.1	0.02	NA
12-14	6.0	0.02	NA
15-18	5.2	0.01	NA
Adult	6.2	0.02	0.003

^{a/} Values are from Tables 15a and 15b of **Volume II**. NA=not applicable. Exposure was based on air monitoring data from structural fumigation. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, and an absorption factor of 18% (Mendrala *et al.*, 2002 in **III.A. PHARMACOKINETICS**). Exposures at maximal application rate were assumed to be 14.5-fold of those for the submaximal rate. TRAP=Tarpaulin Removal and Aeration Plan.

Table 23. Sulfuryl fluoride exposure estimates for bystanders at a structural fumigation site during the aeration phase using Stack method.^a

Bystander (Age in years)	Acute-1 hour absorbed dose (mg/kg/day)	Acute-4 hours absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	1 hour/day	4 hours/day	1 day in 1 year	1 day/year for 57 of 75 years
Structural Fumigation at Submaximal Rate				
<1	0.14	0.15	0.0004	NA
1-2	0.12	0.13	0.0004	NA
3-5	0.11	0.12	0.0003	NA
6-8	0.09	0.10	0.0003	NA
9-11	0.09	0.09	0.0002	NA
12-14	0.06	0.07	0.0002	NA
15-18	0.05	0.06	0.0002	NA
Adult	0.07	0.07	0.0002	0.00005
Structural Fumigation at Maximal Rate				
<1	1.4	1.5	0.0041	NA
1-2	1.2	1.3	0.0036	NA
3-5	1.1	1.2	0.0033	NA
6-8	0.9	1.0	0.0028	NA
9-11	0.9	0.9	0.0027	NA
12-14	0.6	0.7	0.0019	NA
15-18	0.5	0.6	0.0016	NA
Adult	0.7	0.7	0.0019	0.0005

^{a/} Values are from Tables 16a and 16b of **Volume II**. NA=not applicable. Exposure was based on air monitoring data from structural fumigation. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, and an absorption factor of 18% (Mendrala *et al.*, 2002 in **IIIA. PHARMACOKINETICS**). Exposures at the maximal application rate were assumed to be 10 times those for the submaximal rate.

Table 24. Sulfuryl fluoride exposure estimates for bystanders at or near a non-food commodity fumigation site.^a

Bystander (Age in years)	Acute-24 hours absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	24 hours/day for 1 day	1 day/year	1 day/year for 57 of 75 years
<1	2.3	0.0063	NA
1-2	1.9	0.0052	NA
3-5	1.8	0.0049	NA
6-8	1.5	0.0041	NA
9-11	1.4	0.0038	NA
12-14	1.0	0.0027	NA
15-18	0.9	0.0025	NA
Adult	1.1	0.0030	0.002

^{a/} Values are from Table 17 of **Volume II**. NA=not applicable. Exposures were based on 5 ppm as the maximum level allowed on the label. The absorbed dose took into account the exposure duration, body weight, inhalation rate, and an absorption factor of 18% (Mendrala *et al.*, 2002 in **III.A. PHARMACOKINETICS**).

IV.C. RISK CHARACTERIZATION

The potential health risk associated with the use of sulfuryl fluoride was considered for occupational, bystander, and residential inhalation exposures. Non-oncogenic effects were characterized in terms of a MOE, defined as the ratio of the NOEL from animal or human studies to the estimated human exposure levels. The NOELs in absorbed doses are listed in Table 18, and the exposure levels for the various exposure scenarios are presented in Tables 19 to 24. Since the exposure durations in the toxicology studies are defined differently than some of the scenarios in the Exposure Assessment (**Volume II**), the applicable NOELs for the exposure durations are presented in Table 25.

In the selection of the NOELs, the important considerations were frequency of exposure (number of days per year) and dissipation characteristics. The acute NOEL was used to address the daily exposures (expressed as short-term exposures) of the fumigators and tent crews and peak exposures (expressed as acute exposures) of residents and bystanders of the structural fumigation as well as handlers and bystanders to commodity fumigation. The overall exposure of residents during the 7 days of reoccupation (short-term exposure) of treated home was not assessed since there was no toxicology study available with continuous dissipation of sulfuryl fluoride over this period. Repeated daily exposures occurred primarily with workers doing structural fumigation. The short-term exposures of fumigators and tent crews were also assessed using a 1-2 week NOEL since these workers could be exposed to sulfuryl fluoride on a weekly basis. Intermediate and annual exposures associated with this use were assessed using subchronic and chronic NOELs, respectively. Annual exposures based on 1 or 7 days of exposure (all residential and bystander exposures) were not assessed because they were considered acute exposures. The lifetime risk of sulfuryl fluoride exposure for all groups was not evaluated since sulfuryl fluoride has not been shown to be oncogenic in either humans or laboratory animals.

The potential risk from exposure to sulfuryl fluoride was assessed with a comparison of margins of exposure to benchmarks or of air concentrations with the reference concentrations¹⁷. For risk assessment under SB 950, DPR evaluates the exposure using a benchmark margin of exposure of 100 when the NOEL for non-oncogenic effects was based on animal data. This benchmark of 100 includes an uncertainty factor of 10 for interspecies extrapolation and a factor of 10 for intraspecies variability. These uncertainty factors assume that the average human is 10 times more sensitive to the effects of a chemical than the most sensitive laboratory animal, and that a sensitive individual is 10 times more susceptible than an average individual (Davidson *et al.*, 1986; Dourson and Stara, 1983).

A higher benchmark of 1000, with an additional database uncertainty factor of 10-fold was considered for sulfuryl fluoride residential and bystander exposures in this RCD because of a lack of a study to fulfill the requirement for a developmental neurotoxicity study by the U.S. EPA (U.S. EPA, 2004a). This factor would be applicable for all age groups as a general approach. Potential developmental neurotoxicity would likely to have greater impact on the

¹⁷ Benchmark and reference concentrations are defined in the Glossary (I.A.). Reference concentrations for sulfuryl fluoride are listed in Table 18.

fetus, infants, and young children with developing central nervous systems. In the dietary risk assessment for ProFume→, the U.S. EPA applied the dietary reference concentration with this additional 10-fold factor to the exposures of all age groups.

For potential listing under AB 1807 as a toxic air contaminant, ambient air exposures as represented by bystander exposures were compared to the reference concentrations. The listing criteria established by DPR (California Code of Regulations, Title 3, Division 6, Section 6890) specified that a pesticide shall be listed if the ambient air concentrations are greater than the following: (1) 10-fold below the reference concentration for pesticides with threshold effects, or (2) 10-fold below the negligible risk concentration. Based on criterion (1), exposures of concern are those higher than 1/10 of the reference concentration. Since the equations for reference concentration and MOEs were related, these were also scenarios where the MOEs for bystander exposures were less than 10,000.

IV.C.1. Occupational Exposure

IV.C.1.a. Structural Fumigation - Fumigators and Tent Crew

For structural fumigation using the submaximal rate of application, the MOEs for individual fumigator activities for all durations were greater than 100 (ranged from 120 to >10,000) (Table 26). For total fumigator activities, the acute, 1-2 week, and subchronic MOEs were greater than 100, but was 67 for chronic exposure. All MOEs for workers doing both fumigation and tent crew activities were less than 100 (range from 5 to 46). For the tent crew, the acute and 1-2 week MOEs were higher than 100 (range from 120 to 1350) for most activities, except for general detarping, ground seam opening, and roof seam opening where the MOEs were 6 to 48. For subchronic exposure, the MOEs ranged from 8 (general detarping) to 168 (ground snake removal). For chronic exposure, the MOEs ranged from 5 (general detarping) to 111 (ground snake removal).

At the maximal application rate, the MOEs for fumigators and tent crew were 14.5 times lower than those for submaximal rate, and were generally less than 100 except for scenarios with minimal exposures such as opening, closing, and testing activities for fumigators (Table 26). The MOEs for the tent crew were all less than 100.

IV.C.1.b. Non-food Commodity Fumigation - Handler

For handlers of non-food commodity fumigation, the MOE was 126 for acute exposure (Table 26).

IV.C.2. Resident and Bystander Exposures

IV.C.2.a. Structural Fumigation – Residents

For residents reoccupying fumigated homes after clearance, the acute MOEs ranged from 95 (<1 year old) to 186 (9-11 years old) for younger children (Table 27). For the older children and adults, the acute MOEs ranged from 225 (adults) to 270 (15-18 years old).

IV.C.2.b. Structural Fumigation - Bystanders

For bystander exposures during submaximal rate application, the acute (first 12-hours) MOEs for bystanders ranged from 150 (<1 year old) to 386 (15-18 years old) (Table 28). The MOEs for 24-hour exposure during the application phase ranged from 108 (<1 year old) to 270 (15-18 years old). At the maximal application rate, the acute MOEs for all age groups were 10-fold lower than those for the submaximal rate, and were at or less than 39.

During aeration using the TRAP method after application at the submaximal application rate, the acute MOEs for the bystanders ranged from 60 (<1 year old) to 150 (15-18 years old) (Table 29). For aeration using the Stack method, the acute MOEs for the first hour ranged from 386 (<1 year old) to 1080 (15-18 years old) (Table 29). Over the 4-hour period, the MOEs ranged from 360 (<1 year old) to 900 (15-18 years old). At the maximal application for either aeration methods, the acute MOEs were at or less than 10 for the TRAP method, and at or less than 108 for the Stack method.

IV.C.2.c. Non-food Commodity Fumigation – Bystanders

The acute MOEs for bystanders near a commodity fumigation facility ranged from 23 (<1 year old) to 60 (15-18 years old) (Table 30).

IV.C.2.d. Bystander Exposures and Reference Concentration

Bystander exposures were compared to the reference concentration as another approach to assess the risk. Since infants had the highest exposure, their acute exposures were compared to the acute reference concentration calculated for this age group. For both application and aeration phases in structural fumigation, the estimated exposures as 24-hour time-weighted averages were much higher than the reference concentrations (Table 31). For structural fumigation, infant estimated exposure was as much as 1,667% of the reference concentration (during aeration using TRAP method). For non-food commodity fumigation with the assumed air level of 5 ppm and exposure for 24 hours, the estimated exposure for infants near a non-food commodity fumigation site was over 4,000% of the reference concentration.

Table 25. Exposure duration and applicable no-observed-effect levels (NOELs) for margin of exposure calculations.

Groups/tasks	Worker and Resident Exposure Durations		NOELs ^a
Structural fumigation			
Fumigator and tent crew	Short-term	Upper bound exposure values for ≤ 7 days	Acute 1-2 weeks
	Intermediate	Mean exposure values for ≥ 7 days to < 1 year	Subchronic
	Annual	Mean exposure values 49 weeks/year	Chronic
	Lifetime	40 years/75 years	NA
Resident after clearance for reentry	Acute-24 hours	14 to 17 hours on first day of reoccupation	Acute
	Short-term	7 days during reoccupation with continuous decay	NA
	Annual	7 days/year	NA
	Lifetime	7 days/year for 57 of 75 years	NA
Bystander during application	Acute- 12 hours	First 12 hours of application phase	Acute
	Acute- 24 hours	24 hours for 1 day	Acute
	Annual	1 day/year	NA
	Lifetime	1 day/year for 57 of 75 years	NA
Bystander during aeration using TRAP or Stack method	Acute-1 hour	1 hour/day (for Stack method only)	Acute
	Acute-2 and 4 hours	TRAP: 2 hours/day Stack: 4 hour/day	Acute
	Annual	1 day/year	NA
	Lifetime	1 day/year for 57 of 75 years	NA
Non-food Commodity Fumigation (Assume 5 ppm)			
Handler^b	Acute- 8 hours	8 hours/day	Acute
	Annual	1 day/year	NA
	Lifetime	1 day for 40 years of 75 years	NA
Bystander	Acute-24 hours	24 hours for 1 day	Acute
	Annual	14-17 hours for 1 day in a year	NA
	Lifetime	1 day/year for 57 of 75 years	NA

a/ The NOELs and endpoints are listed in Table 18. The acute NOEL was 300 mg/kg/day (absorbed dose of 54 mg/kg/day) for no FOB effects in rats after two days of exposure (Albee *et al.*, 1993a). The 1-2 weeks NOEL was 40 mg/kg/day (absorbed dose of 7.2 mg/kg/day) for brain lesions in rabbits after 2 weeks of exposure (Eisenbrandt *et al.*, 1985). The subchronic NOEL was 12 mg/kg/day (absorbed dose of 2.2 mg/kg/day) for brain lesions in rabbits after 13 weeks of exposure (Nitschke *et al.*, 1987b). The chronic NOEL was 4 mg/kg/day (absorbed dose of 0.72 mg/kg/day) for lung pathology in rats in a 2-generation reproductive toxicity study (Breslin *et al.*, 1992). NA=there is no applicable NOEL for the exposure duration.

b/ Commodity Handler values would apply to all commodity workers (*i.e.* fumigators and commodity post-fumigation handlers) assuming on-site air levels did not exceed 5 ppm.

Table 26. Margins of exposure (MOEs) for structural and non-food commodity fumigation workers.^a

Work Task	Acute MOE	1-2 weeks MOE	Subchronic MOE	Chronic MOE
Structural Fumigation at Submaximal Rate				
<i>Fumigators</i>				
Introducing fumigant	1800	240	220	120
Opening structure	>10,000	>10,000	>10,000	>10,000
Closing	>10,000	>10,000	>10,000	>10,000
Testing for clearance	6279	837	244	157
Total activities	1421	189	110	67
Fumigator +tent crew	46	6	7	5
<i>Tent Crew</i>				
Ground seam opening	180	24	44	29
Roof seam opening	174	23	31	20
Ground snake removal	1350	180	168	111
Tarpaulin folding	900	120	140	94
General detarping	48	6	8	5
Structural Fumigation at Maximal Rate				
<i>Fumigators</i>				
Introducing fumigant	129	17	13	8
Opening structure	>10,000	3600	4400	3600
Closing structure	>10,000	>10,000	>10,000	>10,000
Testing for clearance	6000	800	256	157
Total activities	126	17	13	8
Fumigator +tent crew	3	0.4	1	0.3
<i>Tent Crew</i>				
Ground seam opening	12	2	3	2
Roof seam opening	12	2	2	1
Ground snake removal	92	12	12	8
Tarpaulin folding	68	9	10	6
General detarping	3	0.4	1	0.3
Non-food Commodity Fumigation				
Handlers	126	NA	NA	NA

^{a/} Based on exposure values in Table 19 and applicable NOELs in Table 25. NA=not applicable since exposures were not estimated for these scenarios.

Table 27. Margins of exposure (MOEs) for residents following clearance of fumigated homes.^a

Resident (Age in years)	Acute 24-hour MOE
<1	95
1-2	110
3-5	129
6-8	169
9-11	186
12-14	235
15-18	270
Adult	225

^{a/} Based on exposure values in Table 20 and applicable NOEL in Table 25.

Table 28. Margins of exposure (MOEs) for bystanders at a structural fumigation site during the application phase.^a

Bystander (Age in years)	Acute 12-hour MOE	Acute 24-hour MOE
Structural Fumigation at Submaximal Rate		
<1	150	108
1-2	174	126
3-5	193	138
6-8	235	164
9-11	245	169
12-14	318	235
15-18	386	270
Adult	318	225
Structural Fumigation at Maximal Rate		
<1	15	11
1-2	17	13
3-5	19	14
6-8	23	16
9-11	25	17
12-14	32	23
15-18	39	27
Adult	32	23

^{a/} Based on exposure values in Table 21 and applicable NOEL in Table 25.

Table 29. Margins of exposure (MOEs) for bystanders at a structural fumigation site during the aeration phase using TRAP and Stack aeration methods.^a

Bystander (Age in years)	TRAP aeration	Stack aeration	
	Acute 2-hour MOE	Acute 1-hour MOE	Acute 4-hour MOE
Structural Fumigation at Submaximal Rate			
<1	60	386	360
1-2	69	450	415
3-5	77	491	450
6-8	93	600	540
9-11	96	600	600
12-14	132	900	771
15-18	150	1080	900
Adult	126	771	771
Structural Fumigation at Maximal Rate			
<1	4	39	36
1-2	5	45	42
3-5	5	49	45
6-8	6	60	54
9-11	7	60	60
12-14	9	90	77
15-18	10	108	90
Adult	9	77	77

^{a/} Based on exposure values in Tables 22 and 23 and applicable NOEL in Table 25.

Table 30. Margins of exposure (MOEs) for bystanders at or near a non-food commodity fumigation site.^a

Bystander (Age in years)	Acute 24-hour MOE
<1	23
1-2	28
3-5	30
6-8	36
9-11	39
12-14	54
15-18	60
Adult	49

^{a/} Based on exposure values in Table 24 and applicable NOEL in Table 25.

Table 31. Comparison of infant bystander exposures with the acute reference concentration.

Scenario	Air level ^a	Hours exposed ^a	Air level as 24-hour time-weighted average	% RfC ^b	MOE ^c
Structural Fumigation at Submaximal Rate					
Application phase					
First 12-hours	1.6 ppm	12	0.8 ppm	667%	150
24 hours	1.12 ppm	24	1.12 ppm	933%	108
Aeration phase					
TRAP method					
2 hours	24 ppm	2	2 ppm	1,667%	60
Aeration phase					
Stack method					
1 hour	7.33 ppm	1	0.31 ppm	255%	386
4 hours	1.97 ppm	4	0.33 ppm	274%	360
Non-food Commodity Fumigation					
24 hours	5 ppm	24	5 ppm	4,167%	24

^{a/} Based on information in Tables 14a, 15a, 16a, and 17 in **Volume II**.

^{b/} The reference concentration for infants was 0.12 ppm (Table 18).

^{c/} The MOEs were those shown in Tables 28-30.

IV.D. COMPARISON WITH U.S. ENVIRONMENTAL PROTECTION AGENCY RISK ASSESSMENT

The risk assessment conducted in this RCD was compared with the U.S. EPA risk assessment for ProFume→ (U.S. EPA, 2004 b and c) and Reregistration Eligibility Document for Vikane→ (U.S. EPA, 1993b).

IV.D.1. Hazard Identification and Reference Concentrations

The endpoints and NOELs selected by DPR were compared with those used by U.S. EPA in the establishment of food tolerances which represented the U.S. EPA most current values (U.S. EPA 2004 a, b, and c) as shown on Table 32. There were several differences:

1. DPR determined an acute inhalation NOEL from a 2-day study. While the NOEL was based on more than one day of exposure, DPR considered it appropriate to use since there are exposure scenarios where humans are exposed to sulfuryl fluoride on consecutive days at similar air concentrations, and the NOEL was comparable to those from single day exposures of a few hours. On the other hand, the U.S. EPA determined that there was no need to address inhalation risk from a single exposure because there was no toxicity endpoint from a single exposure.
2. While both U.S. EPA and DPR selected the same studies and same NOELs (in terms of ppm) to address repeated exposures of less than 1 year, the NOELs as mg/kg/day were different due to different default inhalation rates used for rabbits. The DPR and U.S. EPA inhalation rates for rabbits were 0.54 m³/kg/day and 0.38 m³/kg/day¹⁸, respectively.
3. For chronic inhalation exposure, DPR selected the NOEL of 4 mg/kg/day from a 2-generation toxicity study with lung pathology as the endpoint. DPR considered this endpoint appropriate since similar effects were observed in other inhalation toxicity studies. In comparison, the U.S. EPA used a NOAEL (8.5 mg/kg/day) for brain lesions from a subchronic toxicity study and applied a 3-fold uncertainty factor (estimated chronic NOEL of 2.8 mg/kg/day) to derive the chronic reference dose and chronic reference concentration for dietary and inhalation exposures, respectively. The rationale was that the effect on the lung (U.S. EPA calculated NOAEL of 3.6 mg/kg/day) from the inhalation exposure was not appropriate to address dietary exposure. While DPR agreed with this rationale for dietary exposure, DPR considered the lung effect an appropriate endpoint to address chronic inhalation exposure.

¹⁸ This value was back-extrapolated from the U.S. EPA calculation assuming the following equation was used to convert the NOAEL of 30 ppm to 8.5 mg/kg/day. The rabbit inhalation rate (IR) was 0.38 m³/kg/day and is consistent with the allometric equation for rabbits inhalation rate (I) in m³/day=0.46 Body weight^{0.8307} and body weight of 3 kg (U.S. EPA, 1988).

$$30 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 / \text{ppm} \times \text{IR}_{\text{rabbit}} \text{ m}^3 / \text{kg} / \text{day} \times \frac{5 \text{ days}}{7 \text{ days}} \times \frac{6 \text{ hours}}{24 \text{ hours}} = 8.5 \text{ mg} / \text{kg} / \text{day}$$

It should be noted that the U.S. EPA no longer uses the above equation and the current rabbit mean inhalation rates are 0.55 m³/kg/day and 0.52 m³/kg/day for males and females, respectively, based on values provided in the 1994 document for reference concentration (U.S. EPA, 1994).

IV.D.2. Exposure Assessment

The exposure assessments conducted by U.S. EPA (U.S. EPA, 1993b and 2004c) and DPR showed differences in exposure estimates mainly due to different approaches/assumptions used in the absence of adequate exposure data. Also, DPR based its estimates on use scenarios in California while the U.S. EPA considered exposures at a national level. The following are some of the differences:

1. For structural fumigation, the U.S. EPA estimated worker exposures to Vikane→ were stated as 0.08 ppm for fumigator and 0.17 ppm for tent workers. In comparison, DPR calculated exposures for individual and combined activities for fumigators and tent workers with a wide range of exposure levels (**Volume II**).
2. For structural fumigation, the U.S. EPA stated that risks to residents returning to fumigated homes were negligible (U.S. EPA, 2004c). In comparison, DPR calculated exposures for residents upon reentry as well as bystander exposures during application and aeration phases. Some of these exposures were significant and lead to MOEs of less than 100 (Tables 27 to 29).
3. For non-food commodity fumigation with Vikane→, the U.S. EPA did not estimate exposures for handlers or bystanders. DPR used the limit of 5 ppm to estimate the exposures for these groups.

IV.D.3. Risk Characterization

A comparison of margins of exposures showed significant differences between DPR and the U.S. EPA (Table 33). These differences were primarily the result of differences in the exposure estimates. It should be noted that U.S. EPA applied the dietary reference concentration in the dietary risk assessment for the food-use label (ProFume→) for all age groups. The residential reference concentrations were, however, not used in the U.S. EPA risk assessments since residential and bystander inhalation exposures for the use of Vikane→ were not estimated.

Table 32. Comparison of critical no-observed-effect levels (NOELs) and endpoints for risk characterization between the Department of Pesticide Regulation and U.S. Environmental Protection Agency.^a

DPR		U.S. EPA	
Duration	NOEL and endpoint	Duration	NOEL and endpoint
Acute (1 day)	2-day rat: no FOB effect (Albee <i>et al.</i> , 1993a) NOEL= 300 ppm (300 mg/kg/day) Occupational RfC=3 mg/kg/day (UF=100) Residential/Bystander =0.3 mg/kg/day (UF=1000)	Acute (1 day)	No toxicity endpoint for single exposure
Short- term (1 to 7 days)	2-week rabbit: brain lesions (Eisenbrandt <i>et al.</i> , 1985) NOEL= 100 ppm (40 mg/kg/day) Occupational RfC=0.4 mg/kg/day (UF=100) Residential/Bystander RfC=0.04 mg/kg/day (UF=1000)	Short-term 1-30 days	2-week rabbit: brain lesions (Eisenbrandt <i>et al.</i> , 1985) NOAEL = 100 ppm (30 mg/kg/day) Occupational RfC=0.30 mg/kg/day (UF=100) Residential RfC= 0.03 mg/kg/day (UF=1000)
Inter- mediate (7 days to 1 year)	90-day rabbit: brain vacuoles (Nitschke <i>et al.</i> , 1987b) NOEL=30 ppm (12 mg/kg/day) Occupational RfC=0.12 mg/kg/day (UF=100) Residential/Bystander RfC=0.012 mg/kg/day (UF=1000)	Inter- mediate term (1-6 months)	90-day rabbit: brain vacuoles (Nitschke <i>et al.</i> , 1987b) NOAEL=30 ppm (8.5 mg/kg/day) Occupational RfC=0.085 mg/kg/day (UF=100) Residential RfC=0.0085 mg/kg/day (UF=1000)
Annual (>49 weeks/ year)	2-generation rat: lung pathology (Breslin <i>et al.</i> , 1992) NOEL=5 ppm (4 mg/kg/day) Occupational RfC=0.04 mg/kg/day (UF=100) Residential/Bystander RfC=0.004 mg/kg/day (UF=1000)	Long-term (>6 months)	90-day rabbit: brain vacuoles (Nitschke <i>et al.</i> , 1987b) NOAEL=30 ppm (8.5 mg/kg/day) Occupational RfC=0.028 mg/kg/day (UF=300) Residential RfC=0.0028 mg/kg/day (UF=3000)

^{a/} When the NOEL in terms of ppm is the same for both DPR and U.S. EPA, differences in the dosages were due to differences in the default inhalation rates for the laboratory animals used. The DPR default inhalation rates for rats and rabbits are 0.96 m³/kg/day and 0.54 m³/kg/day, respectively. The U.S. EPA default inhalation rate for rabbit was 0.38 m³/kg/day (see footnote 16). For the reference concentrations (RfC), the uncertainty factors (UF) were 100 (10x each for intraspecies and interspecies extrapolation), 300 (10x each for intraspecies and interspecies extrapolation, 3x for subchronic to chronic NOAEL extrapolation), 1000 (10X each for intraspecies and interspecies extrapolation, and 10x for developmental neurotoxicity study data gap), and 3000 (10X each for intraspecies and interspecies extrapolation, 3x for subchronic to chronic NOAEL extrapolation, and 10x for developmental neurotoxicity study data gap). These NOELs were not corrected for absorption. FOB=functional observation battery. Equations for reference concentration calculations are in **Appendix E**.

Table 33. Comparison of margins of exposure (MOEs) from the Department of Pesticide Regulation and U.S. Environmental Protection Agency.

Uses	DPR MOEs ^a		U.S. EPA MOEs ^b
Structural fumigation			
Fumigator ^c	<u>Submaximal rate:</u> Acute: 46 to >10,000 1-2 week: 6 to >10,000 Intermediate: 7 to >10,000 Annual: 5 to >10,000	<u>Maximal rate:</u> Acute: 3 to >10,000 1-2 week: 0.4 to >10,000 Intermediate: 1 to >10,000 Annual: 0.8 to >10,000	Short-term: 440 Intermediate and long term: 130
Tent Crew	<u>Submaximal rate:</u> Acute: 48 to 1350 1-2 week: 6 to 178 Intermediate: 8 to 168 Annual: 5 to 111	<u>Maximal rate:</u> Acute: 3 to 92 1-2 week: 0.4 to 12 Intermediate: 1 to 12 Annual: 0.3 to 8	Short-term: 210 Intermediate and long term: 60
Resident-reentry	Acute: 95 to 270		Risk stated as negligible, MOE not given in risk assessment
Bystander-application	<u>Submaximal rate:</u> Acute 12 hours: 150 to 386	<u>Maximal rate:</u> Acute 12 hours: 15 to 38	Not assessed
Bystander-aeration	<u>TRAP aeration</u> <u>Submaximal rate:</u> Acute 1 hour: 60 to 150 <u>Stack aeration</u> <u>Submaximal rate:</u> Acute 1 hour: 386 to 1080 Acute 4 hours: 360 to 900	<u>TRAP aeration</u> <u>Maximal rate:</u> Acute 1 hour: 4 to 10 <u>Stack aeration</u> <u>Maximal rate:</u> Acute 1 hour: 39 to 108 Acute 4 hours: 36 to 90	Not assessed
Non-food Commodity fumigation			
Handlers	Acute: 126		Not assessed
Bystander	Acute: 23 to 60		Not assessed

^{a/} MOEs from Tables 26 to 30.

^{b/} U.S. EPA, 1993b and 2004c.

^{c/} Including the scenario where the fumigator doing both fumigation and tent crew activities.

V. RISK APPRAISAL

V.A. INTRODUCTION

The human health risk assessment of sulfuryl fluoride was conducted for occupational, residential, and bystander exposures. Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that adverse effects of a substance will occur under specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. The degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment of sulfuryl fluoride are delineated in the following discussion.

V.B. HAZARD IDENTIFICATION

The uncertainties associated with the selection of the endpoints and the NOELs have already been discussed under **IV.A. HAZARD IDENTIFICATION**. The critical and most sensitive endpoint for acute, 1-2 weeks of exposure, and subchronic exposures was neurotoxicity. This endpoint, in particular vacuolation in brain tissues, is also of concern by the U.S. EPA (U.S. EPA, 2004b and c). The critical endpoint for chronic exposure was lung effects (pathology, alveolar macrophage aggregates) in the rat (Breslin *et al.*, 1992). DPR considered these chronic effects relevant since they were the result of inhalation exposure, treatment related, and also observed in the dog (Table 14). The NOEL for this endpoint is lower than that for brain lesions in the chronic toxicity studies.

In addition to the toxicological endpoints identified, the potential of sulfuryl fluoride to cause developmental neurotoxicity had not been studied. This potential stemmed from the observation of vacuolation in the adult brain tissue of several species after inhalation exposure to sulfuryl fluoride. Since the U.S. EPA waived the developmental neurotoxicity study requirement (Dellarco and Baetcke, 2004), it was not known if the NOEL for this endpoint would be higher or lower than those for neurotoxicity in the adult. In the absence of such a study, the concern would be addressed using an additional uncertainty factor (see discussion in **V.E.1. Pre- and Post-natal Sensitivity**). In addition, studies on the mechanism of action, effects of short exposure durations, toxicity of metabolites especially with regard to fluoride contribution to non-dental endpoints, and potential additional toxicity with chloropicrin would be helpful for further hazard identification of sulfuryl fluoride.

With regard to specific critical NOELs used to calculate the MOEs, there was some uncertainty on the magnitude of the acute NOEL. This NOEL was selected from a 2-day (6 hours/day) study (Albee *et al.*, 1993 a and b) specifically designed to evaluate the neurotoxicity of sulfuryl fluoride after two-days of exposure. At the highest dose (300 ppm) tested, there were no treatment-related effects observed. There were two related issues in the use of this NOEL for

acute exposure: derivation of a one-day NOEL, and application of this NOEL for the MOE calculation. The Albee *et al.* study (1993) was the only study of sufficient quality to be considered for the derivation of a critical acute NOEL. DPR recognizes that this NOEL was for a two-day study but consideration of other studies supported this NOEL as a single day NOEL. The DPR calculated the NOEL as a daily dosage (300 mg/kg/day) is shown in the following equation:

$$300 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 / \text{ppm} \times 0.96 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hours}}{24 \text{ hours}} = 300 \text{ mg} / \text{kg} / \text{day}$$

In comparison, the registrant used the same NOEL (300 ppm) and asserted that the daily dosage should be 567 mg/kg/day (Dow AgroSciences, 2004a). This calculation assumed that the two 6-hour separate exposure periods was equivalent to a single 12-hour exposure in 30 hours based on a certain dose-time assumption between these two durations of exposure. This 30-hour duration was then used to calculate the equivalent NOEL for a 24-hour time-weighted-average NOEL as shown by the following equation:

$$300 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 / \text{ppm} \times 1.13 \text{ m}^3 / \text{kg} / \text{day} \times \frac{0.5 \text{ days}}{1.25 \text{ days}} = 567 \text{ mg} / \text{kg} / \text{day}$$

This approach used by the registrant resulted in a 24-hour NOEL (567 mg/kg/day) that is 1.9-fold higher than that (300 mg/kg/day) calculated by DPR. When compared to single dose studies, the registrant calculated NOEL might be too high (Table 4). An acute toxicity study in rats reported lethargy after 4-hour exposure to 750 ppm (500 mg/kg/day) (Miller *et al.*, 1980). Morbidity and death between 2nd and 6th dose were observed in rats exposed to 600 ppm (600 mg/kg/day) (Eisenbrandt *et al.*, 1985). Therefore, DPR considered 300 mg/kg/day as a reasonable NOEL to address acute exposure scenarios, given the limitations in the toxicology database.

The application of this acute NOEL based on continuous 6-hours exposure to fewer hours or scenarios of declining air concentration resulted in uncertainty to the risk estimates (further discussion is in **V.D. RISK CHARACTERIZATION**). This uncertainty was minimized to a limited extent by addressing peak exposure periods as well as the entire measured dissipation period. Additional toxicology studies were needed to determine the toxicity of few hours to 1-day exposure scenarios.

For repeated exposures, the NOELs were amortized to account for more than 5 days per week exposure since the label did not specifically limit the exposure to 5 days per week or number of weeks. In addition, amortization was a means to reflect a lower potential NOEL due to repeated weekly exposures. In practice, workers are more likely to be exposed for several consecutive weeks during the year. While the use of the 2-week NOEL may overestimate the risk for 1-week only exposures, it actually underestimated the risk for repeated weekly exposures, up to 13 weeks. For 13 weeks of exposure, the MOE was calculated using a subchronic NOEL of 12 mg/kg/day (3.5-fold lower than the 2-week NOEL).

While the hazard identification discussed only the toxicity of sulfuryl fluoride, humans

are exposed to chloropicrin at the same time. There were no toxicity studies conducted with these compounds administered as mixtures. It was not known whether exposure to chloropicrin, an irritant, would result in enhanced sulfuryl fluoride toxicity, in particular pulmonary toxicity. DPR placed all products containing chloropicrin into reevaluation in 2001. Under the reevaluation, chloropicrin registrants are required to submit worker exposure studies and ambient air quality monitoring studies. DPR also requested that the Air Resources Board conduct monitoring of an application site in 2004. A risk characterization document for chloropicrin is being prepared.

V.C. EXPOSURE ASSESSMENT

There were uncertainties associated with the estimated exposures since the database was limited and protective factors were used to compensate for the data uncertainties (more detailed discussion is in **Volume II**). In order to refine the exposure estimates, additional studies should include: use of maximal application rate for structural fumigation, non-food commodity fumigation, longer (7 days) monitoring period and multiple sites in fumigated homes. For all these studies, sufficient number of replicates should be collected and all parts of the collected samples should be analyzed.

V.C.1. Occupational Exposures

For workers of structural fumigation, there were sources of under- and over-estimation of exposures. The actual exposures could be higher if residues from the back section of charcoal tubes used to monitor exposure were included, or if there was improper use of Self-Contained Breathing Apparatus (SCBA). The worker exposures could be lower if the application rate was lower than those assumed for submaximal or maximal rates in the exposure assessment.

For handlers in non-food commodity fumigation, the exposure was assumed at no higher than 5 ppm (an 8-hour time-weighted average, maximum allowed by the label) and only once per year. This exposure could be higher if food uses for sulfuryl fluoride are approved in California.

V.C.2. Residential and Bystander Exposures

For residents reentering the fumigated homes, the exposures could be underestimates due to lack of continuous monitoring of air concentration, slower dissipation of sulfuryl fluoride than assumed, longer indoor residence time than assumed, and more than one application per year to the home. At the same time, the latter three sources could result in the overestimation of risk under the conditions of more rapid gas dissipation, shorter indoor residence time, and less frequent than one application per year. Another source of overestimation was the assumption that reentry occurred according to label (6 or 8 hours) rather than typical practice of 1 day when the air concentration is lower. The bystander exposure during aeration of structural fumigation could be overestimated because it was based on the level for fumigation workers doing general detarpering activities.

For bystanders near a non-food commodity fumigation facility, the exposure was assumed to be no higher than 5 ppm in a 24-hour period and only 1 day per year. This exposure could be higher if the use was more frequent, especially when food uses are approved in California. On the other hand, the exposure could be lower with shorter time spent outdoors.

V.D. RISK CHARACTERIZATION

Uncertainties in the risk estimates were the result of limitations in the pharmacokinetic and toxicology study designs to address specific exposure scenarios, and inadequate exposure data to derive the actual human exposure. To be health protective, conservative assumptions were made in the application of the NOELs and in the exposure estimates. The sources of over- and under-estimation of the risks already discussed are summarized in Table 34. Until additional data are available, the margins of exposure calculated and comparisons with reference concentrations in this RCD should be considered reasonable for use in risk management.

In this RCD, the human absorbed dose after inhalation exposure was calculated using an absorption factor of 18%, based on a pharmacokinetic study in rats since there is no such data available for humans. The default assumption was that the absorption of sulfuryl fluoride in humans after inhalation exposure is similar to that for rats. There is certainly some degree of uncertainty associated with this approach. Physiologically-based-pharmacokinetic (PBPK) modeling studies showed that the parameters important for interspecies extrapolation included chemical-specific characteristics (*i.e.*, structure and solubility) and species-dependent biological characteristics (*i.e.*, animal ventilation rate, tissue blood flow, metabolic activity, and elimination processes) (Beliveau *et al.*, 2003 and 2005; Gerde and Scott, 2001).

The potential influence of two parameters (solubility and inhalation frequency) was examined to show the complexity involved in estimating the human absorbed dose for sulfuryl fluoride from laboratory animal data. The higher rat inhalation frequency (80-100 breathes/minute), compared to those for humans (10-12 breathes/minute), suggests that more residential time in the alveolar space for the transfer of sulfuryl fluoride from the air to the blood, and therefore, a higher absorbed dose may be expected for humans. However, the extent of the uptake of sulfuryl fluoride from the air to the blood could be limited by the relative chemical solubility between these two compartments. In an *in vitro* system, Gargas *et al.* (1989) showed more than 100-fold difference in the blood: air partition coefficients for 36 low-molecular weight volatile compounds¹⁹. The range of human blood: air partition coefficient was 1.16 (vinyl chloride) to 187 (1-nitropropane). The range of rat blood: air partition coefficient was 1.39 (cyclohexane) to 223 (1-nitropropane). These coefficients did not correlate with the magnitude

¹⁹ Methanes: methyl chloride, dichloromethane, chloroform, carbon tetrachloride, and chlorodibromomethane.
 Ethanes: chloroethane, dichloroethanes (2), trichloroethanes (2), tetrachloroethanes (2), hexachloroethane, and 1-bromo-2-chloroethane.
 Propanes: chloropropanes (2); 1,2-dichloropropane; n-propyl bromide; isopropyl bromide; and nitropropanes (2).
 Aliphatics: n-heptane; cyclohexane; 2,2,4-trimethylpentane; and JP-10.
 Ethylenes: vinyl chloride; cis- and trans-1,2-dichloroethylene; trichloroethylene, tetrachloroethylene; and vinyl bromide.
 Aromatics: benzene, chlorobenzene, and xylenes (3).
 Number in parenthesis indicates number of chemicals with the same structural formula.

of their octanol: water partition coefficients ($\log K_{ow}$) (Basak *et al.*, 2003). For example, the range of $\log K_{ow}$ for the methanes and ethanes tested in this study was 0.91 (methyl chloride) to 4.24 (hexachloroethane), while the range of human blood: air partition coefficients for these chemicals ranged from 2.48 (methyl chloride) to 116 (1,1,2,2-tetrachloroethane). A blood: air partition coefficient for sulfuryl fluoride in the rat or human has not been determined.

Furthermore, comparison of coefficients between rats and humans in the Gargas *et al.* study (1989) showed most compounds (32/36) showed 1.5 to 2-fold higher coefficients in rats (male F-344) than those for humans. The remaining four chemicals (methyl chloride; cyclohexane; 2,2,4-trimethylpentane; p-xylene) showed similar rat and human blood: air partition coefficients. These findings suggested that the chemical level in the rat blood may be the same or higher than those for human, contrary to that expected by considering inhalation frequency alone.

Given that many factors are involved in the determination of the absorbed dose, and the uncertainty associated with the use of only rat pharmacokinetic and toxicity data to estimate the human absorbed dose, DPR applied a default interspecies uncertainty factor of 10 for both pharmacokinetic and pharmacodynamic factors to the reference concentration and margin of exposure benchmark for sulfuryl fluoride. The use of this factor effectively sets the human exposure limit lower than a level based on the rat data alone.

V.D.1. Margins of Exposure

For risk assessment under SB 950, the exposures were evaluated using the benchmark MOEs of 100 and 1000 for occupation, and bystander/residential exposures, respectively (**IV.C. RISK CHARACTERIZATION**). For sulfuryl fluoride, the 10-fold interspecies factor was considered appropriate, since the sensitivity of humans and laboratory animals to sulfuryl fluoride toxicity could not be compared due to the lack of adequate data on humans. For intraspecies variation in the response to the toxicity of sulfuryl fluoride, many factors can potentially contribute to the variation. Among these are age, gender, genetic disposition, health and nutritional statuses, and environmental factors. However, there were insufficient data to quantify these variations as greater than the default factor of 10-fold. Similarly, the concern for developmental neurotoxicity was addressed with a default uncertainty factor of 10-fold. These three 10-fold factors should be assumed adequate until additional data become available.

There was a wide range of MOEs for workers depending on work activities (Table 26). The MOEs for opening and closing structures were greater than 10,000, while they were less than 100 for some fumigator and tent crew activities (Table 26). For these scenarios, it is unlikely that more comprehensive acute toxicity studies of less than 6 hours would significantly increase the MOE to meet the benchmark level. Current data from acute LC_{50} -type studies showed NOELs in the same range as the critical NOEL based on 6 hours of exposure (Table 4). On the other hand, the MOEs could be increased or decreased with additional exposure data.

Table 34. Sources of over- and under-estimation of risks for sulfuryl fluoride inhalation exposure.

Scenarios	Exposure	NOEL ^a	Risk is overestimated if:	Risk is underestimated if:
Fumigator workers and tent crew	Acute 0.17 to 3.73 hrs	6 hours	NOEL is higher for < 6 hrs exposure. Less than sub or maximal application rates were used.	Exposure is higher by including back sections of monitoring tubes and improper use of SCBA.
	Short-term 1 to 7 days	2 weeks	Exposure is less than sub or maximal rates, and is for shorter duration than the NOEL.	NOEL is lower for longer than NOEL duration. Exposure is higher due to back sections and SCBA concerns.
	Intermediate 7 day to < 1 m	13 weeks		
	Chronic 1 year	2 years		
Residential reentry	Acute <u>SF level:</u> declining over 2 days <u>Duration:</u> 24 hours	6 hours	NOEL is higher when there is continuous SF decline. Exposure is lower from more rapid dissipation, shorter indoor time, longer reentry time, and fewer fumigation.	Exposure is higher due to slower dissipation, longer residence time, and more than once a year fumigation.
Bystander during application	Acute <u>SF level:</u> Constant on 1 st 12 hours, loss on 15 th hour <u>Duration:</u> 24 hours/day	6 hours	NOEL is higher for the second 12-hours with continuous decline. Exposure is lower due to fewer hours outdoor.	NOEL is lower for 12-hours of exposure.
Bystander during TRAP method aeration	Acute <u>SF level:</u> Peak in 2 hours <u>Duration:</u> 2 hours	6 hours	NOEL is higher for 2 hours of exposure. Exposure is lower than assumed in detarping activities	
Bystander during Stack method aeration	Acute <u>SF level:</u> Peak 1 hour, then decline, <u>Duration:</u> 4 hours	6 hours	NOEL is higher for 1 or 4 hours of exposure. Exposure is lower than assumed in general detarping activities	
Non-food commodity fumigation-Handlers	Acute <u>SF level:</u> 5 ppm <u>Duration:</u> 8 hours in 1day	6 hours	Exposure is lower if actual is lower than 5 ppm maximum allowed on the label	NOEL is lower for > 6 hours. Exposure is higher for more than once a year use.
Non-food commodity fumigation-Bystander	Acute <u>SF level:</u> 5 ppm <u>Duration:</u> 24 hours	6 hours	NOEL is higher with continuous decline in SF. Exposure is lower, and fewer hours outdoor per day.	NOEL is lower for > 6 hours. Exposure is higher for more than once a year use.

^{a/} The duration of the toxicology studies. SF=sulfuryl fluoride.

For adult residential exposures to structural fumigation (reentry, application, and aeration) at submaximal application rate, the acute MOEs for peak sulfuryl fluoride concentrations were generally greater than 100 (Tables 27 to 29). However, the MOEs for young children were about 100, much lower than the benchmark of 1000. A higher MOE might be achieved if the NOEL was based on studies conducted with declining sulfuryl fluoride concentration, although it would unlikely to be 10-fold higher than the current acute NOEL. The exposure estimates for bystanders could be refined with monitoring data to address the assumptions used, such as 24 hours of indoor and outdoor exposure, and exposure at air levels experienced by workers doing detarping activities. In addition, the Stack aeration method with lower bystander exposures, instead of TRAP aeration, might be considered for California. As shown in Table 29, there was about a 7-fold difference in the MOEs between these two methods. For bystanders to non-food commodity fumigation, the MOEs were all less than 100 (Table 30). These were based on the assumption of 24 hours of continuous exposures at 5 ppm. These MOEs would likely to be changed with actual monitoring data for indoor and outdoor air levels of sulfuryl fluoride.

V.D.2. Reference Concentrations

Since the bystander exposures showed MOEs of less than 10,000 (Tables 28-30), they exceeded the limit of no more than 1/10 of the reference concentrations (Table 18). Sulfuryl fluoride would, therefore, meet the listing criteria established by DPR.

V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

V.E.1. Pre- and Post-natal Sensitivity

In this RCD, the potential of higher risks for children, compared to adults, was accounted for in part by using estimated exposures by age groups, and by using the higher infant's inhalation rate to calculate the reference concentrations for residents and bystanders. With respect to the toxicology of sulfuryl fluoride, there was no evidence for potentially increased sensitivity by infants and children to the prenatal and post-natal toxicity (excluding developmental neurotoxicity, see discussion in the next paragraph) of sulfuryl fluoride based on the comparison of NOELs for effects observed in the adult and the young. The developmental (**III.G.**) and reproductive (**III.F.**) toxicity studies showed decreased fetal or pup body weight in some studies with NOELs higher than those for maternal effects. For example, the reproductive NOEL was 20 ppm for decreased pup weight while the maternal NOEL was 5 ppm for lung lesions (Breslin *et al.*, 1992). No teratogenic effects were observed in the developmental toxicity studies (Hanley *et al.*, 1980, 1981, and 1989). U.S. EPA concluded that a FQPA factor for this concern was not necessary (U.S. EPA, 2004c).

There was a concern for potential developmental neurotoxicity in humans exposed to sulfuryl fluoride, which caused vacuoles in the adult brain after repeated exposures in multiple species of laboratory animals (Table 16). This concern was consistent with the U.S. EPA weight of evidence for developmental neurotoxicity study considerations, which included: neuropathology, endocrine disruption, behavioral/functional effects, structure-activity-relationship, and neurotoxic potency (Makris, 1998). The consequence of this vacuolation lesion

in the adult was unclear. In majority of the studies, the presence of brain vacuoles occurred without clinical signs (Table 16). In the 2-week mouse study, functional observational battery tests showed no treatment-related effect in the presence of vacuolation in the brain. It was unknown if the same lesion would occur from *in utero* or milk exposure because fetal and pup brains were not examined histologically in the developmental toxicity studies and 2-generation reproductive toxicity study. In the reproductive toxicity study, a comparison of reproductive effects between the F0 and F1 generation did not show any additional reproductive toxicity in the F1 generation, which was exposed to sulfuryl fluoride from *in utero* to adulthood.

Results from a developmental neurotoxicity study would provide important information regarding potential effects in the young that were not examined in these developmental and reproductive toxicity studies (U.S. EPA, 1998 and 1999c). However, such a study will not be conducted because the U.S. EPA waived the data requirement in their evaluation of the registrant's petition to add food uses (Dellarco and Baetcke, 2004). The main justification of the waiver was that both chronic dietary exposure and residential inhalation exposures were expected to be relatively low. At the same time, the U.S. EPA indicated that they remained concerned about this effect and retained the 10-fold FQPA database uncertainty factor in the calculation of reference concentrations for chronic dietary and residential exposures. Therefore, an additional 10-fold factor was included in the reference concentration calculation, and margins of exposure considerations. While DPR preferred to have experimental data to address this concern, this approach expedites the completion of the risk assessment for this compound (Gee, 2004; **Appendix F**). The use of this 10-fold default factor resulted in uncertainty of the risk estimate, which might be an over- or under-estimation of the actual risk.

V.E.2. Aggregate Exposure

In this RCD, only inhalation exposure was addressed since Vikane→ is not used directly on food. When ProFume→ is allowed to be used in California, there could be aggregate exposures of sulfuryl fluoride and fluoride from inhalation and dietary exposures. This will be addressed in the dietary risk assessment document for this product. Based on the dietary exposure estimated by the U.S. EPA, inhalation exposure would likely be a major component of the aggregate exposure to sulfuryl fluoride. Sulfuryl fluoride levels estimated in this document (Tables 19 to 24) for inhalation exposure were much higher (in mg/kg/day to µg/kg/day range) than those for dietary chronic exposure (1 ng/kg/day to 4 ng/kg/day) associated with the use of ProFume→ (U.S. EPA, 2004a).

For aggregate exposure to fluoride, the dietary exposure would be a major contributor because of fluoride in the drinking water. As discussed in **IV.A.4. Critical NOELs and Reference Concentrations**, Using the average fluoridation level of 1 ppm in the drinking water, the average exposures to fluoride are 0.1 mg/kg/day and 0.03 mg/kg/day for a 10-kg child and 70-kg adult drinking 1 liter and 2 liters of water/day, respectively. Human exposures at the chronic reference concentrations for sulfuryl fluoride would result in fluoride exposures of 0.4% and 10% of the average drinking water levels, respectively, for infants and adults.

V.E.3. Cumulative Toxicity

There is a potential for cumulative toxicity of fluoride from various sources. In the ProFume→ evaluation, U.S. EPA was concerned only with dietary exposure from commodities treated with sulfuryl fluoride and cryolite²⁰ use, fluoridated water, and background fluoride levels in food (U.S. EPA, 2004a). For the various population subgroups, 67% to 93% of total fluoride exposures were from water.

For this evaluation of Vikane→, cumulative exposure of fluoride from multiple sources and exposure routes under three scenarios were estimated (Table 35). In all cases, fluoride levels in the drinking water and in the diet from sulfuryl fluoride, cryolite, and food in general were maintained at the same levels. The first scenario could be considered the worst case scenario with the exposure based on high fluoride levels in brewed tea (4.7 ppm) from the U.S. Department of Agriculture (USDA) survey (USDA, 2004), and for the highest sulfuryl fluoride exposed worker (2.1 mg sulfuryl fluoride/kg/day or 0.78 mg fluoride/kg/day for tent crew at the maximum application rate, Table 19). The total exposure would be 0.85 mg fluoride/kg/day with occupational exposure as the primarily contributor to the total. This level is clearly much higher than existing reference concentrations for fluoride (Table B3 in **Appendix B**).

The second scenario is based on average fluoride residue values for tea, and submaximal application rate exposure for the tent crew. The total exposure in this case would be 0.11 mg fluoride/kg/day, much lower than Scenario 1, and probably reflects current exposures. This level also exceeds existing reference concentrations for fluoride.

Scenario three showed much lower total fluoride exposure when the exposure limit for the tent crew was based on the reference concentration calculated in this document. The chronic reference concentration for sulfuryl fluoride was 0.18 mg/m³, or a fluoride level of 0.003 mg/kg/day²¹. The total fluoride exposure would be 0.062 mg/kg/day with 0.028 mg/kg/day from the drinking water, as the main source, and the worker exposure contributing 0.5% to the total fluoride level.

V.E.4. Endocrine Effects

The current database did not show sulfuryl fluoride to cause endocrine disruption effects. However, hypertrophy and decreased in colloid in the thyroid gland were noted in the mouse after repeated exposures (Nitschke and Quast, 1993; Quast *et al.*, 1993b). Additional research is needed in this area.

²⁰ Cryolite (sodium fluoroaluminate, Na₃AlF₆) is an insecticide used to control leaf-eating insects on fruits, vegetables, and ornamentals. It is primarily used on grapes, potatoes, and citrus. It is also a naturally-occurring chemical.

²¹ Absorbed fluoride level in adults= mg sulfuryl fluoride/m³ x 38/102 x absorption factor x human inhalation rate. The absorption factor was 18% based on a pharmacokinetic study in rats (Mendrala *et al.*, 2002). The adult inhalation rate was 0.28 m³/kg/day.

Table 35. Estimated fluoride levels in adults after chronic exposure to multiple sources.

Fluoride sources	Fluoride (mg/kg/day)			Reference
	Scenario 1	Scenario 2	Scenario 3	
Drinking water 2 L/day at 1 ppm	0.028	0.028	0.028	Appendix B of this volume
Brewed Tea Two 8 oz cup/day at 4.7 ppm (max) at 3.5 ppm (mean)	0.032 -	- 0.024	- 0.024	USDA, 2004
Food ^a -Sulfuryl fluoride -Cryolite -Background	0.0003 0.0005 0.0057	0.0003 0.0005 0.0057	0.0003 0.0005 0.0057	U.S. EPA, 2004a
Work ^b (tent crew) Maximal application rate Submaximal application rate at RfC	0.78 - -	- 0.05 -	- - 0.003	Table 19 of this volume
Total	0.85	0.11	0.062	

^{a/} Dietary exposure was based on U.S. EPA estimated fluoride residue levels in the food from the uses of sulfuryl fluoride and cryolite, and background level in the food supply. Cryolite (Na₃AlF₆) is an insecticide used in many commodities including grapes, potatoes, and citrus.

^{b/} The occupational exposure to sulfuryl fluoride of tent crew (as absorbed dose) was converted to fluoride using the 38/102 molar ratio. at RfC= exposure was estimated based on the chronic RfC value of 0.18 mg/m³.

VI. CONCLUSION

The human health risk associated with the use of sulfuryl fluoride in structural and non-food commodity fumigation was evaluated in this Risk Characterization Document. The critical toxicity endpoints were derived from laboratory animals: neurotoxicity in rats and rabbits for acute, 1-2 week, and subchronic exposures; and lung pathology in rats for chronic exposure. The primary route of exposure was inhalation for workers, residents, and bystanders. Estimated risks of human exposures were evaluated in terms of margins of exposure, and comparisons with the reference concentrations. The estimated acute exposures for bystanders exceeded 1/10 of the reference concentrations, thus would meet the criteria established by DPR for listing under the AB 1807 Toxic Air Contaminant Act. The MOEs for the following scenarios and exposure duration posed health concerns with MOEs less than 100 for occupational (adult) exposure or 1000 for residential and bystander exposures:

1. Structural fumigation:

- a. Workers at submaximal application rate: total fumigator activities (chronic), fumigator and tent crew tasks (all durations), ground seam opening (1-2 weeks, subchronic and chronic), roof seam opening (1-2 weeks, subchronic and chronic), tarpaulin folding (chronic), and general detarping (all durations).
- b. Workers at maximal application rate: introducing fumigant (1-2 weeks, subchronic, and chronic), total fumigator activities (1-2 weeks, subchronic, and chronic), fumigator and tent crew tasks (all durations), and all tent crew activities (all durations).
- c. Residents following clearance: all age groups (acute).
- d. Bystanders during application phase: all age groups (submaximal and maximal rate application, acute 12-hours and 24-hours).
- e. Bystanders during TRAP method of aeration: all age groups (submaximal and maximal rate application, acute 2-hours).
- f. Bystanders during Stack method of aeration: all age groups, except 15-18 years (submaximal rate application, acute 1-hours), all age groups (submaximal rate application, acute 4-hours; maximal rate application, acute 1-hour and 4-hours).

2. Non-food commodity fumigation: all bystanders (acute 24-hours).

The potential for health concerns in these scenarios should be viewed in the context of the limitations and uncertainties discussed in this RCD. The toxicology database, while complete with respect to registration requirements in California, did not include a developmental neurotoxicity study. This study would be helpful to determine the neurotoxicity potential of sulfuryl fluoride in infants and children. The assumption was that the NOEL would be 10-fold lower than the critical NOELs. Additional acute toxicology studies with shorter observation periods or declining doses could better characterize the potential toxicity associated with some exposure scenarios. Additional exposure data, in particular those with maximal application rate and for commodity fumigation, would provide better estimates of actual exposure. At the time of this risk assessment, no air monitoring data were available for the non-food commodity fumigation scenario. Therefore, the worker exposure was assumed at 5 ppm, the maximum air concentration allowed by the label for workers not wearing SCBA. For bystanders, 5 ppm was also assumed to be the highest potential acute exposure after considering use practices

for this scenario and 3 ppm as the highest monitored air concentration during structural fumigations. Since the Use Report indicates few uses of sulfuryl fluoride for non-food commodity fumigation, repetitive bystander exposure was considered unlikely. However, an expansion of uses to include food commodity fumigation may lead to more frequent exposures to sulfuryl fluoride by both workers and bystanders. This could produce greater risks than those calculated in this document. This prospect should be considered in the regulation of current and futures uses of sulfuryl fluoride.

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VIII. APPENDICES

- A. Glossary and Abbreviations
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APPENDIX A. GLOSSARY AND ABBREVIATIONS

AB 1807: California Assembly Bill 1807, the Air Toxic Contaminant Act

ACGIH American Conference of Government Industrial Hygienists

Acute Exposure: (see: Exposure Frequency)

Aeration: The release of fumigant from fumigated structure. Active aeration is accomplished using an exhaust fan. (see: Stack and Tarpaulin Removal and Aeration Plan)

Annual Exposure: (see: Exposure Frequency)

Benchmark Margin of Exposure (Benchmark MOE): A numerical level for margin of exposure used to determine whether the human exposure is of health concern. When the MOE is based on the toxicity from an animal study, a MOE of 100 is generally used as the benchmark. This takes into account of a 10-fold uncertainty factor each for interspecies extrapolation and intraspecies variation in response to a particular chemical. Higher benchmark level may be considered to account for uncertainties in the risk assessment. (see: Margin of Exposure, Uncertainty Factor, Interspecies Extrapolation, Intraspecies Variation)

Chronic Exposure: (see: Exposure Frequency)

Commodity (non-Food) Fumigation: The use of a gaseous fumigant to control pests in non-food items placed inside a chamber or other containers. After treatment, the chamber is aerated to allow the release of the fumigant into the atmosphere.

Clearance: A state when sulfuryl fluoride air concentration is not greater than 5 ppm inside a fumigated structure.

Critical Endpoint: The toxicity endpoint, which is used to select the NOEL for risk characterization (see: Endpoint, Critical NOEL, and NOEL).

Critical No-Observed-Effect Level (Critical NOEL): The no-effect level in a toxicological database for the critical endpoint and is used to calculate the margin of exposure or reference concentration (see: Margin of exposure, Reference concentration).

Default: An approach, assumption, or specification that is used in the absence of data or evidence to the contrary

Dose-Response Relationship: The relationship between the level of exposure (or dose) and the magnitude, severity, or probability of response.

Exposure Frequency: The duration of exposure for toxicity studies with laboratory animals are usually grouped into 4 categories:

Acute: 1 to a few days

Subchronic: 14 to 90 days in an animal study

Chronic: beyond 1 year in an animal study

Lifetime: 2 years for rodents

The exposure frequency for workers and residents are:

Acute: upper bound exposure values for up to 24 hours

Short-term: Upper bound exposure values for < 7 days

Intermediate: Mean exposure values for ≥ 7 days to < 1 year

Annual: Mean exposure values for 49 weeks per year

Lifetime: Mean exposure values for 40 years in a 75-year lifetime

Endpoint: An effect observed in a toxicity study noted for its biological significance and used as an indicator for health concern.

ENEL: Estimated No-Effect Level

EUP: Experimental Use Permit

FIFRA: Federal Insecticide Fungicide and Rodenticide Act

Food Quality Protection Act (FQPA): Food Quality Protection Act of 1996 that amended the Federal Food, Drug, and Cosmetic Act (FFDCA) and Federal Insecticide, Rodenticide, and Fungicide Act (FIFRA) to require greater health and environmental protection for pesticide use. It also requires special consideration for the protection of infants and children using an additional safety factor in setting exposure standard.

Functional Operational Battery (FOB): A systematic checklist in a screening test for neurobehavioral changes that include observations in home-cage and through handling, behavior in open field and activity chamber, reflex response and physiological parameters and encompass both the Autonomic and CNS Excitability domains.

Health Advisory (HA): A non-regulatory standard for contaminants in the drinking water, at which adverse non-carcinogenic health effects would not be anticipated over specified exposure durations (i.e., one-day, ten-day, longer-term, and lifetime). Chemical-specific HAs are developed by the U.S. Environmental Protection Agency Office of Drinking Water.

IDLH: Immediately Dangerous to Life or Health concentration

Intraspecies Variation: The variability in response among individuals within the same species. The NOEL is decreased by a factor, generally 10-fold, with the assumption that there can be up to a 10-fold variation in susceptibility between different people, due to factors such as age, sex, race-ethnicity, and genetic predisposition.

Interspecies Extrapolation: The use of toxicity data from one species to address the potential toxicity in another species. The NOEL is decreased by a factor, generally 10-fold, with the assumption that humans can be up to 10 times more susceptible than the most susceptible

animals at their most sensitive toxicological endpoints.

Intermediate Exposure: (see: Exposure Frequency)

LC50: Lethal concentration for 50% mortality.

Lifetime Exposure: (see: Exposure Frequency)

Lowest-Observed-Effect Level (LOEL): The lowest dose level in a toxicological study at which biologically and/or statistically significant effects are observed.

Margin of Exposure (MOE): A term to express the risk at a human exposure level. It is the ratio of the NOEL to the exposure. The NOEL is the highest dose level in a toxicological study at which no effects are observed.

Maximal Application Rate: The maximum rate allowed on the Vikane→ label for use in structural and non-food commodity fumigation. Since this rate was not used in the monitoring studies, the sulfuryl fluoride air concentration was extrapolated using an adjustment factor with the assumption that exposure was directly proportional to the application rate (see Submaximal application rate). The extrapolation factor was either 14.5-fold or 10-fold depending on the rates used in the monitoring studies.

Maximum Contaminant Level (MCL): The maximum level of a contaminant permitted to be present in water delivered to users of public water system. It is established under Safe Drinking Water Act.

mg·h/liter: mg x hours of fumigation/ liter volume

NAS: National Academy of Sciences

No-Observed-Adverse-Effect Level (NOAEL): The highest dose level in a toxicological study at which no biologically and/or statistically significant adverse effects are observed.

No-Observed-Effect Level (NOEL): The highest dose level in a toxicological study at which no biologically and/or statistically significant effects are observed.

NTP: National Toxicology Program

Permissible Exposure Level (PEL): The legal limit for occupational exposure to airborne risk agents established by the U.S. Occupational Safety and Health Agency.

PETE: Polyethylene terephthalate

PHG: Public Health Goal

Potency Factor: The slope of the dose-response curve for an oncogenic response. Its statistical

95th upper confidence bound is usually taken as the potency factor.

Reentry: When the occupants are allowed to enter a fumigated structure (see Structural Fumigation)

Reference Concentration (RfC): An estimate of a daily inhalation exposure concentration for the human population that is likely to be without an appreciable risk of deleterious non-carcinogenic effects.

Reference Dose (RfD): An estimated daily oral dose for the human population that is likely to be without an appreciable risk of deleterious non-oncogenic effects.

RED: Reregistration Eligibility Document

REL: Recommended Exposure Limit

Risk Characterization Process: The risk characterization process involved the identification of health effects of concern and determination of the risk for human exposure.

SB 950: California Senate Bill 950, the Birth Defect Prevention Act

SCBA: Self-contained Breathing Apparatus

Short-term Exposure: (see: Exposure Frequency)

SMCL: Secondary Maximum Contaminant Level

Stack Method: A Stack method is an alternative aeration procedure, which is being investigated for the use in California. The main difference is the longer aeration time with the Stack method compared to TRAP method (see: Tarpaulin Removal and Aeration Plan). It involves 12 hours of active ventilation through an exhaust stack with the tarpaulin in place except for a small opening on the side opposite the exhaust fan to allow fresh air in under the tarp. After 12 hours, the tarpaulin is removed and the home is tested for clearance.

STEL: Short-Term Exposure Level (see: TLV)

Structural Fumigation: The use of a gaseous fumigant to control pests inside a structure such as a house or warehouse. The building is covered with a tarp and sealed to keep the fumigant inside the structure. After treatment, the structure is aerated to allow the release of the fumigant into the atmosphere. After the fumigant air concentration is at or below an established limit (5 ppm for sulfuryl fluoride), the structure is deemed cleared (clearance) and the occupants are allowed to reenter (reentry) the homes or building.

Subchronic Exposure: (see: Exposure Frequency)

Submaximal Application Rate: The application rate used in the human exposure studies; it is

lower than the maximum rate allowed on the Vikane→ label.

Threshold Limit Value (TLV): Work place exposure limits recommended by American Conference of Government Industrial Hygienists (ACGIH). There are three categories of TLVs:

TLV-TWA (Time Weighted Average): The average concentration for a normal 8-hour workday and a 40-hour workweek.

TLV-STEL (Short Term Exposure Limit): 15-minute TWA. Exposure at the STEL should not be repeated more than 4 times per day. There should be at least 60 minutes between successive exposures at the STEL.

TLV-C (Ceiling): The concentration that should not be exceeded during any part of the workplace exposure.

Tolerance: The maximum concentration of pesticides that may remain in or on food and animal feed.

Tarpaulin Removal and Aeration Plan (TRAP): A standard aeration practice used in California to allow the release of the fumigant from a structure. It involves tarpaulin removal after 10 minutes of active ventilation through a plastic duct (secured at the roof line) followed by approximately 60 minutes of active aeration. The home is then closed until the following morning at which time it is tested for clearance (*i.e.*, sulfuryl fluoride level not greater than 5 ppm).

Uncertainty Factor (UF): A numerical value to express the uncertainty in the toxicological database, as well as uncertainty in the variability of response between species (interspecies) and individual humans (intraspecies).

Weight of Evidence (WOE): An evaluation approach which takes into account considerations and strength of evidence from the available data in its entirety. The areas generally include *in vivo* studies and observations in humans and laboratory animals, *in vitro* studies (e.g., pharmacokinetic, pharmacodynamic, mechanism of action), cytotoxicity and genotoxicity data, and quantitative or qualitative structure-activity relationship. WOE approach has routinely been used in identifying chemicals for their likelihood to cause cancer, reproductive, developmental, or neurotoxicological effects in humans. It can also be applied to other areas of toxicity identification (e.g., endocrine disruption).

APPENDIX B. REVIEW ON FLUORIDE

A. Introduction

This Appendix is a summary on fluoride ion (referred to as fluoride), which is a metabolite of sulfur dioxide. The information is derived from comprehensive reviews conducted by the Agency for Toxic Substances and Disease Registry (ATSDR, 2003), World Health Organization (WHO, 2002), and National Academy of Sciences (NAS, 1993), and is updated with recently published papers and the NAS report (NAS, 2006; see Section F. Additional Information). Fluorides are substances that contain the element fluorine. They are ubiquitous in the environment and found in the air, soil, and water. The natural sources of fluorides include fluorine, volcanic emissions, weathering and dissolution of fluoride containing minerals, and marine aerosols (Table B1). There are many anthropogenic sources since fluorides are used in industry processes and chemical productions, and as a metabolite of pesticides (cryolite and sulfur dioxide). Fluoride is also added to water as a prophylaxis against dental caries in both children and adults. In preerupting teeth, the cariostatic effect of fluoride is due to its uptake by the enamel crystallites to form fluorhydroxyapatite, which is less acid soluble than hydroxyapatite. In erupted teeth, the presence of fluoride in the saliva and dental plaque inhibits demineralization and promotes enamel remineralization. Human exposure to fluoride is regulated by federal and state agencies.

B. Human Exposure to Fluoride

The total human exposure to fluoride varies because of the multiple sources of exposure with varying concentrations. These sources include air, drinking water, food, and consumer products. The estimated non-occupational oral intakes (water, food, dentifrice, and supplements) for people in the U.S., Canada, and North America are shown in Table B2. The total exposure ranged from 0.01 to 0.27 mg/kg/day with infants and children having higher exposure (per kg of body weight basis; up to 0.27 mg/kg/day) than adults (up to 0.06 mg/kg/day) (WHO, 2002; ATSDR, 2003; NAS, 1993). The U.S. Environmental Protection Agency (U.S. EPA) estimated total chronic fluoride from dietary sources²² was 0.0347 mg/kg/day for the general population, and a range of 0.1531 mg/kg/day for infants (<1 year) to 0.0316 mg/kg/day for adults (20 to 49 years old) (U.S. EPA, 2004).

Of the total exposure, fluoride in the drinking water is the most significant contributor in some cases. The fluoridation level is generally between 0.7 to 1.2 mg/L. Assuming consumption rates of 1 and 2 liters/day of 1 mg fluoride/L (1 ppm) in the water, the exposures from the drinking water are 0.1 mg fluoride/kg/day and 0.029 mg fluoride/kg/day, for a 10 kg child and 70 kg adult, respectively. For infants, the U.S. EPA estimated a higher level of 0.1424 mg/kg/day (U.S. EPA, 2004). Bottled water and processed beverages (*e.g.*, soda pop and juices) may also contain fluoride and have replaced household drinking water as the primary source of fluid for some individuals. In one survey, the samples showed varied fluoride levels with some samples exceeding 1 ppm. The ranges (mean) were: 0.07 to 1.37 ppm (0.28 ppm) for soda, 0.01 to 1.70 ppm (0.36 ppm) for juices, 0 to 1.44 ppm (0.33 ppm) for punches, 0.61 to 6.68 ppm (2.5 ppm)

²² The sources are sulfur dioxide and cryolite treated commodities, background food, water, toothpaste, and air.

for tea, and 0.02 to 1.04 ppm (0.85 ppm) for Gatorade→ (ATSDR, 2003). Tea plant is known to accumulate fluoride from the soil and the leaves have been found to contain high levels of fluoride. About 25-84% of the fluoride is released during brewing (ATSDR, 2003). While these processed beverages contained fluoride, Marshall *et al.* (2003) showed that the increased risk of dental caries in young children (ages 1 to 7) was associated with the high consumption of soda pop beverages, which are high in acidity.

Another important source of exposure, in particular for young children, is fluoride-containing toothpaste. For children exposure to fluoride in toothpaste with 1 mg of fluoride/gram of product (1 ppm), the estimated exposures range from 1.0 mg/use for children who swallow all of the toothpaste to 0.25 mg/use for those with control of swallowing reflex. An average of 25% of the toothpaste is swallowed (ATSDR, 2003). There are various estimates of intake for other dentifrice products and supplements. Dental products contained as much as 230 ppm (mouth rise) to 2,300 pm (phosphate fluoride gel). However, the exposure for each individual to these products is determined by personal habits in terms of frequency and amount used.

Fruits and vegetables are also sources of fluoride due to uptake from the soil, atmospheric deposition on foliage, and use of fluoride-containing agricultural chemicals such as sulfuryl fluoride. Tea leaves contained the highest levels of fluoride, as discussed already. The U.S. EPA regulates the fluoride content in the food from the use of fluoride-containing pesticides. Using sulfuryl fluoride as an example, the tolerances²³ for fluoride levels in the treated commodities ranged from 3 ppm (fried fruits) to 130 ppm (wheat germ and milled wheat) (U.S. EPA, 2004).

The inhalation exposure to fluoride in the ambient air is relatively low, ranging from 1.0 to 7.5 $\mu\text{g}/\text{m}^3$ (1 $\mu\text{g}/\text{m}^3$ is equivalent to 0.59 $\mu\text{g}/\text{kg}/\text{day}$ ²⁴) for the general population (ATSDR, 2003). For occupational settings where fluorides are used or released, workers are exposed to much higher levels. For example, the time-weighted-average air fluoride concentration in several aluminum plants has been estimated in the mg/m^3 range.

²³ Tolerance- maximum residue level allowed on treated commodity.

²⁴ Using the DPR default infant breathing rate of 0.59 $\text{m}^3/\text{kg}/\text{day}$ and fluoride air concentration of 1 $\mu\text{g}/\text{m}^3$.

Table B1. Sources and uses of fluorides.^a

Chemical	Sources and Uses	
	Natural	Anthropogenic
Fluorine (gas)	Natural element	<ul style="list-style-type: none"> - Use to make uranium hexafluoride for nuclear reactors and nuclear weapons - Release from nuclear power plants and other high temperature processes
Fluorides	Sources: Volcanic eruptions, marine aerosols, weathering of rocks and soils	<p><u>Hydrogen fluoride:</u></p> <ul style="list-style-type: none"> -Release in combustion of coal, minerals, and clays. -Use in the production of aluminum fluoride, motor gasoline alkylates and chlorofluorocarbons, and fluoride-containing chemicals (phosphate fertilizers, pesticides, pharmaceuticals). -Use in the etching of semiconductor devices, cleaning and etching glass, cleaning brick and aluminum and tanning leather, rust removal, as well as petrochemical manufacturing processes. <p><u>Calcium fluoride:</u></p> <ul style="list-style-type: none"> -Use in steel, glass, enamel, and aluminum production; hydrofluoric acid and anhydrous hydrogen fluoride synthesis <p><u>Sodium fluoride:</u></p> <ul style="list-style-type: none"> -Use in water fluoridation (tap and bottled water); dentifrice products, glue and wood preservative; glass, enamel, steel and aluminum production, and pest control <p><u>Fluorosilic acid and sodium hexafluorosilicate:</u></p> <ul style="list-style-type: none"> -Use in water fluoridation <p><u>Fluorapatite:</u></p> <ul style="list-style-type: none"> -Use as a source of phosphate in fertilizer production <p><u>Cryolite and sulfuryl fluoride:</u></p> <ul style="list-style-type: none"> -Use as pesticides

^{a/} Information was compiled from ATSDR, 2003; WHO, 2002; U.S. EPA, 2004.

Table B2. Estimated total intake of fluoride from non-occupational exposures.^a

Population	Drinking water level mg F/liter	Estimated intake of fluoride mg F/day (mg F/kg/day)
Foodstuff (including infant formulas) and beverages, drinking water ^a		
Infants	<0.3	0.23 (0.028)
	>0.7	0.42 (0.052)
Children (2 years)	<0.3	0.21 (0.017)
	>0.7	0.62 (0.05)
Children (up to 6 years)	NS	0.05 to 1.23 (0.01 to 0.16)
Infant formula or breast fed, cereal, juices, drinking water (fluoridated and not fluoridated), dentifrices, fluoride supplements ^a		
Infants (6 months)	NS	0.4 to 1.4 (0.05 to 0.19)
Children (1 year)	NS	0.32 to 0.73 (0.03 to 0.08)
Children (2-3 years)	NS	0.76 to 1.23 (0.06 to 0.09)
Foods, beverages and dentifrices ^a		
Children (16- to 40-months)	0.8 to 1.2	0.97 (0.07)
Ambient air, foodstuffs (including formula or breast fed), drinking water (fluoridated and not fluoridated), soil, dentifrices ^a		
Infants (up to 6 months)	NS	<0.01 to 0.65 (<0.001 to 0.09)
Children (7 months to 4 years)	NS	0.6 to 2.1 (0.05 to 0.16)
Adolescents (5 to 11 years)	NS	0.7 to 2.1 (0.03 to 0.08)
Adults (20+ years)	NS	2.2 to 4.1 (0.03 to 0.06)
Drinking water and food ^b		
Children Adults	<0.7 ppm	1 (0.1)
		1 (0.01)
Children Adults	>0.7 ppm	2.7 (0.27)
		2.7 (0.04)
Drinking water and food ^c		
Adults	fluoridated	1.2 to 2.2 (0.026 to 0.031)

^{a/} From WHO, 2002 for U.S., North America, and Canada. NS=not specified in the report. F=fluoride.

^{b/} From ATSDR, 2003 and mg/kg/day calculated using 10 kg and 70 kg as default body weights for child and adult, respectively.

^{c/} From NAS, 1993 and mg/kg/day calculated using 70 kg as default body weights for adult.

C. Regulatory and Recommended Fluoride Exposure Levels

Various international and U.S. agencies have established regulatory and guideline levels for human exposures to fluorides. Extensive lists are in the review by ATSDR (2003); some of these levels are listed in Table B3. For inhalation exposure to fluoride, the occupational exposure limits are set at 2.0 mg hydrogen fluoride/m³ and 2.5 mg fluoride/m³ by the American Conference of Governmental Industrial Hygienists (ACGIH), Occupational Safety and Health (OSHA), and NIOSH (National Institute for Occupational Safety and Health).

For oral exposure, the U.S. Public Health Service (PHS) and U.S. Environmental Protection Agency (U.S. EPA) establish recommendations for drinking water fluoride levels to maximize the benefit of dental caries and minimize the risk of dental fluorosis. The PHS recommended fluoride concentration is 0.7 mg/L (79.3 to 90.5°F) to 1.2 mg/L (50.0 to 53.7°F) in the drinking water, depending on the average daily air temperature. The assumption is that people in a hotter climate would drink more water, thus the amount of fluoride in their water should be lower, as compared to those in cooler climate, to achieve an adequate fluoride level. However this assumption may no longer be applicable with the use of air conditioners, bottled water, and sports drinks. Further complication is that bottled water, unless specifically added, may have different fluoride levels, which are not indicated on the labels. The maximum fluoride concentration allowed in the bottled water is 1.5 mg/L, a level higher than the PHS recommendation.

Under the Safe Drinking Water Act, U.S. EPA recommends a Maximum Concentration Limit (MCL) of 4.0 mg/L (0.11 mg/kg/day²⁵) to minimize skeletal fluorosis (U.S. EPA, 1986). A Secondary Maximum Contaminant Level (SMCL) is 2.0 mg/L (0.06 mg/kg/day) to minimize dental fluorosis. The oral chronic reference dose (RfD) is 0.06 mg/kg/day and is the sum of fluoride levels in the diet (0.01 mg/kg/day) and drinking water (0.05 mg/kg/day) with no uncertainty factor applied (U.S. EPA, 1989). For the dietary exposure, the fluoride No-Observed-Effect Level (NOEL) was 1 ppm since fluoride at 0.1 to 1.0 ppm showed no effect on the teeth of children in an epidemiological study (Hodge, 1950). Fluoride at 2 ppm to 10 ppm in the water showed a dose-related increase in the severity of the teeth mottling. The 1.0 ppm in the water is equivalent to 0.05 mg/kg/day (assume 1 L/day water consumption and 20 kg body weight for children).

In 2003, the U.S. EPA requested the National Academy of Sciences to evaluate the scientific and technical basis of the fluoride levels in the drinking water. For this project, the subcommittee will advise the U.S. EPA on the adequacy of its fluoride MCL and SMCL to protect children and others from adverse effects. The subcommittee will determine the relative contribution of various fluoride sources (*e.g.*, food, dental-hygiene products) to total exposure, and determine data gaps and make recommendations for future research relevant to setting the MCL and SMCL for fluoride (see Section F).

²⁵ based on 70 kg body weight and 2 L/day water consumption.

Table B3. Regulatory and recommended fluoride levels.

Agency	Description	Fluoride	Reference ^a
U.S.-Air			
ACGIH	TLV-TWA STEL (ceiling)	2.5 mg NaF/m ³ -	ATSDR, 2001
OSHA	PEL (8-hr TWA)	2.0 mg HF/m ³ 2.5 mg F/m ³	
NIOSH	REL-a (TWA)	2.5 mg NaF/m ³	
ATSDR	MRL	Inhalation for HF 0.02 ppm (acute)	ATSDR, 2003
U.S.- Water and Food			
U.S. EPA- Water	MCLG MCL Secondary MCL	4.0 mg F/L 4.0 mg F/L 2.0 mg F/L	U.S. EPA, 1986
Public Health Service-Water	Recommendation	0.7 mg F/L (79.3 to 90.5°F) to 1.2 mg F/L (50.0 to 53.7°F)	PHS, 1962
FDA- Bottled water	No fluoride added Fluoride added	1.4 mg F/L (79.3 to 90.5°F) to 2.4 mg F/L (<53.7°F) 0.8 mg F/L (79.3 to 90.5°F) to 1.7 mg F/L (<53.7°F)	Adair <i>et al.</i> , 2001
U.S. EPA	Chronic RfD	0.01 mg F/kg/day in diet 0.05 mg F/kg/day in water	U.S. EPA, 1989
ATSDR	Oral MRL Chronic	0.05 mg F/kg/day	ATSDR, 2003
California			
DHS	Drinking water standard	0.7 to 1.2 mg F/L depending on air temperature	DHS, 2003
OEHHA	Air: acute REL-b Air: chronic REL-b Oral RfD	240 µg F/m ³ 13 µg F/m ³ 0.04 mg F/kg/day	OEHHA, 1999 OEHHA, 2003 OEHHA, 2003
OEHHA	PHG	1 ppm (1 mg F/L)	OEHHA, 1997

^{a/} ACGIH=American Conference of Governmental Industrial Hygienists; DHS=Department of Health Services, California; EPA=U.S. Environmental Protection Agency; F=fluoride, HF=hydrogen fluoride, IARC=International Agency for Research on Cancer; L=liter; MCL=maximum contaminant level; MCLG=maximum contaminant level goal; MRL=Minimum Risk Level, NaF=sodium fluoride, NIOSH=National Institute for Occupational Safety and Health; OEHHA=Office of Environmental Health Hazard Assessment, California; OSHA=Occupational Safety and Health Administration; PEL=permissible exposure limit; PHG=public health goal; REL-a=recommended exposure limit for 8 hour shift over a 40-hour work week; REL-b=reference Effect Level for chronic exposure; RfD=reference dose; STEL=short term exposure limit; TLV=threshold limit values; TWA=time-weighted average; WHO=World Health Organization.

In California, the Department of Health Services (DHS) establishes water fluoridation standards (DHS, 2003). The optimal fluoride levels range from 1.2 ppm to 0.7 ppm and are the same as those established by the PHS (NAS, 1993). The Office of Environmental Health Hazard Assessment (OEHHA) has established a Public Health Goal (PHG) of 1 ppm (1 mg/L) for fluoride in the drinking water for lifetime exposure (OEHHA, 1997)²⁶. This PHG is based on a NOEL of 1 mg/L for the onset of dental fluorosis in children from several human studies. The PHG was used to calculate an oral chronic reference effect level of 0.04 mg/kg/day (1 mg fluoride/L is equivalent to 720 µg/day from drinking 720 ml of water/day for a 18 kg child, 0.04 mg/kg/day) (OEHHA, 2003). Intraspecies factor was not applied since the NOEL was based on both adults and children.

OEHHA has also established 1-hour acute and chronic Reference Exposure Levels (REL) for inhalation exposures to fluorides (OEHHA, 1999). The acute 1-hour REL, protective against mild adverse effect, is 240 µg hydrogen fluoride/m³ (0.3 ppm). This REL was calculated from a NOEL of 2.4 mg/m³ for eye, nose, and throat irritation in male adult volunteers and an intraspecies extrapolation factor of 10-fold (Lund *et al.*, 1997). Higher 1-hour RELs were established for severe adverse effects (1 ppm, 0.83 mg fluoride/m³) and life-threatening effects (50 ppm, 41.5 mg fluoride/m³). The chronic 1-hour REL was 13 µg fluoride/m³ or 14 µg hydrogen fluoride/m³ based on a benchmark dose analysis of the data for skeletal fluorosis in workers of a fertilizer plant (Derryberry *et al.*, 1963). The benchmark dose at 5% response rate was 0.37 mg fluoride/m³, and factors were used to account for exposure duration, and intraspecies extrapolation²⁷.

D. Disposition of Fluoride in Mammals

The disposition of soluble fluoride (e.g., sodium fluoride) after oral ingestion is similar in humans and laboratory animals. Fluoride is rapidly and completely (estimated at 75 to 90%, NAS; 1993) absorbed as hydrogen fluoride from the stomach and small intestines. The presence of food and fluoride-binding substances (e.g., calcium or magnesium salts, antacids/aluminum hydroxide, phosphorus, and milk) reduces the absorption. The absorption of fluoride after inhalation exposure takes place at the upper respiratory tract. The amount absorbed depends on the solubility and particle size. There is more absorption with gaseous fluoride than fluoride particulates. The absorption of fluoride via the skin is also considered rapid.

Once absorbed via any route, it was rapidly distributed by blood with plasma levels reflecting the exposure levels or intake. Almost all (99%) of the body fluoride is found in the calcified tissues such as bone and teeth (ATSDR, 2003). Fluoride is initially retained on the surface of the crystallites by ionic exchanges. With continuous exposure, fluoride is incorporated into the crystal lattice structure of teeth and bone as hydroxyapatite and converted to fluoridated hydroxyapatite. The binding of fluoride to the bone is apparently reversible. Studies of people

²⁶ PHGs established by OEHHA exert no regulatory burden and represent only non-mandatory goals (OEHHA, 1997). PHGs were provided to California DHS for establishing drinking water standards.

²⁷ The calculation was: $0.013 \text{ mg F/m}^3 = 0.37 \text{ mg F/m}^3 \times 10 \text{ m}^3/20 \text{ m}^3 \times 5 \text{ days}/7 \text{ days}$ in a week. The 10/20 factor was based on OEHHA risk assessment guidelines that specified 10 of the 20 m³ total inspired volume per 24 hours is breathed during the work period when activity levels are higher compared to those at home.

with reduction in fluoride exposure, due to a change to non-fluoridated water or jobs, showed loss of fluoride from the bone. Fluoride is also distributed to the fetus from the maternal circulation, and is readily taken up by the fetal bone and teeth. Studies with rats and ewes showed low levels of fluoride in the brain, less than 10% of plasma concentration (ATSDR, 2003).

The primary route of excretion for fluoride is via the urine. About half of the absorbed fluoride is eliminated from the body within 24 hours. It is also excreted in the breast milk. Studies cited by WHO (2002) showed that the fluoride level in the breast milk may not reflect the fluoride intake in the drinking water because of multiple sources of fluoride.

E. Toxicity in Mammals

In mammals, fluoride exerts local and systemic effects. Fluorides at high concentrations are irritants causing irritation at site of contact. After absorption, the best-known target organs for fluoride toxicity are the teeth and bone. The following is a summary, which highlights effects in some organs/tissues after inhalation and oral exposures. Dermal exposure at high concentrations causes skin damage. Dermal toxicity is not discussed in this section because there are very few studies and dermal exposure is a minor exposure route. ATSDR (2003) is a comprehensive review of the toxicological effects for all routes of exposure.

E.1. Inhalation Toxicity

Workers are exposed to fluoride by inhalation in plants where fluoride-containing compounds are used or released during manufacturing processes. The primary target organs are the respiratory tract and skeleton.

E.1.a. Respiratory Effect

Acute and short-term exposures of humans and laboratory animals to high concentrations result in irritations of the eyes and the upper respiratory tract. This effect has been well documented in published articles for workers exposed to fluoride-containing gases, such as hydrogen fluoride. For example, in a study cited by ATSDR, workers in an aluminum plant showed lower forced expiratory volume and increased cough and sputum production. However, respiratory effects under occupational settings, *i.e.*, aluminum smelters, might be due to fluoride and other chemicals and particulates at these sites. Acute exposure of the general population has been limited to accidental release such as an incident with hydrogen fluoride in Texas. The residents complained of respiratory irritation (throat burning, shortness of breath, sore throat, and cough). When questioned 2 years after the exposure, they reported breathing, throat, and nose (sneezing, runny nose, and problems smelling food) problems. It is unclear if these symptoms were indications of long-term effects since there was no medical confirmation.

Respiratory effects are also observed in laboratory animals. The severity of the toxicity is related to the concentration and duration of exposure, and the site of deposition. Toxic effects include mild nasal irritation, pulmonary hemorrhage, respiratory distress, and death.

A study with rats and rabbits showed that exposure to hydrogen fluoride at 31 ppm for 5

weeks resulted in pulmonary hemorrhage, and local hemorrhage was observed at a lower dose of 8.2 ppm in the dogs. Adjusting for breathing rate differences²⁸, the effect doses for rats, rabbits, and dogs were 124 mg/kg/day, 70 mg/kg/day, and 13 mg/kg/day, respectively. In another study, rats exposed to non-lethal concentrations of hydrogen fluoride via a tracheal cannula for 2- or 10-minutes showed effects in the broncho-alveolar regions. On the other hand, effects were confined to the nose in rats exposed to fluoride by nose-only inhalation, and they included tissue necrosis, rhinitis, and hemorrhage.

E.1.b. Skeletal effect

Chronic inhalation exposure of workers to fluoride dust and/or hydrogen fluoride alone resulted in elevated incidences of skeletal fluorosis (more discussion of this effect is under E.2.a. Skeletal Effects in Human). In one study, early signs of fluorosis were detected only in workers with more than 10 years of exposure in an aluminum plant, but not in those with fewer years of employment. While their exposure levels were unknown, the actual airborne fluoride levels were 0.2 mg/m³ hydrogen fluoride and 0.28 mg/m³ fluoride dusts during the study. Skeletal fluorosis was also reported for workers in a fertilizer plant exposed to fluorides by inhalation.

There are few studies on the chronic inhalation toxicity of fluorides in animals; they did not show any skeletal effects. ATSDR (2003) cited one study where the rats showed duration and concentration-related increases in tooth and bone fluoride levels following exposure to 8.2 to 31 ppm fluoride as hydrogen fluoride. However, the report did not indicate whether the animals exhibited dental or skeletal effects.

E.1.c. Other effects

Liver:

No liver effects, as determined by liver function test, were reported in a study of a large cohort of aluminum workers. Liver effects (fatty degeneration, focal necrosis, and fibroblastic encroachment of periportal spaces) were observed in guinea pigs and rabbits exposed to 18 ppm fluoride as hydrogen fluoride for 50 days.

Kidney:

Studies of aluminum workers exposed to fluoride up to 6 mg/m³ (time-weighted average) showed no renal effects. There were some laboratory animal data, which indicated that fluoride might be nephrotoxic. Rats (31 ppm fluoride or 124 mg/kg/day for 5 weeks), rabbits (18 ppm fluoride or 41 mg/kg/day), and guinea pigs (effective level not reported) exposed to fluoride showed various renal effects (degeneration and necrosis of the cortex or convoluted tubules). However, these experiments used few animals and there were no control groups.

Nervous system:

While there is no clear indication of neurological effects in humans after exposure to hydrogen fluoride, there is some evidence in laboratory animals. Rats exposed to 50% of the LC50 concentration showed general weakness and decreased activity. Subchronic exposure to 0.03 or

²⁸ Inhalation rates were 0.96 m³/kg/day, 0.54 m³/kg/day, and 0.39 m³/kg/day for rat, rabbit, and dog, respectively.

0.1 ppm fluoride as hydrogen fluoride for 5 months showed central nervous system dysfunction (diminished conditioned responses and increased time before motor nerve response). The 0.1 ppm rats showed changes in the nerve cell synapses.

E.2. Oral Toxicity

Oral exposure is the primary route of exposure to fluoride for the general population. Compared to the inhalation route, there is more toxicity information on this route. Dental and skeletal effects are reported in both human and laboratory animals after oral exposure. In addition, various effects have been reported for other organs/tissues in the body. There are more studies on the reproductive and developmental toxicity of fluoride via the oral than the inhalation route of exposure. Some effects were ameliorated to some extent by co-administration of other chemicals in the diet. For example, calcium carbonate has been shown to decrease serum fluoride concentration (Ekambaram and Paul, 2002). Some vitamins reduce the incidences of some fluoride-induced developmental and maternal effects (see discussion in the following section).

E.2.a. Dental and Skeletal Effects in Human

The primary effect of low-level fluoride chronic oral exposure is dental fluorosis. Dental fluorosis is characterized by brown stain, surface pitting, and brittleness of the teeth. Fluoride causes degeneration of ameloblast cells, resulting in porosity and hypoplasia of the tooth. Since it does not affect the function of the teeth, the U.S. EPA has considered fluorosis as an “objectionable” cosmetic effect and not an adverse effect (U.S. EPA, 1996). At the PHS recommended level of 0.7 to 1.2 mg fluoride /L water (0.035 mg/kg/day²⁹), the prevalence of dental fluorosis in humans is expected to be about 10% of the population and mild to very mild in severity. However, there is an increasing prevalence of dental fluorosis among populations consuming either fluoridated or non-fluoridated drinking water (Maupome *et al.*, 2003; and NAS, 1993). This increased prevalence of fluorosis has been attributed to the widespread intake of fluoride from sources other than the drinking water, especially in areas served by non-fluoridated water.

Chronic oral exposure to high concentrations of fluoride also results in skeletal fluorosis in humans. The first stage of skeletal fluorosis results in occasional stiffness or pain in joints and some osteosclerosis of the pelvis and vertebra. The second and third stages involve calcification of ligaments, osteosclerosis, exostoses, possibly osteoporosis of long bones, muscle wasting, and neurological defects due to hypercalcification of vertebra. Signs of skeletal fluorosis range from increased bone density to severe deformity, known as crippling skeletal fluorosis (complete rigidity of the spine, often accompanied by kyphosis (humpbacked) or lordosis (arched back)). Skeletal fluorosis is most common in countries, *e.g.*, India and China, with high exposures from multiple sources (water, indoor burning of fluoride-rich coal for cooking and heating, fluoride-rich food). Based on studies from these countries, the estimated total intake is 14 mg fluoride/day for a clear excess risk of skeletal adverse effects, and is 6 mg fluoride/day for suggested evidence of increased risk. In the U.S., there are reported cases of osteosclerosis and

²⁹ Assuming water consumption of 1 L/day for a 20 kg child, and water fluoride concentration of 0.7 mg/L.

knee/hip stiffness after exposure to 8 mg fluoride/L for 7 years, and 5 cases of “crippling skeletal fluorosis” from intake of 15-20 mg fluoride/day over a 20 year period (daily intake of 230 to 310 µg fluoride/kg/day).

There is conflicting evidence for potential increased risk of bone fractures with chronic exposure to fluoridated drinking water in humans. Some reports showed an association between the exposure and increased incidences of bone (*e.g.*, hip) fractures while others did not support such a finding. WHO also reviewed cases from other countries, and did not find any clear correlation between these two parameters. The differences may be due to the exposure dose as low dose fluoride may not have any effects while high dose fluoride causes the bone to be brittle.

Since fluoride increases bone density, it has been used for the treatment of osteoporosis. However, studies showed that it increased the density of some but not all bone tissues. Furthermore, fluoride treatment has been found to result in weaker bones, which may be more susceptible to fractures.

E.2.b. Dental and Skeletal Effects in Laboratory Animals

Dental fluorosis is the most common effect observed in rodents after chronic exposure to fluorides. Studies conducted by the National Toxicology (NTP) Program showed dose-related increases in incidences of dental fluorosis in the control and sodium fluoride (25, 100, or 175 ppm) treated B6C3F1 mice and F344/N rats (NTP, 1990). In rats, the fluoride levels were 0.2 (control), 0.8, 2.5, and 4.1 mg/kg/day in the males; and 0.2, 0.8, 2.7, and 4.5 mg/kg/day in the females³⁰. Mottling of teeth was found in all groups (% of animals affected in males/females) and was 5%/0% (control), 85%/26% (25 ppm), 96%/94% (100 ppm), and 100%/98% (175 ppm). Similar results were reported for mice. In mice, the fluoride levels were 0.6 (control), 1.7, 4.9, and 8.1 mg/kg/day in the males; and 0.6, 1.9, 5.7, and 9.1 mg/kg/day in the females³¹. Mottling of teeth was found in all groups (% of animals affected in males/females) and was 26%/15% (control), 64%/45% (25 ppm), 86%/94% (100 ppm), and 95%/98% (175 ppm). In mice, structural tooth changes and microscopic changes in bone structures of femur and tibia were detected in the two high dose groups.

In a Procter-Gamble Company study, rats were given sodium fluoride (0, 4, 10, or 25 mg/kg/day) in the diet for two years (Maurer *et al.*, 1990). All treated groups showed dose-related increased incidences of incisor defects, which included ameloblastic dysplasia, fracture/malformation, and enamel hypoplasia. There were also increased incidences of bone subperiosteal hyperostosis (irregular deposition of bone in subperiosteal locations) leading to excessively thick cortices of bone. The cranium was most affected with dose-related increased incidences. Other bones (femur, cervical vertebrae, premaxilla, maxilla, and mandible) were affected primarily at mid and/or high dose.

³⁰ The Medical Toxicology Branch calculated fluoride bioavailability as 60% from dietary fluoride and 100% from the drinking water.

³¹ The Medical Toxicology Branch calculated fluoride bioavailability as 60% from dietary fluoride and 100% from the drinking water.

Repetitive dosing studies with hydrogen fluoride in rodents also showed other effects to the bone tissue. These effects included: inhibition of endosteal bone formation, reduction in cancellous bone volume, delayed fracture healing and a reduction of collagen synthesis, increase in dermatan sulfate and chondroitin-6-sulfate in the tibia, reduction in bone matrix, alteration in femoral bone bending strength, and reduced vertebral bone quality.

E.2.c. Other Effects

Respiratory System

There is no report on the respiratory effect in humans after oral exposure to fluorides. There is only one laboratory animal study cited by the ASTDR (2003). Rabbits exposed to 4.5 or 9 mg fluoride/kg/day in the diet for 6 months were reported to have congestion, edema, and desquamation of the respiratory epithelium. At 9 mg fluoride/kg/day, there was an additional finding of inflammatory cell infiltrate.

Liver

There are no reports of liver effects in humans after oral exposure to fluorides. Studies with laboratory animals showed various effects. In mice exposed to 0.95 mg fluoride/kg/day in the drinking water for 7 to 280 days, the liver showed fatty granules and pale granular hepatocytes. Enlarged hepatocytes were reported in mice exposed to ≥ 33 mg fluoride/kg/day for 6 months.

Kidney

The kidney is a potential target tissue for fluoride toxicity since fluoride is excreted via the urine. However, human epidemiological studies have not shown any association between renal diseases and fluoride in the drinking water. Acute nephrosis (multifocal degeneration and necrosis of the tubular epithelium) was reported in mice given ≥ 33 mg/kg/day fluoride in the drinking water for 26 weeks, but no kidney toxicity was reported in rats exposed to ≥ 20 mg/kg/day. No kidney effects were reported in the 2-year study in mice (≥ 8.1 mg/kg/day in males or 9.1 mg/kg/day in females), or rats (≥ 4.1 mg/kg/day in males or 4.5 mg/kg/day in females).

Nervous System

Some of the symptoms (tetany, paresthesia, paresis, and convulsions) observed in humans exposed to fluorides at high doses may be caused by fluoride-induced hypocalcemia rather than a direct effect on the nervous system.

In laboratory animals, there are few reports of nervous system effects (ATSDR, 2003). A decrease in motor activity was noted in rats exposed to sodium fluoride (9 mg fluoride/kg/day) by gavage for 60 days. At a slightly lower dose (6.0 or 7.5 mg fluoride/kg/day for 6 weeks), another study reported changes in spontaneous behavior in female rats.

More recently, Bhatnagar *et al.* (2002) studied the effect of sodium fluoride (30 ppm, 60 ppm and 120 ppm of fluoride for 30 days) on the hippocampal sub-regions to determine if fluoride impaired memory and learning. The data showed nerve cell body degeneration in the CA3, CA4, and dentate gyrus areas of the hippocampal sub-regions of female mice at all doses (average

body weight 30 g³²). Histology showed dark cells, apoptotic cells, vacuolated spaces between cells, cells without cytoplasm, condensed nuclei, clumping and darkening of chromatin material. However, only the 120 ppm group performed poorly in the motor coordination tests (akinesia, catalepsy tests), swimming endurance test, and maze tests, compared to the control.

Long *et al.* (2002) studied the molecular mechanism underlying the brain dysfunction caused by chronic fluorosis. Rats treated with 30 ppm or 100 ppm of sodium fluoride (control sodium fluoride of 0.6 ppm) in the drinking water and low-fluoride diet (4 ppm fluoride) for 7 months showed a reduction in the number of neuronal nicotinic acetylcholine receptors (nAChRs), which are important in the cognitive processes such as learning and memory. Western blot studies showed a reduction in certain subunits, which led the authors to hypothesize that the loss might be due to altered transcription, translation, or post-translation processes, as well as modified receptor-ligand interaction and receptor turnover.

Cardiovascular System

High fluoride intake may cause hypocalcemia and hyperkalemia. Hypocalcemia can result in tetany, decreased myocardial contractility, and possibly cardiovascular collapse. Hyperkalemia can cause ventricular fibrillation and eventual death. However, epidemiological studies with relatively large populations (i.e., pot room workers in an aluminum plant) with varying levels of fluoride (including high levels defined at >1 ppm) did not show any association with incidences of cardiovascular diseases.

Few studies showed effects on the cardiovascular system in laboratory animals. In the NTP study, about half of the mice (both genders) that died showed mineralization of the myocardium after 6-months of exposure to 67-71 mg fluoride/kg/day or 272.4 mg fluoride/L (cited in WHO, 2002; ATSDR, 2003). Some female mice showed myocardial degeneration.

Gastrointestinal System

In humans, high doses of fluoride have resulted in acute gastrointestinal (GI) effects (nausea, vomiting, and gastric pain) due to the irritation from the formation of hydrofluoric acid. But there is no evidence of gastrointestinal effects from fluoride at the levels used in the drinking water.

A high concentration of fluoride is also irritating to the GI tract of laboratory animals. Rats showed necrosis and hyperplasia in the glandular stomach after exposure to 7 mg fluoride/kg/day, and more severe effects (stomach ulcers) at 20 mg fluoride/kg/day in the drinking water for 26 weeks. Rabbits showed roughened duodenal mucosa and “cracked-clay” appearance of the absorptive cells after exposure to 5 mg/kg fluoride via gavage for 24 months. On the other hand, no GI effects were observed up to 9.1 mg/kg/day for 2 years in mice, up to 67-71 mg/kg/day in mice for 26 weeks, or 4.5 mg/kg/day in rats for 2 years (NTP, 1990).

³² Assuming a drinking water consumption rate of 0.008 L/day based U.S. EPA equation $0.10Bwt \text{ in Kg}^{0.7377}$ (U.S. EPA, 1988) and mean body weight of 0.03 kg from the study, the estimated doses are 8 mg/kg/day, 16 mg/kg/day, 32 mg/kg/day.

Developmental and Reproductive System

Since fluoride readily crosses the placental-maternal barrier and there is a direct relationship between maternal fluoride and fetal fluoride levels, there are concerns regarding the potential developmental and reproductive toxicity of fluoride. In humans, epidemiological studies have not shown any evidence of an association between the consumption of fluoridated water by mothers and increased risk of spontaneous abortion or birth defects. Reports of an association between fluoride use and reduced fertility, Down's syndrome, spina bifida, lower intelligence quotient were considered uncertain due to study design flaws and potential confounders such as small group size and lack of information on folic acid level.

In laboratory animals, toxicity studies of various protocols showed sperm and testicular damage, and reduced fertility at doses higher than those in the drinking water. Sperm toxicity cited by the WHO (2002) included: decrease in percentage of seminiferous tubules containing spermatozoa in rats (4.5 mg fluoride/kg/day for 60 days); damage to spermatid and epididymal spermatozoa in rabbits (4.5 mg fluoride/kg/day for 18 months); complete cessation of spermatogenesis in rabbits (4.5 mg fluoride/kg/day after 29 months); as well as decreased sperm counts, sperm motility, and sperm viability in rats, mice (2.3 mg fluoride/kg/day) and guinea pigs (4.5 mg fluoride/kg/day). High concentrations (generally greater than 4 mg/kg/day with repeated exposures) of fluoride also caused reduction in fertility (male rabbits at >9.1 mg fluoride/kg/day for 30 days, male mice at 4.5 mg fluoride/kg/day for 30 days). However, there were no effects on the testis structure and spermatogenesis or endocrine functions in rats exposed to 12.8 mg fluoride/kg/day during *in utero* and during lactation and for 14 weeks post-weaning (Sprando *et al.*, 1997 and 1998).

Ghosh *et al.* (2002) showed that rats given sodium fluoride (20 mg/kg/day for 29 days) by oral gavage showed significantly increased relative wet weights of testis, but decreased relative wet weights for prostate and seminal vesicle. The increased testis weight was attributed to increased fluid accumulation in the dilated seminiferous tubules. In addition, there were significant reductions in testicular delta-beta-hydroxysteroid dehydrogenase (HSD) and 17-beta-HSD activities, plasma testosterone levels, epididymal sperm count, and mature luminal spermatozoa (as determined by histology). These changes were hypothesized to be due to lipid peroxidation since there were increased levels of conjugated dienes in the testis, epididymis, and epididymal sperm pellet.

In a recent report, rats were given sodium fluoride in the drinking water for three generations (Collins *et al.*, 2001a and b). The only developmental effect observed was a decrease in the ossification of the hyoid bone of F2 fetuses from the high dose group (250 ppm or mean intake of 11.7 mg fluoride/kg/day for F1 females) (Collins *et al.*, 2001a). This effect on the hyoid bone was not observed in previous studies with single generation exposure (Collins *et al.*, 1995; Heindel *et al.*, 1996). There was no reproductive toxicity (such as litter size, mating index, fertility index, pup survival, pup weight) up to a dose of 12.8 mg fluoride/kg/day (Collins *et al.*, 2001b).

There is some evidence that fluoride causes developmental toxicity in laboratory animals. ATSDR (2003) cited one study where there were increased incidences of average number of fetuses per litter with at least three skeletal variations at the highest dose tested (11.4 mg

fluoride/kg/day); however, these were considered secondary to reduced maternal water and food consumption and decreased body weight gain.

Other studies with sodium fluoride at a higher concentration (40 mg/kg/day) in rats have shown maternal (reduced body weight and feed consumption) and fetal toxicity (Verma and Sherlin, 2001 and 2002). The fetal toxicity included reduction in the number of implantations and live fetuses, and increased incidences of skeletal variations and visceral abnormalities (subcutaneous hemorrhage). The maternal effects were mitigated by co-treatments with vitamins C, D, and E in combinations. The authors hypothesized that vitamin E and C served as free radical scavengers, while D maintained serum calcium and phosphorus for cellular processes. For fetal toxicity, vitamin C was more effective than vitamin E in reducing the number of abnormalities.

E.3. Oncogenicity

The oncogenicity potential of sodium fluoride in humans has been studied and debated for many years. More than 50 epidemiological studies have been conducted with no clear indication that fluoridation of the drinking water results in increased risk of cancer. The problem may be that these studies are insensitive to small increases in incidences, or that there are too many confounding factors, such as exposure to other chemicals, and other sources of fluoride. Based on results from the chronic toxicity in animals, genotoxicity studies, and human epidemiological studies, the general view is that fluoride in the drinking water is not likely to result in increased risk of cancer.

With laboratory animals, the reviews generally considered the evidence for oncogenicity as equivocal. In the study conducted by the National Toxicology Program, rats were given fluoride in the drinking water (11, 45, or 79 mg/L) and given a low-fluoride diet (actual fluoride level not reported) (cited in NAS, 1993; NTP, 1990). The evidence for oncogenicity was considered “equivocal” in males (osteosarcoma) and “no evidence” in females. The incidences of bone osteosarcoma were 1/50 in the 100 ppm males (2.3 mg/kg/day) and 3/80 in the 175 ppm (3.9 mg/kg/day) males. There was no evidence of oncogenicity for female rats or either gender in mice. In a subsequent chronic toxicity study with higher doses (1.8, 4.5 or 11 mg/kg/day; the highest dose was 3 times higher than the NTP study) of sodium fluoride in rats and mice via the diet, there were increased incidences of osteomas (benign bone tumors from osteoplasts) in mice, but not rats (Maurer *et al.*, 1990). Reexamination of the histological slides revealed additional tumors of the bone with no dose-response relationship. Osteosarcoma was reported for one low dose female and one high-dose male. The results of this study may be confounded since all mice were infected with a type C-retrovirus, and not all bone sections in the treated groups were examined.

There were positive and negative results from genotoxicity studies. Fluoride has not been shown to be mutagenic in standard bacterial systems but it induces chromosomal aberrations and gene mutations in cultured mammalian cells (*e.g.*, Chinese hamster ovary cells). *In vivo* clastogenicity studies have shown mixed results. Both the ATSDR and NAS have concluded that sodium fluoride at concentrations used in the drinking water would not be genotoxic. The *in vitro* clastogenicity effects have been hypothesized to be due to fluoride inhibition of DNA synthesis and/or repair, and not a direct interaction between fluoride and DNA.

F. Additional Information

Since the completion of a draft (June 2005) of this document, the NAS Committee completed their evaluation of the U.S. EPA maximum contaminant level goal (MCLG) of 4 mg fluoride/L in the drinking water (NAS, 2006). While the final report is not yet available, conclusions were released to the public in preprints of the report. The Committee concluded that the MCLG should be lowered, and the U.S. EPA should conduct a risk assessment to determine the appropriate level. The current level of 4 mg fluoride/L increases the risk of children to develop severe enamel fluorosis, which the Committee considered an adverse health effect. In addition to the effects of fluoride already discussed in this Appendix, the Committee reported that fluoride could be considered an endocrine disruptor because of its effects on normal endocrine function or response. These effects included altered thyroid hormone status, increased goiter incidences, elevated calcitonin levels, elevated parathyroid hormone, impaired glucose tolerance, and sexual maturity. They could be caused by direct or indirect effects of fluoride on the affected tissues; additional research was needed.

On the oncogenicity of fluoride, the NAS Committee summarized all available data from animals and humans, genotoxicity assays, and studies of mechanisms of action. The conclusion was that the evidence on the potential of fluoride to cause cancer, in particular of the bone, was "tentative and mixed". Of the greatest recent interest and debate was the finding from the thesis by E. Bassin of Harvard University, which examined the data from a hospital-based case-control study collected between 1989 to 1992. The author found a positive association (odds ratio as high as 5.46) between fluoride exposure in the drinking water and incidence of osteosarcoma in 6 to 8 years old boys. This thesis has since been published with the same conclusion (Bassin *et al.*, 2006). In a Letter to the Editor in the same journal, however, Douglass and Joshipura urged caution in the interpretation of the findings in Bassin *et al.* (2006) (Douglass and Joshipura, 2006). One reason was that their own study with another set of cases (1993 and 2000) collected at the same hospitals and methodology, did not show any association between fluoride level within the bone and excess risk of osteosarcoma. Fluoride levels were measured in bone specimens taken proximal to the osteosarcoma lesion and the contra lateral hip. This study is not published yet. Douglass and Joshipura (2006) also mentioned a 1992 NTP study that was not posted until recently (NTP, 2006). The purpose of this study was to examine the effect of sodium fluoride on the induction of bone tumors by ionizing radiation. In this study, rats were given sodium fluoride (250 ppm) in the drinking water, and with or without radiation treatment. No increased incidences of osteosarcoma were found for any treatment groups. Overall, information presented in this Appendix (E.3. Oncogenicity), studies summarized in the NAS report, and recently available data as discussed in this section, show some indication that fluoride can potentially be oncogenic in humans. The relationship between fluoride in the bone and osteosarcoma in humans may become clearer after the Douglass and Joshipura study is published.

G. Conclusion

Fluoride is recognized as an effective agent to prevent dental caries. There is increasing concern that humans may be overexposed to fluoride from the multitude and increasing number of sources. Some estimates of exposure exceed the current regulatory limits for exposure. There is a considerable database on the toxicity of fluorides. The primary effects are dental fluorosis and skeletal fluorosis for both inhalation and oral exposures. Effects in other organs/tissues have been studied mainly in laboratory animals. The review by the National Research Council will provide a more current assessment of human fluoride exposure and potential health effects.

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APPENDIX C. TOXICOLOGY SUMMARY OF SULFURYL FLUORIDE

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
SULFURYL FLUORIDE

Chemical Code # 000618, Tolerance # 50223
SB 950 # 498

August 1, 1986

Revised 2/27/87, 8/25/89, 9/17/90, 1/30/91, 4/10/92, 7/24/92, 9/14/94, 11/17/98, 4/23/02, and
6/2/04

I. DATA GAP STATUS

Chronic, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect (not oncogenicity)
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time (see special studies)

Toxicology one-liners are attached.

In the one-liners below:

** indicates an acceptable study. **Bold face** indicates a possible adverse effect.

All relevant record numbers through 210013 (Document No. 50223-067) and all relevant records of the series 900000+ were examined. This includes all records listed in the DPR Data Index as of 6/2/04.

Updated by C. Aldous, 1/30/91; H. Green, C. Aldous, and J. Gee on 4/10/92; Gee, 7/24/92; and

Kishiyama, Green, Kellner and Aldous, 9/14/94; C. Aldous, 11/17/98 and 4/23/02; P. Leung, 6/2/04

File name: T20040602.wpd.

I. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED (CHRONIC and ONCOGENICITY), RAT

****50223-029 125637** "Sulfuryl Fluoride: 2-Year Inhalation Chronic Toxicity/Oncogenicity Study in Fischer 344 Rats", (J. F. Quast, G. J. Bradley and K. D. Nitschke, The Dow Chemical Co., Toxicology Research Laboratory, Lab Project Study ID K-016399-040, 8/18/93). Sulfuryl fluoride, stated purity 99.8%, was administered via inhalation at concentrations of 0, 5, 20, or 80 ppm to 50 Fischer 344 rats/sex/group for 6 hours/day, 5 days/week (except holidays) for 24 months. Fifteen additional rats/sex/dose level were included for a 12-month neurotoxicity study (Record No. 130056). Formally, the NOEL = 5 ppm, based on "very slight" degree of dental fluorosis (statistically significant in males). Since the fluorosis is considered as a biomarker of exposure rather than as an adverse effect, a practical NOAEL is 20 ppm, based on a host of changes at 80 ppm. The primary target organ was kidney. An exacerbation of the normal process of chronic progressive glomerulonephropathy was the primary cause of premature deaths in both sexes at that dose, with mineralization in a variety of tissues as common secondary effects. High dose females had increased incidence of brain vacuolation in cerebral cortex and in thalamic and hypothalamic areas, limited to "very slight" degree. Possible direct responses of respiratory tissues would include aggregates of alveolar macrophages in lungs (already evident at 1 year interim sacrifice), and inflammation of larynx and trachea. Findings in this study had either not appeared or had not reached advanced degree until well beyond the first year of the study, consistent with the majority of effects being secondary to renal toxicity. **Acceptable, with "possible adverse effect"** (chronic renal disease). No oncogenicity was evident. Kishiyama and Aldous, 9/14/94.

50223-042 161152 U.S. EPA review of Record #125637, above. Recent reviews of 3 study types were included in this record. The review corresponding to the above record agreed with the 1994 DPR review above in acceptability status, and in the determination that no oncogenic effect was indicated. There are no fundamental differences in study interpretation between the DPR and U.S. EPA reviews, except that the U.S. EPA placed the NOEL at 20 ppm whereas the DPR review placed the NOEL at 5 ppm. The difference was based on the use of dental fluorosis as a determinant of the LOEL by DPR, which finding was not considered by either reviewer as a pivotal endpoint for chronic/oncogenicity outcomes. Aldous, 11/17/98.

CHRONIC TOXICITY, DOG

****50223-033 126744** "Sulfuryl Fluoride: One-Year Inhalation Toxicity Study in Beagle dogs", (J. F. Quast, M. J. Beekman, and K. D. Nitschke; Dow Chemical Company, Midland, MI; Report # K-016399-044; 21 October 1993). Sulfuryl fluoride, 99.8% purity. Four beagle dogs per sex per group were exposed via whole-body inhalation at 0, 20, 80, and 200 ppm for 6 hours per day, 5 days per week, for 1 year. High dose animals were killed at 9 months due to severe clinical signs of toxicity. NOEL = 20 ppm (very slight degree of chronic active inflammation in alveoli of the lungs of two 80 ppm females, multifocal aggregates of alveolar macrophages in both sexes, and very slight dental fluorosis). Alveolar inflammation was the main cause of rapid

deterioration of health of most high dose dogs by about 9 months. A focal malacia in the caudate nucleus of the brain was identified in 5 high dose dogs, without apparent functional sequelae. **Acceptable. No adverse effects** are indicated, since subacute studies (see especially Record No. 097246) had already shown marked functional toxicity at 300 ppm, whereas about one-fourth of that daily dose in this chronic study caused only slight chronic effects. H. Green and C. Aldous, July 5, 1994.

50223-042 161152 U.S. EPA review of Record #126744, above. Recent reviews of 3 study types were included in this record. The review corresponding to the above record agreed with the 1994 DPR review above in acceptability status and NOEL. Aldous, 11/17/98.

50223-023 113430 Nitschke, K. D., Beekman, M. J., and Quast, J. F., "Sulfuryl fluoride: 13-week inhalation toxicity study in beagle dogs". The Toxicology Research Laboratory, Health and Environmental Sciences, Dow (Midland), 2/24/92. Four beagles/sex were dosed with SO₂F₂ by inhalation for 6 hr/day, 5 days/wk for 13 weeks. Doses were 0, 30, 100, and 200 ppm as whole body exposures in dynamic airflow chambers. High dose males and females gained less weight than other groups (final body weights of 200 ppm males and females were 12% and 4% lower than respective controls). The only clinical signs noted were one 200 ppm male with "lateral recumbency, tetany, tremors, salivation, and incoordination" noted on day 19 of the study only. Histopathology attributed to treatment was gliosis and vacuolation of focal areas of the putamen in one male and one female at 200 ppm. Microscopic changes are "possible adverse effects", however the presence of predictable clinical signs at the same dose level suggest that dose levels which do not elicit transient clinical signs are unlikely to cause marked histopathologic changes. The NOEL was 100 ppm. Results suggest that the chronic study should employ comparable dose levels to this subchronic study. Aldous, 4/1/92 (no separate worksheet).

50223-020 097246 Nitschke, K. D. and Quast, J. F., "Sulfuryl fluoride: Two-week inhalation toxicity study in beagle dogs". The Toxicology Research Laboratory, Health and Environmental Sciences, Dow (Midland), 4/30/91. Beagles, 1/sex, were dosed with nine 6-hr inhalation treatments of sulfuryl fluoride (SO₂F₂) over two weeks. Concentrations were 0, 30, 100, or 300 ppm. The major clinical observation was intermittent tremors and tetany in both 300 ppm dogs from day 5 onward. The effects were severe enough on day 9 that exposure was terminated after 5.5 hr. Dogs rapidly recovered to normal appearance and behavior at the end of each exposure period. Nasal turbinates of 300 ppm dogs had a slightly greater degree of inflammation than background level, and a similar slight inflammatory response in mucosa of the trachea was noted in the 300 ppm female. The NOEL was 100 ppm. No separate DPR written review is needed for this study. Aldous, 4/1/91.

ONCOGENICITY, RAT
(see combined, rat, above)

ONCOGENICITY, MOUSE

****50223-028 125636** "Sulfuryl Fluoride: 18-Month Inhalation Oncogenicity Study in CD-1 Mice", (J. F. Quast, G. J. Bradley and K. D. Nitschke, Dow Chemical Co., Toxicology Research Laboratory, Lab Project Study ID K-016399-039, 8/19/93). Sulfuryl fluoride, 99.8% purity, was administered via inhalation at concentrations of 0, 5, 20, or 80 ppm to 50 CD-1 mice/sex/group for 6 hours/day, 5 days/week for 18 months. Ten additional mice/sex per dose level were included for sacrifice at 12 months. NOEL = 20 ppm. Primary concern was increased mortality in females (mainly due to increased incidence of severe degree of bilateral amyloidosis in glomeruli). Possibly treatment-related findings in males were food impaction in esophagus and

inflammation and/or abscesses in the head and/or oral cavity at 80 ppm. Lesser changes at 80 ppm included very slight vacuolation of brain, particularly of cerebral external capsule (M and F), and very slight hypertrophy of thyroid epithelial cells (especially in males). This study is considered to indicate a "**possible adverse effect**", based on the exacerbation of geriatric renal disease in high dose females. Considering how high the NOEL and LOEL of this study are to levels which cannot be tolerated in acute and subacute toxicity exposure, this flagging of a "possible adverse effect" should not be taken to indicate unusual concern. No oncogenicity effects. **Acceptable**. Kishiyama and Aldous, Sept. 14, 1994.

50223-042 161152 U.S. EPA review of Record #125636, above. Recent reviews of 3 study types were included in this record. The review corresponding to the above record agreed with the 1994 DPR review above in acceptability status, NOEL, and in the determination that no oncogenic effect was indicated. Aldous, 11/17/98.

REPRODUCTION, RAT

**50223-022 112308 Breslin, W. J., Liberacki, A.B., Kirk, H. D., Bradley, G. J., and Crissman, J. W. "Sulfuryl fluoride: Two-generation inhalation reproduction study in Sprague-Dawley rats". The Toxicology Research Laboratory, Health and Environmental Sciences, Dow (Midland), Jan. 7, 1992. Sprague-Dawley rats were dosed 6 hr/day, 5 days/wk with sulfuryl fluoride at doses of 0, 5, 20, or 150 ppm. Thirty rats/sex/group were dosed for 10 wk or 12 wk prior to mating (F0 and F1 parents, respectively): dosing was continued to end of weaning period for both sexes, except that females were taken off treatment for 5 days beginning shortly before expected parturition. Pups were not exposed to sulfuryl fluoride prior to weaning. Parental NOEL = 5 ppm (aggregates of alveolar macrophages in lungs of both sexes, both generations: dose related). At 150 ppm, adults of both generations had body weight decrements of about 10% (generally statistically significant). This group had discolored teeth (fluorosis), chronic inflammation of lungs, and "very slight" to "slight" vacuolation of myelinated fiber tracts of the caudate putamen. Reproductive effects NOEL = 20 ppm (reduced pup body weights in F1 and F2 generations). Study is ACCEPTABLE. No adverse reproductive effects. The comparatively low NOEL for systemic effects may nevertheless be useful in eventual risk assessment. Aldous, 4/8/92.

50223-018 095931 Draft protocol for 50223-022 112308, above.

TERATOLOGY, RAT

**006 36089 Rat Teratology, 833. (Toxicology Research Laboratory, Dow Chemical, 10/26/81). "Vikane: Inhalation teratology study in rats and rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity) at 0, 25, 75, or 225 ppm by inhalation for 6 hours/day on days 6 through 15 of gestation. Dose levels based on a probe study. Maternal and developmental NOEL's > 225 ppm (HDT). J. Parker evaluation (7/24/86) found study unacceptable but possibly upgradeable; B. Davis evaluation (2/6/87) was complete and ACCEPTABLE with supplemental data (007:051087).

007 051087 Data supplemental to a rat teratology study 006:036089, above. (Toxicology Research Laboratory, Dow Chemical, 11/19/80). "Vikane: Probe teratology study in Fischer 344 rats and New Zealand white rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity). Results from a range-finding study show decreases in maternal body weight, body weight gain, and food consumption, and increases in water consumption and kidney weights at the 300 ppm exposure level, with no toxicity at 100, 30, or 0 ppm. Summary and individual antemortem observations, individual necropsy data, and individual litter and fetal data are provided. This supplement

removes all deficiencies and the teratology is complete and acceptable. B. Davis 2/6/87.

TERATOLOGY, RABBIT

**006 36088 (Toxicology Research Laboratory, Dow Chemical, 10/26/81). Rabbit teratology (833). "Vikane: Inhalation teratology study in rats and rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity) at 0, 25, 75, or 225 ppm by inhalation for 6 hours/day on days 6 through 18 of gestation. Maternal (decreased weight gain) and developmental (decreased fetal weight) NOEL's = 75 ppm. J. Parker evaluation (7/24/86) found study unacceptable but upgradeable; B. Davis evaluation (2/6/87) was complete and ACCEPTABLE with supplemental data (007 050992).

007 050992 Data supplemental to a rabbit teratology study in 006:036088. (Toxicology Research Laboratory, Dow Chemical, 11/19/80). "Vikane: Probe teratology study in Fischer 344 rats and New Zealand white rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity). Results from a range-finding study show decreases in maternal body weight, body weight gain, and liver weights at the 300 ppm exposure level, with similar but not statistically significant toxicity at 100 ppm. Summary and individual antemortem observations, individual necropsy data, and individual litter and fetal data are provided. This supplement removes all deficiencies of the teratology study. B. Davis 2/6/87.

GENE MUTATION

** 016 091291 "Evaluation of Sulfuryl Fluoride in the Ames Salmonella/Mammalian-Microsome Bacterial Mutagenicity Assay." (Gollapudi, B. B., Samson, Y. E. and Zempel, J. A.; Health and Environmental Sciences-Texas, Dow, TXT:K-016399-037, 8/17/90). Sulfuryl fluoride gas, lot 874, 99.6%, was tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 with and without activation with rat liver S9. Overnight cultures were plated in top agar, then exposed without lids for 4 hours in glass desiccators. Atmospheres of 0, 300, 1000, 3000, 10,000 and 30,000 ppm were tested. After exposure, plates were incubated an additional 2 days, then the colonies were counted. Triplicate plates per concentration and two trials were studied. There was no evidence of an increase in reversion rate. The number of revertants was decreased somewhat at 30,000 ppm suggesting cytotoxicity. The positive controls were acceptable. ACCEPTABLE. (Gee, 9/14/90).

CHROMOSOME EFFECTS

**014, 017 090476, 091576 "Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test" (Gollapudi, B. B., McClintock, M. L. and Nitschke, K. D., Toxicology Research Laboratory, Dow, Project ID: TXT:K-016399-033, 2/16/90). Sulfuryl fluoride, Lot WP880329 752 MAR/88, 99.6%, was administered to CD-1 mice in an inhalation chamber for a 4 hour exposure period. Actual concentrations of sulfuryl fluoride were 0, 48, 180 and 520 ppm, TWA. Benzene was a positive control with a target concentration of 9000 ppm. Cyclophosphamide was an additional positive control at 120 mg/kg by gavage. The positive controls were sampled 24 hours after exposure, the negative control and treated animals were sampled 24, 48 or 72 hours after exposure, 5/sex/group for each time point. 1000 PCE/animal were evaluated and the percent PCE determined. No increase in the number of micronucleated cells. ACCEPTABLE. (D. Shimer and J. Gee, 9/14/90).

025 115686 "Response to U. S. EPA Comments on the Study Entitled 'Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test' Laboratory Project ID:

TXT:K-016399-033" (K. D. Nitschke and B. B. Gollapudi, DowElanco, 1991) The U. S. EPA rejected the study as unacceptable based on the following: 1) No evidence for an MTD and 2) several parameters of exposure were not provided, namely, identity of the inhalation chamber, use of Miran-1A infrared spectrophotometry, no location for sampling devices or placement of animals in the chamber. The submission contains DowElanco's response. The study was ACCEPTABLE to DPR. No change in status. No worksheet. Gee, 7/24/92.

DNA DAMAGE

** 50223-021 093262, "Evaluation of Sulfuryl Fluoride in the Rat Hepatocyte Unscheduled DNA Synthesis (UDS) Assay", (B. Bhaskar Gollapudi, et al., Health and Environmental Sciences-Texas, The Dow Chemical Co., Report # K-016399-043, 10/7/91). Sulfuryl fluoride (gas fumigant), 97.4% purity, was tested in the unscheduled DNA synthesis assay using hepatocytes of Sprague-Dawley outbred Crl:CD BR male rats at concentrations of 0 (air), 204, 408, 612, 816, 1020, or 1530 ppm. No increase in unscheduled DNA synthesis by autoradiography. ACCEPTABLE. (H. Green and J. Gee, 4/10/92)

NEUROTOXICITY

Acute hen studies are not routinely required for this class of chemicals. Nevertheless, several specialized studies have been done, as follows.

50223-035 130056 "Sulfuryl Fluoride: Chronic Neurotoxicity Study in Fischer 344 Rats-Final Report" (P. J. Spencer, G. J. Bradley and J. F. Quast, Dow Chemical Co., Toxicology Research Laboratory, Lab. Project ID K-016399-040B 3/24/94). Sulfuryl fluoride (purity 99.8%, lots WP 880329-752, WP 901011-907, WP 910321-918, WP 910826-929 and WP 920131-940) was administered via whole-body inhalation (6 hours/day, 5 days/week) for 1 year at concentrations of 0, 5, 20 or 80 ppm to 15 Fischer 344 rats/sex/group (satellite rats from concurrent 2-year chronic toxicity/oncogenicity study). NOEL (for neurotoxicity) = 80 ppm. **No Adverse Effects. Functional observational battery, grip performance, landing foot splay and motor activity tests showed no evidence of neurotoxicity. ACCEPTABLE. Supplemental information. Kellner, Aldous and Gee, 9/14/94.

50223-031 126406 Exact duplicate of Appendix IV of Record No. 130056.

50223-010 071482 Mattsson, J. L., Albee, R. R., Eisenbrandt, D. L., and Nitschke, K. D. "Neurological examination of Fischer 344 rats exposed to sulfuryl fluoride (Vikane) gas fumigant) for 13 weeks". (Mammalian and Environmental Toxicology Research Laboratory, Dow, study ID K-016399-026, 11/21/86). Vikane, Lot TWP 830919-408, 99.8%, was administered to Fischer 344 rats, 7/sex/group, 6 hours/day, 5 days/week, for 13 weeks at 0, 30, 100 or 300 ppm. Rats were implanted with epidural electrodes, and a battery of neurological tests was performed on the rats after 13 weeks of exposure. At 300 ppm, rats had increased latencies of certain components of various evoked response wave patterns (visual, somatosensory, cerebellar, auditory). In addition, visual and somatosensory evoked responses were noted as statistically significantly slowed in females at 100 ppm, and the latency of the auditory brainstem response in 100 ppm males appeared to be increased. Thus the NOEL was 30 ppm. The only brain microscopic findings at the end of the treatment period were vacuoles in the white fiber tracts of the caudate-putamen. Auditory brainstem response was tested in controls and high dose rats (2/dose/sex) after 2 months of recovery, at which time rats were sacrificed and brains were examined microscopically. After recovery, 300 ppm rats had normal evoked responses and normal brain histology. Brain functional changes are **possible adverse**

effects. Useful supplemental data. D. Shimer/ C. Aldous, 9/13/90.

009 071478 "Subchronic Neurotoxicity in Rats of the Structural Fumigant, Sulfuryl Fluoride" (Health and Environmental Sciences, Dow Chemical Co., Mattsson, J. L., R. R. Albee, D. L. Eisenbrandt and L. W. Chang, Neurotoxicol. Teratol. 10(2) 127-133. 1988., 3/11/87). This is the published version of study 50223-010:071482 (see above).

50223-030 126302 "Sulfuryl Fluoride: Electrodiagnostic, FOB and Motor Activity Evaluation of Nervous System Effects from Short-Term Exposure", (R. R. Albee, P. J. Spencer, and G. J. Bradley, Dow Chemical Co., Toxicology Research Laboratory, Lab. Project ID K-016399-045, K-016399-045D, K-016399-045E, K-016399-045F, and K-016399-045G, 5/3/93). This study was requested by U.S. EPA to achieve limited objectives as indicated in the title. Previous studies had addressed histopathology and other features commonly included in neurotoxicity studies. Sulfuryl fluoride, purity 98.3-99.8%, was administered via whole-body inhalation (6 hours/day for 2 consecutive days) at concentrations of 0, 100 or 300 ppm to 12 non-pregnant female Fischer rats/group. NOEL = 300 ppm. Functional observational battery, grip performance, landing foot splay, motor activity and electrodiagnostic responses were examined within 24 hr of the final exposure. There was no evidence of neurotoxicity. Not applicable to fill guideline FIFRA study data gaps, but useful information. (Kishiyama and Aldous, 9/7/94).

SUBCHRONIC, INHALATION

****50223-012 071484** Nitschke, K. D., Zimmer, M.A., and Eisenbrandt, D. L. "Sulfuryl Fluoride (Vikane) Gas Fumigant): 13-Week Inhalation Toxicity Study with Rabbits" (Mammalian and Environmental Toxicology Research Laboratory, Dow Chemical Company, Study ID K-016399-025B, 11/16/87). Vikane, sulfuryl fluoride, Lot No. TWP 830919-408, 99.8%, was administered to New Zealand White rabbits via inhalation for 6 hours/day, 5 days/week for 13 weeks at 0, 30, 100 or 300 ppm. Seven animals per sex per group. NOEL = 30 ppm; [cerebral vacuolation in regions of internal and external capsules, putamen, and globus pallidus of one female: and nasal tissue inflammation in one male]. At 300 ppm, common brain findings were vacuolation to severe malacia of cerebrum (both sexes, in the above regions), and gliosis and/or hypertrophy of vascular endothelial cells in some females in the same regions. Common nasal tissue findings at 300 ppm in both sexes were degeneration and inflammation of epithelial tissues. Collectively, these findings are **possible adverse effects. Acceptable subchronic study.** D. Shimer/ C. Aldous, 9/10/90.

****50223-012 071485** Nitschke, K. D., Dittenber, D.A., and Eisenbrandt, D. L. "Sulfuryl Fluoride (Vikane Gas Fumigant): 13-Week Inhalation Toxicity Study with Rats" (Mammalian and Environmental Toxicology Research Laboratory, Dow Chem. Co., Project ID K-016399-025R, 11/16/87). Vikane, sulfuryl fluoride, Lot TWP 830919-408, 99.8%, was administered by inhalation to Fischer 344 rats, 10/sex/group, at 0, 30, 100 or 300 ppm for 6 hours/day, 5 days/week, 13 weeks. NOEL = 30 ppm (based on mottled incisors in all rats at 100 and 300 ppm). A practical NOAEL relevant to adults likely to be exposed chronically is 100 ppm. Major findings at 300 ppm included: marked body weight decrements (M & F), cerebral vacuolation [caudate-putamen area, white fiber tracts of the internal capsule; (M and F)], kidney hyperplasia (F) and decreased protein droplets in kidneys (M), inflammation of nasal mucosae (M & F), and subpleural histiocytosis in the lungs (M & F). Brain findings constitute **possible adverse effects. Acceptable** as a subchronic study. Shimer/Aldous; 9/17/90.

50223-018 095933 Exact duplicate of record No. 071485, above.

50223-018 095932 Eisenbrandt, D. L., Nitschke, K. D., Streeter, C.M., Wolfe, E. L. "Sulfuryl fluoride (Vikane[®] Gas Fumigant): 2-Week inhalation toxicity probe with rats and rabbits". Dow Chemical Co., Midland MI, April 2, 1985. Dose levels were 0, 100, 300, or 600 ppm in both species. Animals were exposed for 6 hr/day for a total of 9 days. Nine out of 10 rats administered 600 ppm sulfuryl fluoride died. Kidneys of these rats were severely affected. Minor kidney damage was noted in 300 ppm rats. There were no other apparent effects at that dose level. Reviewed by Aldous, 1/30/91 in the context of a protocol review for a reproduction study scheduled to begin in Feb., 1991. (See CDFA protocol comments of 1/30/91).

50223-034 128669 ADowElanco sulfuryl fluoride: Thirteen-week inhalation study in CD-1 mice[®] (329 pages). Source Lab: The Dow Chemical Company, Midland, MI. Study Date: 12/93. Study was not reviewed by DPR, but an abstract was included in the oncogenicity study for which this study served as a dose range-finding study (see review of Record No.125636). Aldous, 11/17/98.

****50223-055 186125** Nitschke, K. D. and J. F. Quast, A Sulfuryl fluoride: two-week inhalation toxicity study in CD-1 mice,[®] The Dow Chemical Co., Midland, MI, 2/11/02. Laboratory Project Study # K-016399-029. Five mice/sex/group were dosed 6 hr/day, 5 days/wk, for 9 exposures at 0, 30, 100, and 300 ppm sulfuryl fluoride, 99.6% purity. Associated exposures of treated groups were 0.13, 0.42, and 1.3 mg/l of chamber air. Mice were sacrificed 1 day after the last exposure, at which time they were subjected to limited hematology and clinical chemistry studies, gross necropsy and histopathology. NOEL = 30 ppm (A very slight[®] cerebral vacuolation in six of ten 100 ppm mice). The 300 ppm exposure proved to be excessive: 9/10 of these mice did not survive the 11-day duration of the study. Deaths were preceded by inanition (statistically significantly body weight losses, decreased ingesta in digestive tract, decreased body fat), and associated pathology (stomach erosions/ulcers, hepatocellular atrophy judged to be due to inanition). Most decedents had A roughened hair coat[®] and at least 3 of the males had whole body tremors. All high dose mice, except for 2 with sufficient autolysis to impede microscopic evaluation, showed cerebral vacuolation, usually of A moderate[®] degree. Five high dose mice had very slight vacuolation of the medulla. These brain lesions are A possible adverse effects.[®] Also, nine high dose mice had lacrimal/Hardarian gland atrophy. **Acceptable.** Aldous, 4/23/02.

50223-036 131289 (2 pages of additional information related to 50223-034 128669, above).

SPECIAL STUDIES

009 071479 "Incapacitation and Treatment of Rats Exposed to a Lethal Dose of Sulfuryl Fluoride" (Health and Environmental Sciences, Dow Chem. Co., Nitschke, K. D., Albee, R. R., Mattsson, J. L. and Miller, R. R. (1986) Fundam. Appl. Toxicol. 7, 664-670. Sulfuryl fluoride, 99.8% was administered to Fischer 344 rats in exercise chamber at 400, 10,000, 20,000 or 40,000 ppm to determine "time to incapacitation" and to see if calcium gluconate (treatment for fluoride ion toxicity) would alleviate effects of a lethal dose. Rats exposed to 4000 ppm for 45 minutes could walk for 45 minutes, then died about 2.5 hours after exposure terminated. Four out of five rats treated with calcium gluconate prior to exposure survived at least 3 days. Three anticonvulsants: diphenylhydantoin, phenobarbital, and diazepam, were given to some groups prior to treatment. Phenobarbital was effective in controlling convulsions. Potentially useful supplemental information, however not relevant to SB-950 data review at this time. No DPR worksheet has been done, nor is one anticipated at present. D. Shimer, 8/25/89. (Comments by Aldous, 9/17/90: no toxicologist review).

METABOLISM

**50223-0067 210013, ASulfuryl Fluoride: Pharmacokinetics and Metabolism in Fischer 344 Rats®, (A. L. Mendrala, *et.al.*, Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Study ID 001166, 22 May 2002). 4 jugular vein cannulated Fischer 344 male rats and 4 non-cannulated males per group received nose-only inhalation exposure (4 hours) to ³⁵S-Sulfuryl Fluoride at 30 and 300 ppm. Additionally, 18 non-cannulated males per group were exposed (4 hours, nose-only inhalation) to non-radiolabelled sulfur fluoride at 30 and 300 ppm and 8 non-cannulated males served as a vehicle control (dry, compressed air) group. Time-weighted actual exposure concentrations over the 4-hour treatment period with ³⁵S-sulfuryl fluoride were 28.4 ppm (0.26 µCi/l of atmosphere) and 274 ppm (2.8 µCi/l of atmosphere) at the 30 ppm and 300 ppm nominal levels respectively. Values were 31.2 ppm and 312 ppm at 30 ppm and 300 ppm respectively for non-radiolabelled sulfur fluoride exposures. Venous blood samples (~0.15 ml) were collected from cannulated rats at 0.25, 0.5, 1, 2, 3, and 4 hours during inhalation exposure and 0.5, 1, 2, 4, 6, 12, 24, 36, 48, 72, 96, 120, and 168 hours post-exposure. 3 animals per group exposed to non-radiolabelled sulfur fluoride were sacrificed after 2 and 4 hours of exposure and 2, 4, 8, and 20 hours post-exposure to measure fluoride ion content in plasma, brain, and kidney. Additionally, fluoride ion content was determined in plasma, brain, and kidney of 2 control rats per group at the beginning and end of exposure and 4 and 8 hours post-exposure. No radioactivity was detected in expired air of the 300 ppm group animals at 24 hours post-exposure, therefore, collection of expired air was not continued for the remaining sampling intervals of the group and not performed at all for 30 ppm animals. Plasma and RBC Radioactivity after ³⁵S-Sulfuryl Fluoride Exposure. Plasma levels of radioactivity peaked at 5.2 and 37.7 µg-equivalents/g (µg-eq./g) at 30 and 300 ppm respectively at the end of exposure. From the end of exposure to 24 hours post-exposure (α phase), half-lives were 2.6 and 2.4 hours at 30 and 300 ppm respectively, and from 24 hours post-exposure on (β phase), half-lives were 82.7 and 56.2 respectively. RBC radioactivity reached 4.7 and 40.3 µg-eq./q RBC at 30 and 300 ppm respectively at the end of exposure. α phase half lives were 2.5 and 1.1 hours and β phase half-lives were 222 and 139 hours at 30 and 300 ppm respectively. Urinary and Fecal Excretion after ³⁵S-Sulfuryl Fluoride Exposure. Urine contained 85.6% to 88.9% of excreted radioactivity through 7 days post-exposure (580.636 and 4618.051 µg-eq at 30 and 300 ppm respectively). 47% (273 µg-eq.) and 60% (2766 µg-eq) were excreted during the 4 hour exposure period at 30 and 300 ppm respectively. 73 and 777 µg-eq. of radioactivity were recovered in feces through 7 days post-exposure at 30 and 300 ppm respectively. 70 and 704 µg-eq. respectively were recovered through 48 hours post-exposure. Tissue Distribution after ³⁵S-Sulfuryl Fluoride Exposure. The lungs had the highest concentration of radioactivity, 0.77 and 6.30 µg-eq./g at 30 and 300 ppm respectively 7 days post-exposure. Respiratory turbinates contained 0.312 and 3.491 µg-eq./g, olfactory turbinates - 0.285 and 3.233 µg-eq./g, spleen - 0.394 and 3.075 µg-eq./g, and kidneys - 0.368 and 2.756 µg-eq./g at 30 and 300 ppm respectively. Metabolites Identified Following ³⁵S-Sulfuryl Fluoride Exposure. Two radiolabelled metabolites, sulfate and fluorosulfate, both hydrolysis products of sulfur fluoride, were identified in whole blood and urine. Fluoride Ion Analysis Following Non-Radiolabelled Sulfuryl Fluoride Exposure. Metabolic release of fluoride ions was proposed as the cause of toxicity in sulfur fluoride exposure (Nitschke, *et. al.* (1986), and Nitschke and Eisenbrandt (2001)), therefore, quantification was performed. Elevated levels of fluoride ion were detected in urine, plasma, kidney, and brain during and after exposure to non-radiolabelled sulfur fluoride. Most returned to background levels at varying times post-exposure. Acceptable. (Green and Gee, 6/1/04).

APPENDIX D. INDIVIDUAL ANIMAL FLUORIDE AND LESION DATA FROM 13-WEEK TOXICITY STUDIES.

Table D1. 13-Week Mouse Study with 0 to 100 ppm sulfuryl fluoride by inhalation (Nitschke and Quast, 1993).

Animal number	0 ppm	10 ppm	30 ppm	100 ppm	
	Fluoride $\mu\text{g/ml}$	Fluoride $\mu\text{g/ml}$	Fluoride $\mu\text{g/ml}$	Fluoride $\mu\text{g/ml}$	Brain lesion
Males					
1	0.128	0.146	0.129	0.355	all animals had vacuoles
2	0.094	0.082	0.160	0.177	
3	0.091	0.114	0.164	0.256	
4	0.113	0.104	0.172	0.246	
Females					
1	0.076	0.113	0.109	0.210	all animals had vacuoles
2	0.11	0.079	0.158	0.223	
3	0.091	0.092	0.136	0.260	
4	0.083	0.068	0.126	0.239	

Table D2. 13-Week Rat Study with 0 to 300 ppm sulfuryl fluoride by inhalation
(Nitschke *et al.*, 1987a).^a

Animal number	0 ppm	30 ppm	100 ppm	300 ppm			
	Fluoride µg/ml	Fluoride µg/ml	Fluoride µg/ml	Fluoride µg/ml	Brain lesion	Nasal inflammation	Kidney hyperplasia
Males							
1	0.558	1.014	0.568	1.164	all had vacuoles	v. slight	none
2	2.95	0.808	0.574	1.21		v. slight	
3	0.416	1.156	0.456	0.688		severe	
4	0.592	0.576	0.558	0.66		v. slight	
5	1.038	1.064	0.488	0.908		slight	
6	1.128	0.45	1.014	2.538		severe	
7	1.152	0.39	0.456	1.488		moderate	
8	0.698	0.724	2.626	1.396		slight	
9	0.43	0.612	0.98	0.862		slight	
10	no data	0.356	1.09	0.63		v. slight	
Females							
1	1.57	0.356	0.444	1.056	all had vacuoles	v. slight	v. slight
2	0.338	0.582	0.570	3.272		v. slight	none
3	0.543	0.765	0.969	0.722		v. slight	v. slight
4	0.912	2.374	0.444	0.814		v. slight	v. slight
5	1.136	0.434	0.512	0.890		v. slight	v. slight
6	0.256	0.448	0.486	0.906		v. slight	v. slight
7	0.346	0.470	0.810	1.176		slight	v. slight
8	0.344	0.492	0.408	0.690		v. slight	v. slight
9	0.372	0.274	0.736	1.089		v. slight	v. slight
10	0.252	1.180	0.372	3.046		v. slight	v. slight

^{a/} v=very. Lesions were observed only in the 300 ppm group.

Table D3. 13-Week Rabbit Study with 0 to 300 ppm sulfuryl fluoride by inhalation (Nitschke *et al.*, 1987b).

Animal number	0 ppm	30 ppm	100 ppm		300 ppm				
	Fluoride µg/ml	Fluoride µg/ml	Fluoride µg/ml	Brain lesion	Fluoride µg/ml	Brain lesion	Nasal inflammation	Nasal epithelial hyperplasia	Nasal epithelial degeneration
Males									
1	0.096	0.276	0.402	none	0.72	vacuoles	slight	moderate	moderate
2	<0.06	0.226	0.386		0.606	malacia	slight	moderate	slight
3	<0.06	0.13	0.394		0.592	vacuoles	normal	severe	normal
4	<0.06	0.174	0.416		0.650	malacia	moderate	severe	normal
5	<0.06	0.144	0.462		0.662	vacuoles	normal	slight	normal
6	<0.06	0.178	0.356		0.562	normal	normal	v. slight	normal
7	<0.06	<0.06	0.438		0.554	malacia	moderate	slight	normal
Females									
1	0.576	0.736	0.8	vacuoles	1.086	vacuoles		slight	
2	0.608	0.672	0.814	none	0.974	vacuoles			
3	0.544	0.656	0.752		1.022	vacuoles		slight	
4	0.528	0.608	0.862		0.9	vacuoles	slight	severe	slight
5	0.544	0.688	0.862		0.974	normal		severe	
6	0.560	0.688	0.720		dead	vacuoles		severe	slight
7	0.560	0.83	0.990		0.974	malacia	v. slight	slight	slight

a/ v=very. Lesions were observed in the 100 and 300 ppm groups.

APPENDIX E. CALCULATIONS

Calculation Equations:

1. Conversion of ppm to amortized daily dose (mg/kg/day):

$$\text{ppm} \times 4.17 \text{ mg} / \text{m}^3 \times \text{respiration rate} \times \frac{\text{hours exposed}}{24 \text{ hours}} \times \frac{\text{days exposed}}{7 \text{ days}} \times \text{AF}$$

The term for number of days exposed /7 days is used in the calculation only for studies when the animals were dosed for 5 or more days. The default inhalation rates used are: 0.96 m³/kg/day for rats and 0.54 m³/kg/day for rabbits (Zielhuis and van der Kreek, 1979). An absorption factor (AF) of 18% (Mendrala *et al.*, 2002) is applied only to the critical NOELs when they are used to calculate the margins of exposure.

2. Dosage calculation for acute critical NOEL of 300 ppm in rats (Albee *et al.*, 1993a).

$$300 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 \times 0.96 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hours exposed}}{24 \text{ hours}} = 300 \text{ mg} / \text{kg} / \text{day}$$

$$\text{Absorbed dosage} = 300 \text{ mg/kg/day} \times 0.18 = 54 \text{ mg/kg/day}$$

3. Dosage calculation for 1-2 week critical NOEL of 100 ppm in rabbits (Eisenbrandt *et al.*, 1985).

$$100 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 \times 0.54 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hours exposed}}{24 \text{ hours}} \times \frac{5 \text{ days}}{7 \text{ days}} = 40 \text{ mg} / \text{kg} / \text{day}$$

$$\text{Absorbed dosage} = 40 \text{ mg/kg/day} \times 0.18 = 7.2 \text{ mg/kg/day}$$

4. Dosage calculation for subchronic critical NOEL of 30 ppm in rabbits (Nitschke *et al.*, 1987b).

$$30 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 \times 0.54 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hours exposed}}{24 \text{ hours}} \times \frac{5 \text{ days}}{7 \text{ days}} = 12 \text{ mg} / \text{kg} / \text{day}$$

$$\text{Absorbed dosage} = 12 \text{ mg/kg/day} \times 0.18 = 2.2 \text{ mg/kg/day}$$

5. Dosage calculation for chronic critical NOEL of 5 ppm in rats (Breslin *et al.*, 1992; Quast *et al.*, 1993a).

$$5 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 \times 0.96 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hours exposed}}{24 \text{ hours}} \times \frac{5 \text{ days}}{7 \text{ days}} = 4 \text{ mg} / \text{kg} / \text{day}$$

$$\text{Absorbed dosage} = 4 \text{ mg/kg/day} \times 0.18 = 0.72 \text{ mg/kg/day}$$

6. Margin of Exposure:

$$\frac{\text{NOEL (mg / kg / day)}}{\text{Human Exposure (mg/kg/day)}} = \text{Margin of Exposure}$$

7. Calculation of Reference Concentration in ppm:

The reference concentration in ppm is calculated by first determining the human equivalent NOELs by the following equation. The default adult and child inhalation rates (IR) are 0.28 m³/kg/day and 0.59 m³/kg/day, respectively (Andrews and Patterson, 2000). For acute exposure, there is no amortization of the number of days exposed. The interspecies extrapolation factor of 10 is retained because this equation only addresses the differences in the inhalation rate between animals and human and not other physiological factors. The total uncertainty factor may be 100 for interspecies extrapolation and intraspecies variation, or 1000 with an additional 10-fold factor for database uncertainty for developmental neurotoxicity. The uncertainty factor of 1000 was applied to reference concentrations for residential (children) exposures.

$$\text{Animal NOEL ppm} \times \frac{\text{animal IR}}{\text{human IR}} \times \frac{\text{hours exposed}}{24 \text{ hours}} \times \frac{\text{days exposed}}{7 \text{ days}} = \text{Human equivalent NOEL ppm}$$

$$\text{Human equivalent NOEL in ppm} \times 4.17 \text{ mg} / \text{m}^3 / \text{ppm} = \text{Human NOEL in mg} / \text{m}^3$$

$$\frac{\text{Human NOEL as ppm or mg/m}^3}{\text{Uncertainty Factor of 100 or 1000}} = \text{Reference Concentration}$$

The following is an example of the calculation using the child inhalation rate and the acute NOEL of 300 ppm:

$$300 \text{ ppm} \times \frac{0.96 \text{ m}^3 / \text{kg} / \text{day}}{0.59 \text{ m}^3 / \text{kg} / \text{day}} \times \frac{6 \text{ hours exposed}}{24 \text{ hours}} = 122 \text{ ppm}$$

$$\frac{122 \text{ ppm}}{1000} = 0.122 \text{ ppm or } 0.51 \text{ mg} / \text{m}^3$$

APPENDIX F. DEVELOPMENTAL NEUROTOXICITY DATA WAIVER



Department of Pesticide Regulation



Paul Gosselin
Acting Director

MEMORANDUM

Arnold Schwarzenegger
Governor

TO: Gary Patterson
Supervising Toxicologist
Medical Toxicology Branch

FROM: Joyce Gee [*original signed by Joyce Gee*]
Senior Toxicologist
(916) 324-3465

DATE: July 30, 2004

SUBJECT: Sulfuryl fluoride Rat Developmental Neurotoxicity Study: Waiver request by Dow
for ProFume®

50223-072, DPR record 210020, contains a report from the United States Environmental Protection Agency (US EPA), Hazard Identification Assessment Review Committee (HIARC), dated October 31, 2003, TXR No.: 0052208, regarding sulfuryl fluoride. The author was Jessica Kidwell, addressed to Ed Budd and Michael Doherty, both of the US EPA, Health Effects Division. According to the report, meetings of the HIARC were held on two occasions, April 11, 2001, and October 31, 2003, with the latter recommendations superceding the earlier one, dated May 22, 2001.

The major topic for reconsideration was in regard to the Food Quality Protection Act (FQPA) and potential increased sensitivity of infants and children. In brief, the HIARC concluded that there is concern for neurotoxicity from exposure to sulfuryl fluoride, based on the acute, subchronic and chronic neurotoxicity studies in rats and the developmental studies in rats and rabbits, all using inhalation, and all of which the Agency found acceptable. There is also an acceptable 2-generation reproduction study by inhalation in the rat with no specific evidence of sensitivity of offspring. The conclusion of US EPA from these studies was one of no concern for pre- and/or post-natal toxicity of exposure to sulfuryl fluoride. Based, however, on the evidence of neurotoxicity (clinical signs, histopathology and disturbances in electrophysiological waveforms), the HIARC recommended a developmental neurotoxicity study in rats be required. In the absence of such a study, a 10X uncertainty factor would be used. Page 28 identifies two data gaps, a metabolism/pharmacokinetics study in rats (waived in 1993) and an inhalation developmental neurotoxicity study in rats.

The document also contains evaluation of other studies and the safety factors for various lengths of exposure. These comments, however, are not pertinent to this memorandum.

Federal Register 69 (15): 3253 (January 23, 2004) Rules and Regulations: According to this notice, the Agency was still requiring a developmental neurotoxicity study as of 1/3/04 as a condition of registration of ProFume for food use. The 10X uncertainty factor was still in place, based on the lack of this study. The Agency considered it possible that the NOEL from other



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studies could become an effect level. Based on the data available, EPA had no justification for using any safety factor less than 10X.

US EPA Memorandum, April 22, 2004 This is a memorandum from Vicki L. Dellarco, Health Effects Division, to Lois Rossi, Registration Division, both of the Office of Pesticide Programs, regarding the waiver justification for an inhalation developmental neurotoxicity study in rats, as required in the above citations. Dow submitted a waiver justification to the Agency in which the bases given were (as listed by the Agency):

- Essentially no chronic dietary exposure
- Minimal potential inhalation exposures or short duration (1-2 days)
- Animal welfare concerns (1500 to 4000 animals)
- Potentially confounded scientific and technical aspects of conducting an inhalation DNT study

Dow also mentioned that they had conducted a recent metabolism study in rats showing the rapid release of fluoride. Given the known toxicity of fluoride and the minimal exposure, neurotoxicity to adult or developmental neurotoxicity would be unlikely.

The staff at the Agency agreed with the arguments of Dow regarding minimal exposure potential and unlikelihood of neurotoxicity occurring due to dietary or inhalation exposure. The 10X uncertainty factor, was to be retained for the lack of a DNT study, in addition to the 10X for animal to humans and the 10X for variations in sensitivity among humans (1000X total). This composite safety factor would provide "ample" protection.

DPR comments in reference to the 4 bases of Dow listed by the Agency

The comment about essentially no chronic dietary exposure seems appropriate, based on desorption of sulfuryl fluoride with time. Residue data would confirm dietary estimates.

Duration of exposures of 1-2 days seems questionable for "bystanders" near food use fumigation chambers (as opposed to fumigated structures). With multiple uses of a given chamber, the bystander exposure could be repeated with some frequency.

The number of animals needed (4000) seems excessive. It is assumed that the number, 1500, includes the pups as well as the pregnant dams with sufficient dams per dose group to produce 20 litters with the appropriate numbers of pups per sex. Where 4000 might become involved is unclear. Although DPR is in accord with the efforts to minimize the number of animals used in toxicity testing, the primary responsibility is toward the assessment of health risks to the people of California.

Regarding the last basis, potentially confounded scientific and technical aspects of an inhalation DNT study, a 2-generation reproduction study was conducted by Dow using the inhalation route. A DNT study and a reproduction study should present similar technical

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situations. In the reproduction study, males and females were exposed to 0, 5, 20 or 150 ppm for 6 hours per day. Females (as in a DNT study) were exposed every day during gestation until GD 20 and not exposed until day 5 of lactation. From days 5 - 21 postpartum, pups were separated from the dams while they were exposed to sulfuryl fluoride for 6 hours per day, according to the report. The pups remained in the nesting cages. In that study, no treatment-related effects on pup weights were noted except at the high dose, possibly secondary to decreased maternal body weight. It should be possible to examine pups for DNT parameters during this period of exposure of the dams. It is unclear how the separation of pups from dams for a DNT study differs from the separation for the reproductive toxicity study. The examination of pups for neurotoxic endpoints, such as motor activity, is part of any DNT study, and not specific to an inhalation DNT study. Therefore, the basis of "technical aspects" given by Dow is not adequate alone, since similar technical aspects would have been present in the reproductive toxicity study.

Although not part of the list of bases from DOW in the memorandum of US EPA are the results of a metabolism study in male rats (ID 001155, May 22, 2002) which indicated that sulfuryl fluoride is rapidly absorbed and rapidly converted to fluoride, fluorosulfate and sulfate. Therefore, the metabolism study suggests that no sulfuryl fluoride *per se* should be detectable in blood or urine, for example. The implication is that a DNT study would, in practicality, test fluoride [as should be true of the other studies conducted for toxic effects].

Although the Department would prefer to have actual data from a DNT study to evaluate whether there is any specific sensitivity of the fetus and/or newborn to inhalation of sulfuryl fluoride, the continued use of a 10X uncertainty factor (1000X total) should provide protection of those populations. Therefore, the Department agrees with the waiver given by US EPA to the conduct of a DNT study with sulfuryl fluoride at this time.