OFFICE OF CHEMICAL SAFETY
HEALTH RISK ASSESSMENT
TECHNICAL REPORT

Active Ingredient:	Sulfuryl Fluoride
Product Name:	Profume Gas Fumigant
Company:	Dow Agrosciences Australia Ltd
Registration Submission No:	12588
File Numbers:	2005/064782
APVMA No:	59952
ATS No:	37712
Work Order No:	2167
Proposal:	Approval of new active; Registration of new product

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APPENDIX IV: PRODUCT HAZARD CLASSIFICATION ACCORDING TO NOHSC AND GHS . ERROR! BOOKMARK NOT DEFINED.

1. EXECUTIVE SUMMARY

Dow Agrosciences Australia Ltd have submitted data to support approval of a new active constituent, sulfuryl fluoride, and the registration of a new product, Profume Gas Fumigant, containing 998 g/kg sulfuryl fluoride. Sulfuryl fluoride is a colourless and odourless gas belonging to the chemical family of inorganic acid halides. Profume Gas Fumigant is a pressurised gas formulation and is intended for the control of insects and rodents in a variety of different use situations. Although sulfuryl fluoride is a new active in Australia, it has a long history of use (ca. 40 years) in North America.

The data provided in the submission included toxicology studies on the active and the formulated product 'Vikane Gas Fumigant' (synonyms-Profume Gas Fumigant), containing approximately 99.8% sulfuryl fluoride. Of the 42 submitted studies four were published in peer reviewed scientific journals. Of the remaining 38 unpublished studies, 34 were relied on to support approval of the active and registration of the product. Most studies relied on for this assessment have been conducted in accordance with contemporary test guidelines and are considered adequate for the assessment of the toxicology profile of sulfuryl fluoride and the establishment of Safety Directions for the product. Extensive use was made of the JMPR sulfuryl fluoride evaluation.

Sulfuryl fluoride, when suspended in corn oil, was moderately toxic in rats by the oral route. However, since sulfuryl fluoride is a gas at room temperature a conventional dermal toxicity study was not performed. Sulfuryl fluoride was a low or moderate inhalation toxicant in rats and mice respectively. Skin and eye irritation tests were not performed but animal whole body exposures and extensive in-use product experience did not reveal any eye or skin irritation potential.

No effects on reproduction or fetal development were observed in rats or rabbits that were housed in non-lethal concentrations of sulfuryl fluoride gas for 6 hours/day. The nervous system was not uniquely sensitive to sulfuryl fluoride as the no effect concentration for neurotoxic effects were as high as or higher than the concentrations required to cause general toxicity. Based on negative *in vivo* genotoxicity data and the absence of carcinogenicity in mice and rats, sulfuryl fluoride is unlikely to pose a carcinogenic risk in humans.

Based upon its moderate acute toxicity, low to moderate inhalation toxicity, and intended APVMA classification as a Restricted Chemical Product, sulfuryl fluoride has been included in Schedule 6 of the SUSDP. An ADI of 0.01 mg/kg bw/d has been established for sulfuryl fluoride, based on a NOEC of 20 ppm (approximately equivalent to 1.4 mg/kg bw/d systemic exposure) in a 24-month study of rats and by applying a 100-fold safety factor. The ARfD for sulfuryl fluoride is 0.3 mg/kg bw, based on a NOEC of 300 ppm (approximately equivalent to 31 mg/kg bw/d systemic exposure) observed in an acute neurotoxicity study in rats and by applying a 100-fold factor.

An occupational health and safety risk assessment was based on a consideration of the toxicological hazard and exposure estimates obtained from chemical specific exposure studies. Acceptable margins of exposure were achieved when exposure was mitigated by wearing appropriate PPE. Careful monitoring of sulfuryl fluoride concentration in air prior to re-entry will be required to ensure safety during re-entry.

The toxicology data and other information on the product provided and considered in this assessment justify the Safety Directions established in the present evaluation. Furthermore, the proposed use of 'Profume Gas Fumigant' will not be an undue health hazard to humans according to the criteria stipulated in Section 14 (5)(e) criteria of the Ag/Vet Code Act of 1994. Based on the toxicity profile of sulfuryl fluoride, the approval of the new active constituent sulfuryl fluoride and the registration of the product, Profume Gas Fumigant, is supported.

2. ADVICE & RECOMMENDATIONS TO THE APVMA

- There are no objections on toxicological grounds to the approval of sulfuryl fluoride.
- There are no objections on toxicological grounds and on occupational health grounds to the registration of the product Profume Gas Fumigant, containing 998 g/kg sulfuryl fluoride.

2.1 PUBLIC HEALTH STANDARDS

- The ADI for sulfuryl fluoride is 0.01 mg/kg bw/d. The ADI was established by applying a 100-fold safety factor to a NOEC of 20 ppm (approximately equivalent to 1.4 mg/kg bw/d systemic exposure) in a 24-month rat study.

- The ARfD for sulfuryl fluoride is 0.3 mg/kg bw, based on a NOEC of 300 ppm (approximately equivalent to 31 mg/kg bw/d systemic exposure) in rats and applying a 100-fold safety factor.

- Poison scheduling: At its 47th meeting, in June 2006, the NDPSC agreed that, based upon its moderate acute toxicity, low to moderate inhalation toxicity, and intended APVMA classification as a Restricted Chemical Product, sulfuryl fluoride be included in Schedule 6 of the SUSDP.

2.2 LABEL STATEMENTS

Taking into consideration the potential toxicological hazard, use pattern and likelihood of handler exposure the following first aid instructions and safety directions should appear on the product label:

- **First Aid Instructions (FAI)**

  First Aid Instruction "a" (If poisoning occurs, contact a doctor or Poisons Information Centre. *Phone Australia 131126*) is considered sufficient given the hazard potential of sulfuryl fluoride.

  New Entry Sulfuryl fluoride a

  The code above refers to the following first aid instruction:

  If poisoning occurs, contact a doctor or Poisons Information Centre. a
  Phone Australia 131126; New Zealand 0800 764 766.

- **Safety Directions**

  Based on a consideration of the available toxicological data for the product, the following safety directions will be included in the FAISD Handbook and should be included on the label for Profume Gas Fumigant:

New Entry

		Statement Codes
Sulfuryl fluoride	PS all strengths	129 132 220 222 279 283 290 304 351 360 364

The statement codes above translate into the following safety directions:

Harmful if inhaled. Do not inhale vapour. When using the product, wear supplied air respirator [NB: comment, not for label: this category includes air-hose respirator or air-line respirator or self contained breathing apparatus]. Wash hands after use. After each day's use, wash respirator and if rubber wash with detergent and warm water.

- **Re-entry Statement**

  The following re-entry statements are appropriate for Profume Gas Fumigant:

  "Do not enter treated structures unless instructed to do so by an authorised person"; and

  "Do not allow entry into the treated structures until the concentration of Profume Gas Fumigant is confirmed to be less than 3 ppm, measured with an approved detection device. If prior entry is required, wear supplied air respirator (this includes air-hose respirator or air-line respirator or self contained breathing apparatus)".

- **Warning Statements and General Safety Precautions**

  A suitable stenching agent (e.g. chloropicrin) must be used in conjunction with Profume Gas Fumigant during fumigation.

- **Engineering Controls**

  NIL

3. HAZARD CHARACTERISATION

3.1 CONSOLIDATED SUMMARY OF HAZARD PROFILE

Absorption, distribution, metabolism and excretion in mammals	
Rate and extent of oral absorption	Rapidly absorbed via inhalation exposure (nose only) and maximum concentrations reached near the end of 4-hr exposure. Absorbed dose (radioactivity in urine, faeces and tissues) estimated to be 14% at 30 ppm and 11% of the dose entering lungs at 300 ppm.
Dermal absorption	No data
Distribution	Seven days post-exposure, ^{35}S was evenly distributed among the tissues. Radioactivity was recovered mainly in tissues at the site of first exposure to the gas. Increased fluoride levels were detected in blood and tissues.
Potential for accumulation	No potential for sulfuryl fluoride to accumulate, as sulfuryl fluoride is hydrolysed to fluoride. Repeated exposure may lead to accumulation of fluoride, primarily in teeth or bones.
Rate and extent of excretion	Rapidly excreted, primarily via the urine (>80%). Radioactivity (^{35}S) was rapidly cleared from plasma and RBC with initial half-lives of ~2.5 hr following a 30 ppm exposure and 1-2.5 hr following a 300 ppm exposure. Terminal half-life of radioactivity was *ca* 2.5-fold longer in RBC than plasma.
Metabolism	Initially hydrolysed to fluorosulfate, with release of fluoride, followed by further hydrolysis to sulfate and release of the remaining fluoride.
Toxicologically significant compounds (animals, plants and environment)	Sulfuryl fluoride and fluoride ion.
Toxicologically relevant compounds For Residue Definition	Sulfuryl fluoride and fluoride ion.

Acute toxicity

Rat oral LD_{50} (mg/kg bw)	*ca*. 100 mg/kg bw (bubbled into corn oil, dosed at 40 mL/kg bw)
Worst oral LD_{50} in other species	No data submitted
Rat dermal LD_{50} (mg/kg bw)	No adverse effects from 40300 mg/m^3 (4 hour exposure, whole body except head)
Worst dermal LD_{50} in other species	No data submitted

Rat inhalation LC_{50} (mg/L)	4130-4680 mg/m^3 (4 hour exposure) (991-1122 ppm)
Worst inhalation LC_{50} in other species (only available in mice)	1668 mg/m^3 (4 hour exposure) (400 ppm)
Skin irritation	No skin irritation when exposed to vapours of sulfuryl fluoride in a whole body exposure (head out)
Eye irritation	Lacrimation and rapid blinking observed prior to death in animals exposed to ≥ 6 mg/l in an acute inhalation study.
Skin sensitization	No data submitted, but repeated whole body exposures and human use experience have identified no indications of sensitisation
Short-term toxicity	
Target / critical effect (inhalation)	Local effect on respiratory tract (inhalational exposure): - inflammation (rat, rabbit, dog) & alveolar histiocytosis (rat) Brain–vacuolation (rat/mouse/rabbit/dog) Kidney-mild hyperplasia, tubular degeneration (rat), Overt dental fluorosis (rat)
(oral)	Reduced body weight gain, overt dental fluorosis, renal lesions
Lowest relevant oral NOEL (mg/kg bw/d)	2.5 mg/kg bw/d total fluoride
Lowest relevant dermal NOEL (mg/kg bw/d)	None (no data)
Lowest relevant inhalation NOEC	30 ppm (rat, 2.2 mg/kg bw/d; mouse, 4.1 mg/kg bw/d; rabbit, 1.4 mg/kg bw/d), 100 ppm (dog, 2.9 mg/kg bw/d)
Long-term toxicity and carcinogenicity	
Target/critical effect	Kidney-renal failure (rat); Reduced survival (mice, rats) Brain-minimal vacuolation of cerebrum (mouse, rat) Lung-inflammation & aggregates of macrophages in alveoli (dog)
Lowest relevant NOEC (mg/kg bw/d)	20 ppm (rat, 1.4 mg/kg bw/d)
Carcinogenicity	Not carcinogenic in rats or mice
Reproductive toxicity	
Reproduction target/critical effect	Reproduction: none Parental toxicity: reduced body weight and brain vacuolation Offspring: reduced body weight during lactation
Lowest relevant reproductive NOEC (mg/kg bw/d)	Reproduction-150 ppm (11 mg/kg bw/d)[a] Parental-5 ppm (0.4 mg/kg bw/d) Offspring-20 ppm (1.4 mg/kg bw/d)
Developmental target/critical effect	Rabbit: reduced foetal weights. Not teratogenic.
Lowest relevant developmental NOEC (mg/kg bw/d)	Maternal: 75 ppm (Rabbit, 4.3 mg/kg bw/d) Developmental: 75 ppm (Rabbit, 4.3 mg/kg bw/ d) Teratogenicity: 225 ppm (Rat 16.2 mg/kg bw/d; Rabbits

	4.3 mg/kg bw/d)[a]		
Neurotoxicity / Delayed neurotoxicity			
Acute, 2-day (two 6-hr exposures in 30 hrs) neurotoxicity study in female F344 rats	No effects at the highest concentration tested, 300 ppm (31 mg/kg bw).		
13-week (6-hr exposures, 5 days/week) neurotoxicity study in F344 rats	Mild vacuolation of the brain, slowing of visual auditory and somatosensory evoked potentials at 300 ppm. Evoked potentials slower in female rats and auditory brainstem responses possibly slower in males at 100 ppm. The NOEC was 30 ppm (2.2 mg/kg bw/d). Recovery within 2 months.		
12-month (6-hr exposures, 5 days/week) neurotoxicity study in F344 rats	No effects on the nervous system at the highest concentration tested, NOEC 80 ppm (5.8 mg/kg bw/d).		
Genotoxicity	Some *in vitro* positives, negative *in vivo*.		
Other toxicological studies	None submitted.		
Medical data	In the USA, since 1993, 335 reports of alleged human health effects associated with sulfuryl fluoride. 13 human deaths, primarily from unauthorised entry into the tented fumigated structures. 60% of non-fatal incidents involved symptoms of irritation possibly related to residual chloropicrin (a sensory marker). The next most common (9%) complaint was flu-like symptoms of nausea, diarrhoea, fever, and headache; *ca* 6% complained of shortness of breath or respiratory distress. No findings in production plant workers. Epidemiology studies of fumigators inconclusive.		
Summary	NOEC	Study	Safety factor
ADI = 0.01 mg/kg bw mg/kg bw/d [Reduced survival, renal failure, minimal vacuolation of the cerebrum]	20 ppm (approximately equivalent to 1.4 mg/kg bw/d systemic exposure	Rats, 24-month inhalation study of toxicity and carcinogenicity	100
ARfD = 0.3 mg/kg bw [No effects at the highest dose tested]	300 ppm (approximately equivalent to 31 mg/kg bw systemic exposure)	Rat, acute neurotoxicity inhalation study	100
NOEL for OHS Risk Assessment [Reduced survival, renal failure, minimal vacuolation of the cerebrum]	20 ppm (approximately equivalent to 1.4 mg/kg bw/d systemic exposure	Rats, 24-month inhalation study of toxicity and carcinogenicity	100

[a] Highest level tested

3.2 CHEMISTRY

Approved common name: Sulfuryl fluoride

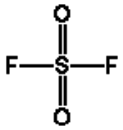
Chemical name: Sulfuryl fluoride (IUPAC)

CAS Registry number: 2699-79-8

Empirical formula: SO_2F_2

Molecular weight: 102.1

Chemical structure:



Isotope label: ^{35}Sulfur

Chemical class: Inorganic acid halides

Chemical and physical properties

Colour:	Colourless
Odour:	The applicant states that odour has not been determined due to hazardous nature of the active constituent. However, the USA EPA RED document on sulfuryl fluoride, the "Fumigation Manual" (Dow AgroSciences, United States Edition), and the IPCS review of sulfuryl fluoride states that sulfuryl fluoride had no odour.
Physical state:	Liquefied gas under pressure
Melting point:	136.7^{0}C (calculation from heat of fusion which was determined cryoscopically)
Density (20^{0}C):	Not determined as the active constituent is a gas
Vapour density	4.3 g/L at 20^{0}C (air is 1)
Specific gravity:	4.18 mg/mL at 25^{0}C and 760 mm Hg
Vapour pressure:	1611467 Pa @ 20^{0}C
Solubility (20^{0}C):	
in water:	1.04 g/L (unbuffered)
in organic solvents:	20 g/L in n-heptane, 25 g/L in xylene & 1,2-dichloroethane, 33 g/L in methanol, 59 g/L in ethyl acetate, 71 g/L in acetone
Hydrolytic Stability:	5.3 days @ pH 2 & 25^{0}C, 3.1 days @ pH 5.9 & 25^{0}C, 6.7 hours @ pH 7 & 20^{0}C, 4.0 min @ pH 9 & 20^{0}C
Flammability:	Non-flammable and will not ignite in the air

Explosive properties:	No danger of explosion when submitted to the effect of a flame or to shock

3.3 TECHNICAL ACTIVE - DECLARATION OF COMPOSITION AND BATCH ANALYSIS

The Declaration of Composition for technical grade sulfuryl fluoride is shown in Appendix I.

3.4 IMPURITIES OF TOXICOLOGICAL CONCERN

An integral part of the safety assessment of an active constituent is a consideration of the chemical composition of the material. Technical-grade active constituents will contain measurable levels of impurities, which can arise during manufacture and/or from subsequent degradation during storage. The chemical identity of these impurities is generally well characterised. The impurities present in the technical-grade material are usually of no particular concern since health standards are established on the basis of toxicology studies conducted using the mixture. However, for those which have high acute toxicity, genotoxicity or teratogenic potential, concentration limits need to be set, so that the toxicological profile of the technical-grade active constituent does not appreciably alter in the event of slight changes in the proportions of the impurities.

The nominal purity of the active constituent as manufactured is 998 g/kg and ethylene dichloride and thionyl fluoride are present as impurities around 1 g/kg with a maximum limit of 3 g/kg (Appendix 1). These impurities present at the indicated levels would not be of any toxicological concern.

3.5 MANUFACTURING OF ACTIVE INGREDIENT AND/OR PRODUCT

Confidential commercial information regarding the formulation details of Profume Gas Fumigant is shown in Appendix II.

The active constituent will be manufactured in USA. The product, Profume Gas Fumigant, will also be formulated in U.S.A. and imported into Australia fully labelled ready for distribution to warehouses and subsequent sale.

3.6 SUMMARY OF TOXICOLOGY STUDIES

All the toxicology studies submitted were performed on a formulated product 'Vikane Gas Fumigant' (synonyms-Profume Gas Fumigant), which contains approximately 99.8% sulfuryl fluoride, the active constituent.

Toxicokinetics and Metabolism Studies

Radiolabelled sulfuryl fluoride was rapidly absorbed via inhalation exposure at 30 or 300 ppm in rats, achieving maximum concentrations of ^{35}S-sulfuryl fluoride-derived radioactivity in both plasma and RBCs near the end of the 4-hr exposure period. Radioactivity was rapidly cleared from plasma and RBCs with initial half-lives of ~2.5 hr following a 30 ppm exposure and 1-2.5 hr following a 300 ppm exposure, but, the terminal half-life of radioactivity was ~2.5-fold longer in RBCs than plasma. Once absorbed, the ^{35}S was rapidly excreted, primarily via the urine (>80%), with a large portion of the absorbed ^{35}S being excreted in the urine during the 4 h

exposure period. Absorbed dose (radioactivity in urine, faeces and tissues) was estimated to be 14% at 30 ppm and 11% of the dose entering lungs at 300 ppm. There is no potential for sulfuryl fluoride to accumulate, as it gets rapidly hydrolysed to fluoride. Repeated exposure may lead to accumulation of fluoride, primarily in teeth or bones (Mendrala et al., 2002).

Percutaneous absorption

Percutaneous absorption studies were not submitted.

Acute Studies

Sulfuryl fluoride was found to be moderately acutely toxic by the oral route (LD_{50}~100 mg/kg bw in rat & guinea pig; sulfuryl fluoride bubbled into corn oil), however, this study was difficult to interpret due to the very high volume of corn oil administered (40 mL/kg bw). A standard dermal toxicity study could not be performed. The acute inhalational toxicity has been investigated in several studies and was found to be low in rats (4130-4675 mg/m^3) but moderate in mice (1668-2800 mg/m^3). Skin and eye irritation tests and a skin sensitisation study have not been conducted.

Short-term Studies

In a 66-day studying rats, animals were fed diets fumigated with sulfuryl fluoride. Growth was retarded in a dose-related manner in all but the lowest dose (19 ppm fluoride) group. There was no mortality reported. The NOEL was 2.5 mg total fluoride/kg bw/d, based on reduced body weight gain and evidence of fluorosis, but this study had limited level of detail in the report and investigated relatively few endpoints (Anon, 1959c).

In a 14-day inhalation study in CD-1 mice, there was no effect in males and females at 30 ppm (125.10 mg/m^3) (approximately equivalent to 4.1 mg/kg bw/d systemic exposure). However, very slight vacuolation in the cerebrum of male and female mice was observed at 100 ppm (417 mg/m^3) (approximately equivalent to 13 mg/kg bw/d systemic exposure) (Nitschke & Quast, 2002)**.**

In a 14 day inhalational toxicity study in F344 rats, there was no effect was at 100 ppm (417 mg/m^3) (approximately equivalent to 7.2 mg/kg bw/d systemic exposure). However, very slight or slight renal hyperplasia was observed in rats at 300 ppm (1251 mg/m^3) (approximately equivalent to 22 mg/kg bw/d systemic exposure) (Eisenbrandt et al., 1985**).**

In a 14-day inhalational toxicity study in rabbits, there was no effect at 100 ppm (417 mg/m^3) (approximately equivalent to 4.1 mg/kg bw/d systemic exposure). However, focal malacia (necrosis) and vacuolation in the cerebrum and inflammation of the respiratory tract was noted at 300 ppm (1251 mg/m^3) (approximately equivalent to 13 mg/kg bw/d systemic exposure) (Eisenbrandt et al., 1985**).**

In a 14-day exploratory inhalation study in Beagle dogs, there was no effect at 100 ppm (417 mg/m^3) (approximately equivalent to 2.9 mg/kg bw/d systemic exposure). However, tremors and tetany were noted beginning with the 5th exposure at 300 ppm (1251 mg/m^3) (approximately equivalent to 8.7 mg/kg bw/d systemic exposure). There were no serum electrolyte or histologic CNS changes found to explain this effect. Also at 300 ppm (1251 mg/m^3), the upper respiratory tract showed histological signs of inflammatory changes (Nitschke and Quast, 1991)**.**

Subchronic Studies

In a 13-week inhalation study in CD-1 mice, the NOEC was 30 ppm (125.10 mg/m^3) (approximately equivalent to 4.1 mg/kg bw/d systemic exposure), primarily based on reduced bodyweight (ca. 10%) and vacuolation in the brain at 100 ppm (417 mg/m^3) (approximately equivalent to 13 mg/kg bw/d systemic exposure). These comprised very slight to slight vacuolation in the cerebrum and thalamus/hypothalamus of males and females (Nitschke and Quast, 1993).

In a 13-week inhalation study in F344 rats, the NOEC was 30 ppm (125.10 mg/m^3) (approximately equivalent to 2.2 mg/kg bw/d systemic exposure), based decreased brain weight in females at exposures levels at 100 ppm (417 mg/m^3) (approximately equivalent to 7.2 mg/kg bw per day) (Nitschke et al., 1987a).

In a 13-week inhalation study in NZW rabbits, the NOEC was 30 ppm (125.10 mg/m^3) (approximately equivalent to 1.4 mg/kg bw/d systemic exposure), based on changes in the upper respiratory tract in one male animal and changes in brain, comprising moderate vacuolation in the cerebrum, in one animal at 100 ppm (417 mg/m^3). At 300 ppm (partially 600 ppm), all rabbits had respiratory tract changes and most had brain changes (Nitschke et al., 1987b).

In a 13-week inhalation study in Beagle dogs, the NOEC was 100 ppm (417 mg/m^3) (approximately equivalent to 2.9 mg/kg bw/d systemic exposure), based on slightly reduced body weights and histopathological changes in the brain at 200 ppm (834 mg/m^3). These comprised very slight, small, bilateral focal vacuolation and gliosis in the putamen region of two of eight dogs at 200 ppm (834 mg/m^3) (the male dog exhibited transient tremors and tetany some time after exposure ended on day 19 but appeared normal at all other times) (Nitschke et al., 1992).

Chronic/Carcinogenicity Studies

Mice (CD-1) were exposed (inhalation-whole body exposure) to targeted concentrations of 0, 5, 20 or 80 ppm (0, 20.85 mg/m^3, 83.4 mg/m^3 or 333.60 mg/m^3) (0, 0.7, 3.0, 12 mg/kg bw/d) sulfuryl fluoride for 6 hours/day, 5 days/week for up to 18 months. The NOEC, for the 1-year study part of the main study, was 20 ppm (83.4 mg/m^3) (approximately equivalent to 3 mg/kg bw/d), based on reduced body weights and microscopic changes in the brain and thyroid at 80 ppm (333.60 mg/m^3) (approximately equivalent to 12 mg/kg bw/d). The NOEC, for the 18-month study, was 20 ppm (83.4 mg/m^3) (approximately equivalent to 3 mg/kg bw/d), based primarily on reduced body weights and microscopic changes in the brain, thyroid, liver and heart at 80 ppm (333.60 mg/m^3) (approximately equivalent to 12 mg/kg bw/d). There was no evidence of oncogenicity in either sex at any exposure concentration. The NOEC for carcinogenicity is 80 ppm (333.60 mg/m^3) (approximately equivalent to 12 mg/kg bw/d), the highest concentration tested. In addition to statistical analyses of the individual tumours, additional statistical procedures (Peto, 1974; McConnell et al, 1996) were carried out to take account of the reduced survival at the highest dose. These did not identify any increases in tumour incidences (Quast et al., 1993a).

Rats (Fischer 344) were exposed (inhalation-whole body exposure) to targeted concentrations of 0, 5, 20 or 80 ppm (0, 20.85 mg/m^3, 83.4 mg/m^3 or 333.60 mg/m^3) (0, 0.4, 1.4, 5.6 mg/kg bw/d) of sulfuryl fluoride for 6 hours/day, 5 days/week for up to 2 years. The NOEC was 20 ppm (83.4

mg/m^3) (approximately equivalent to 1.4 mg/kg bw/d), based on a variety of effects, including increased mortality, low body weights, very slight vacuolation in the brain, kidney pathology with associated clinical chemical effects and effects on other tissues, and pulmonary changes suggestive of irritation at 80 ppm (333.60 mg/m^3) (approximately equivalent to 5.6 mg/kg bw/d). There was no evidence for carcinogenicity in either sex at any exposure concentration up to 80 ppm (333.60 mg/m^3) (approximately equivalent to 5.6 mg/kg bw/d systemic exposure) the highest concentration tested (Quast et al., 1993b).

Dogs (Beagle) were exposed (inhalation-whole body exposure) to targeted concentrations of 0, 20, 80 or 200 ppm (0, 83.4 mg/m^3, 333.60 mg/m^3 or 834 mg/m^3) (0, 0.6, 2.3, 5.8 mg/kg bw/d) sulfuryl fluoride for 6 hrs/day, 5 days/week for one year. However, due to excessive morbidity and mortality by approximately 9 months, the 200 ppm (834 mg/m^3)exposed group of dogs was removed from the study and necropsies. The NOEC was 20 ppm (83.4 mg/m^3) (approximately 0.6 mg/kg bw/d systemic exposure), based on very slight inflammation and aggregates of macrophages in alveoli at 80 ppm (333.60 mg/m^3). The primary effects were respiratory in nature (e.g., severe inflammation) although other changes were evident, notably in the brain (Quast et al., 1993c).

Reproduction Study

Male and female rats were exposed to targeted concentrations of 0, 5, 20 or 150 ppm (0, 20.85 mg/m^3, 83.4 mg/m^3 or 625.5 mg/m^3) (0, 0.4, 1.4, 10.8 mg/kg bw/d) sulfuryl fluoride via inhalation, 6 hours/day, 5 days/week prior to mating. Thereafter, males and females were exposed to these levels for 6 hrs/day, 7 days/week during mating, gestation and lactation (except gestation Day 21 to lactation Day 4, for animal welfare reasons) and through to sacrifice. Sulfuryl fluoride had no effect on reproductive parameters when inhaled by rats at concentration up to and including 150 ppm (625.5 mg/m^3) for 6 hours/day, 5-7 days for up to 20 consecutive weeks. General effects in parental animals were limited to an increased incidence of aggregates of alveolar macrophages in F0 and F1 males and females at 20 ppm (83.4 mg/m^3). At 150 ppm (625.5 mg/m^3), toxicity comprised reduced body weights, dental fluorosis alveolar macrophages and brain vacuolation. The NOEC for reproductive effects was 150 ppm (625.5 mg/m^3) (approximately equivalent to 10.8 mg/kg bw/d systemic exposure), the highest concentration tested. Parental toxicity was evident at 150 ppm (625.5 mg/m^3), toxicity comprised reduced bodyweights, overt dental fluorosis, alveolar macrophages and brain vacuolation. The parental NOEC was 5 ppm (20.85 mg/m^3) (approximately equivalent to 0.4 mg/kg bw/d systemic exposure), based on an increased incidence of aggregates of alveolar macrophages in adult F0 and F1 males and females at 20 ppm (83.4 mg/m^3). Reduced growth in F1 and F2 pups during the lactation period was noted at 150 ppm (625.5 mg/m^3) and was the only effect in offspring. The NOEC in offspring was 20 ppm (83.4 mg/m^3) (approximately equivalent to 1.4 mg/kg bw/d systemic exposure), based on reduced growth during lactation at 150 ppm (625.5 mg/m^3) (Breslin et al., 1992).

Developmental Studies

Mated Fischer 344 rats were exposed to 0, 25, 75 or 225 ppm (0, 104.25 mg/m^3, 312.75 mg/m^3 or 938.25 mg/m^3) (0, 1.8, 5.4, 16.2 mg/kg bw/d) of sulfuryl fluoride via inhalation, for 6 hrs/d on days 6 through 15 of gestation. There was no evidence of maternal toxicity, embryolethality, or fetotoxicity at exposure levels up to 225 ppm (938.25 mg/m^3) of sulfuryl fluoride. The incidences of major malformations, considered either individually or collectively at each exposure level, were not significantly increased in any treatment group when compared to

control values. The incidence of resorptions was not significantly increased among rats in any exposure group indicating that sulfuryl fluoride was not embryolethal at exposure levels as high as 225 ppm (938.25 mg/m^3). The NOEC for maternal and fetotoxicity is 225 ppm (938.25 mg/m^3) (approximately equivalent to 16.2 mg/kg bw/d systemic exposure), the highest dose tested (Hanley et al., 1981).

Inseminated NZW Rabbits were exposed to 0, 25, 75 or 225 ppm (0, 104.25 mg/m^3, 312.75 mg/m^3 or 938.25 mg/m^3) (0, 1.4, 4.3, 13 mg/kg bw/d) of sulfuryl fluoride via inhalation, for 6 hrs/day on days 6 through 18 of gestation. Maternal toxicity, as evidenced by a loss of body weight during gestation, was observed in the 225 ppm (938.25 mg/m^3) exposure group. Decreased foetal bodyweight, indicative of a fetotoxic effect, was also observed at 225 ppm (938.25 mg/m^3). No evidence of maternal toxicity or fetotoxicity was observed among rabbits exposed to 25 ppm (104.25 mg/m^3) or 75 ppm (312.75 mg/m^3) of sulfuryl fluoride. The incidence of resorptions was not significantly increased among rabbits in any exposure group indicating that sulfuryl fluoride was not embryolethal at exposure levels as high as 225 ppm (938.25 mg/m^3)**.** There was no evidence of teratogenicity. The NOEC for maternal and fetotoxicity was 75 ppm (312.75 mg/m^3) (approximately equivalent to 4.3 mg/kg bw/d systemic exposure) (Hanley et al., 1981).

Neurotoxicity Studies

Three studies specifically investigated the neurotoxicity of sulfuryl fluoride: an acute inhalation study in rats, a 13-week inhalation study in rats and a 1-year inhalation study in rats (a satellite group of the chronic / carcinogenicity study).

Fischer 344 rats were exposed to 0, 100 or 300 ppm (0, 417 mg/m^3 or 1251 mg/m^3) sulfuryl fluoride, 6 hrs/day on 2 consecutive days (this was considered to effectively represent an acute exposure of 12 hours in a 30-hour period). The study goals were to evaluate the effects of short-term inhalation exposure to high levels of sulfuryl fluoride on CNS function of Fischer 344 rats. The study was conducted in female rats, as these were considered the most sensitive sex, based on flash evoked potential data, in a 13-week neurotoxicity study. This study focussed on investigating the most sensitive critical (neurological) end-point, visual, auditory and somatosensory evoked potential, when trying to establish an acute NOEC for sulfuryl fluoride. No adverse effects were produced at the highest tested concentration of 300 ppm (1251 mg/m^3) (approximately equivalent to 31 mg/kg bw/d systemic exposure) (Albee et al., 1993).

Rats (Fischer 344) were exposed to 0, 30, 100 or 300 ppm (0, 125.1 mg/m^3, 417 mg/m^3 or 1251 mg/m^3) (0, 2.2, 7.2, 22 mg/kg bw per day) sulfuryl fluoride via inhalation for 6 hr/day, 5 days/week for 13 weeks. Exposure at 300 ppm (1251 mg/m^3) caused diminished weight gain, dental fluorosis, a slight decrease in grooming, slowing of visual, auditory and somatosensory-evoked potentials, mild pulmonary inflammation, and mild vacuolation in the brain (specifically, white fibre tracts of the caudate-putamen). Auditory brainstem responses (ABR's) and brain histopathology were also evaluated two months post-exposure in 2 male and 2 female rats. Both the ABR's and brain histopathology appeared normal at this time, indicating that these treatment effects were essentially reversible. Exposure to 100 ppm (417 mg/m^3) resulted in slight dental fluorosis and minor slowing of some evoked responses. All other measurements, including brain histopathology, were normal. The NOEC was 30 ppm (125.1 mg/m^3) (approximately equivalent to 2.2 mg/kg bw/d systemic exposure), based on alterations in evoked potentials at 100 ppm (417 mg/m^3) in females (Mattson et al., 1986).

The chronic, 1-year, neurotoxicity study was conducted in concert with the 2-year rat inhalation study described earlier (Quast et al, 1993). In this study, rats (Fischer 344) were exposed to target concentrations of 0, 5, 20 or 80 ppm (0, 20.85 mg/m^3, 83.4 mg/m^3 or 333.6 mg/m^3) sulfuryl fluoride via inhalation for 6 hours/day, 5 days/week for approximately 12 months. Sulfuryl fluoride had no effect at any time on handheld and open field observations, grip performance or landing foot splay, and on any aspect of motor activity. Results of the gross and histopathologic evaluations of perfusion fixed tissues for neuropathologic assessment of rats exposed to sulfuryl fluoride for up to 12 months were found to be unaffected by exposure. The neurotoxicologic NOEC for this study was ≥ 80 ppm (333.6 mg/m^3) (approximately equivalent to 5.6 mg/kg bw/d systemic exposure), the highest concentration tested (Sepncer et al., 1994).

Genotoxicity Studies

Sulfuryl fluoride showed no genotoxic potential in *in vitro* tests for bacterial cell mutation or unscheduled DNA synthesis in mammalian cells. The *in vitro* tests for mutagenicity and clastogenicity in mammalian cells (mouse lymphoma TK$^{+/-}$ and rat lymphocytes) were positive, consistent with the database on fluoride ion genotoxicity. An *in vivo* micronuleus test with sulfuryl fluoride was negative. Exposures would be predominantly to fluoride ion as sulfuryl fluoride is a highly reactive compound. Furthermore, fluoride is considered not to represent an *in vivo* genotoxic risk to humans.

Other Studies

Incapacitation study

In order to estimate the rapidity with which sulfuryl fluoride might incapacitate an individual, rats were exposed via inhalation to 4,000, 10,000, 20,000 or 40,000 ppm (16680 mg/m^3, 41700 mg/m^3, 83400 mg/m^3 or 166800 mg/m^3) sulfuryl fluoride in a 14 litre cylindrical chamber that contained a motor-driven activity wheel. There was a clear dose-related decrease in the time the animals maintained the ability to walk as the concentration of sulfuryl fluoride increased. Animals from the 20,000 (83400 mg/m^3) and 40, 000 ppm (166800 mg/m^3) groups were unable to walk within 12 minutes and died less than 10 minutes later. The 10,000 ppm (41700 mg/m^3) group remained functional longer and lived for approximately 60 minutes after the exposure was discontinued. The rats exposed to 4,000 ppm (16680 mg/m^3) were able to walk considerably longer and lived for approximately 2.5 hours after the exposure was stopped. All rats had tonic convulsions prior to death. Necropsy revealed signs compatible with cardiovascular failure and acute death. Generally, there was a concentration-dependent increase in pulmonary congestion, oedema and haemorrhage (Albee et al., 1983).

Study on effect on physiological parameters

Experiments were conducted on rats exposed to 4000 ppm (16680 mg/m^3) or 20,000 ppm (83400 mg/m^3) sulfuryl fluoride via inhalation to investigate EEG, ECG, blood pressure, heart rate, body temperature (with and without water jacket) and respiration rate. The response to sulfuryl fluoride was similar between exposure levels and included a decrease in heart rate, a gradual increase in blood pressure (culminating in a rapid increase in systolic and pulse pressure just prior to death), decreased respiration, occasional spiking and high frequency loss in the EEG, and power loss in the EEG. Grossly, the rats exhibited paleness of the extremities and felt cold when removed from the exposure restraint. All physiological parameters ceased to function at about the same time the animals expired regardless of the dose level. No parameter was affected first and subsequently precipitated the death of the animal. Artificial maintenance of

body temperature did not increase survival time; therefore, the loss of body temperature did not contribute significantly to the cause of death (Gorzinski et al., 1985).

Study on ultrastructural assessment of the lungs of rats exposed to high concentrations of sulfuryl fluoride

An ultrastructural assessment of the lungs of rats exposed to high concentrations of sulfuryl fluoride via inhalation has also been conducted. Morphological changes in the lungs of rats exposed to 4000 ppm (16680 mg/m^3) sulfuryl fluoride were minimal and probably were not a significant factor in the death of the animals. On the other hand, extensive injury to the lungs of rats exposed to 20,000 ppm (83400 mg/m^3) sulfuryl fluoride probably compromised pulmonary function and contributed to the death of the animals. Factors other than pulmonary injury probably were involved in the death of animals at both concentrations (Eisenbrandt et al., 1987).

Antidote study

A study was performed to investigate the protective and therapeutic effectiveness of calcium gluconate (the recommended antidote for fluoride toxicity), and three anticonvulsants (phenobarbital, diazepam or diphenylhydantoin) in animals exposed to lethal concentration of sulfuryl fluoride. This study showed calcium gluconate and phenobarbital, given before or after exposure to sulfuryl fluoride, appeared to ameliorate the acute toxic effects (seizures) and lethality in rats exposed to sulfuryl fluoride at 4,000 ppm (16680 mg/m^3) but not at 10,000 ppm (41700 mg/m^3). Treatment with diazepam followed by exposure to sulfuryl fluoride was relatively effective. However, treatment with diazepam after exposure to sulfuryl fluoride was not effective. Diphenylhydantoin is contra-indicated, inducing more severe seizures than seen in sulfuryl fluoride only animals (Nitschke & Miller, 1985**)**.

Medical data

Sulfuryl fluoride has been used as a structural fumigant under the trade name 'Vikane' for over 40 years. Manufacturing plant health surveillance examinations revealed no significant sulfuryl fluoride-related health problems among employees. Since 1993, 335 reports of alleged human health effects associated with Vikane use have been reported to the U.S. EPA by Dow AgroSciences. There were 13 human deaths, primarily resulting from unauthorised entry into the tented fumigated structures, but the lethal concentration has not been determined. Over 300 incidents of non-lethal, adverse effects had symptoms of irritation of eyes and respiratory tract, headache, nausea, fever and diarrhoea; some of these might be due to exposure to chloropicrin used as a sensory marker.

Two epidemiological investigations of sulfuryl fluoride and methyl bromide fumigators have reported a small number of findings in the sulfuryl fluoride cohorts. Some of these findings appear to be related to physical activities associated with the fumigation process. Others present no clear pattern that can be attributed to the use of sulfuryl fluoride. In neither study, there was any biomonitoring to assess exposure (Anger et al., 1986, Calvert et al., 1998).

3.7 DISCUSSION OF TOXICITY DATA

Dow Agrosciences Australia Ltd has submitted adequate data to characterise the toxicological hazard of the new active constituent sulfuryl fluoride. However, the absence of suitable studies on sulfuryl fluoride following oral exposure is the main deficiency.

Toxicokinetics and Metabolism

Sulfuryl fluoride was rapidly absorbed via inhalation exposure in rats, achieving maximum concentrations in plasma and RBCs near the end of the 4-hr exposure period. Absorbed dose was estimated to be 14% and 11% of the dose entering lungs at 30 and 300 ppm, respectively. Sulfuryl fluoride was rapidly excreted, primarily via the urine (>80%), with a large portion being excreted in the urine during the 4 h exposure period. The identification of fluorosulfate and sulfate in blood and urine suggests that sulfuryl fluoride is rapidly hydrolysed to fluorosulfate, with release of fluoride, followed by further hydrolysis to sulfate and release of the remaining fluoride. This metabolism is supported by increases in fluoride detected in the blood and urine following exposure of rats to sulfuryl fluoride. There is no potential for sulfuryl fluoride to accumulate as it rapidly hydrolysed to fluoride. However, repeated exposure may lead to accumulation of fluoride, primarily in teeth or bones.

Percutaneous absorption

Percutaneous absorptions studies were not submitted. However, as sulfuryl fluoride is gas and will be in the vapour form when released, percutaneous absorption is expected to be low.

Acute toxicity

Sulfuryl fluoride was found to be moderately acutely toxic by the oral route in rats. As sulfuryl fluoride is a gas, standard dermal toxicity study could not be performed. However, whole body (excluding head) exposure did not indicate any significant toxicity via the dermal route. Sulfuryl fluoride was found to be of low to moderate inhalation toxicity in rats and mice, respectively. Skin and eye irritation tests and a skin sensitisation study have not been conducted. However, whole body exposures and experience in humans over a period of 40 years of use indicated that sulfuryl fluoride is not a significant irritant, nor a skin sensitizer. Exposure of humans at high concentrations within enclosed structural fumigation areas has resulted in death. Mechanistic studies on 'time to acute incapacitation' have revealed an approximately linear relationship between concentration and exposure duration.

Repeat dose toxicity

Sulfuryl fluoride have been studied for its short-term (2 week) repeat dose inhalation toxicity in mice, rats, rabbits, and dogs; in most experiments, the exposure period was 6h/day, 5 days /week. Mice were the most susceptible species in these short-term studies and the main effect of brain vacuolation was noted at 100 ppm (417 mg/m^3). Renal hyperplasia was only observed in rats at 300 ppm (1251 mg/m^3). Respiratory tract changes were present in rabbits and dogs at 300 ppm (1251 mg/m^3). In addition, focal malacia (necrosis) and vacuolation in the cerebrum in rabbits and tremors and tetany in dogs were noted at 300 ppm (1251 mg/m^3). In a 66 days oral study in rats fed diets fumigated with sulfuryl fluoride, the main effect noted was reduced body weight gain and the evidence of fluorosis at 53 ppm fluoride in the diet (net amount of fluoride above the control diet value of 36 ppm fluoride in the fumigated diet).

In 90-days/13-weeks inhalation studies, the main effect was noted on the brain in all the species tested. Vacuolation in the brain in mice and rabbits and decreased brain weight in female rats were observed at 100 ppm (417 mg/m^3). In dogs, histopathological changes in the brain (vacuolation & gliosis) were present at 200 ppm (834 mg/m^3). In addition, dental fluorosis (mottled teeth) in rats at 100 ppm (417 mg/m^3) and slightly reduced body weights in males and females were observed in dogs at 200 ppm (834 mg/m^3).

The principal effects of chronic inhalation exposure were observed in brain in mice, kidney and brain in rats and lungs in dogs. In mice, reduced survival and slight vacuolation in the cerebrum was observed at 80 ppm (334 mg/m^3) (approximately equivalent to 12 mg/kg bw/d systemic exposure). The microscopic changes in mice paralleled to some extent the observations made in the subchronic study exposed to 100 ppm sulfuryl fluoride, although the changes in the caudate putamen were not seen in the present study.

The chronic effects in rats were reduced survival, brain vacuolation, pulmonary changes suggestive of irritation, chronic progressive glomerular nephrosis and associated lesions such as fibrous osteodystrophy in both sexes exposed at 80 ppm (334 mg/m^3) (approximately equivalent to 5.6 mg/kg bw/d systemic exposure). It is significant that renal damage was only present in rats and not in mice and dogs during chronic exposure. Because of the lack of renal toxicity in Sprague-Dawley rats (two-generation reproduction study-Breslin et al., 1992, reviewed in this report), CD-1 mice (18-month study), New Zealand White rabbits (subchronic study) and Beagle dogs (1-year study) following sulfuryl fluoride exposure, it is likely that Fischer 344 rats may be uniquely sensitive to developing renal toxicity following repetitive exposure to sulfuryl fluoride.

The chronic effects in dogs were very slight inflammation and aggregates of macrophages in alveoli at 80 ppm (334 mg/m^3) (approximately equivalent to 2.3 mg/kg bw/d systemic exposure). The highest concentration of 200 ppm (834 mg/m^3) was not tolerated beyond approximately 9 months, when this level was terminated due to decline in health status. This does not indicate increased susceptibility of dogs to sulfuryl fluoride as this dose level (200 ppm) was only tested in dogs and not in mice and rats. The highest dose level tested in these species was only 80 ppm (334 mg/m^3).

Slight dental fluorosis was the most sensitive effect in the 13 week rat and 1 year dog studies but it is considered that the slight dental fluorosis was not an adverse finding. Although no specific investigations were performed on other end points associated with excess fluoride exposure e.g. bone density, the NOECs used for risk assessment provided adequate protection for the bone effects of fluoride as such effects are considered to be at least 3 fold less sensitive than dental fluorosis based on human observations.

Reproduction & developmental effects

Sulfuryl fluoride had no effect on reproductive parameters when inhaled by rats in a 2-generation reproduction study at concentrations up to and including 150 ppm (approximately equivalent to 11 mg/kg bw/d), 5-7 days a week for up to 20 consecutive weeks. Sulfuryl fluoride has been tested for developmental effects in both rats and rabbits and showed no teratogenic effect in either species when inhaled. The pregnant rabbits were somewhat more sensitive to sulfuryl fluoride (in terms of toxicity) than were pregnant rats. In the rat, there were no adverse effects on dams or offspring at concentrations up to and including 225 ppm. In rabbits, however, there was slight toxicity to dams and offspring at 225 ppm, which was manifested by reduced bodyweights and lower foetal weights.

Neurotoxicity effects

Three studies specifically investigated the neurotoxicity of sulfuryl fluoride: an acute inhalation study in rats, a 13-week inhalation study in rats and a 1-year inhalation study in rats. The 13-week study (6-hr exposures, 5 days/week) demonstrated that the most sensitive indicator of effects on the nervous system was a change in evoked potentials (visual, auditory and

somatosensory). Visual and somatosensory evoked potentials were significantly slower in female rats and auditory brainstem responses were possibly slower in males at 100 ppm. Only at 300 ppm, there were histological effects evident, in the form of mild vacuolation in the brain (specifically, white fibre tracts of the caudate-putamen). In an acute neurotoxicity study (two 6-hr exposures in 30 hours) in female rats, no adverse effects were produced on neurophysiological and behavioural investigations, including evoked potentials at the highest concentration tested (300 ppm). However, there were no investigations of brain histopathology in this study. In a chronic, 1-year neurotoxicity study (6-hr exposures, 5 days/week) in male and female rats, which included a FOB, motor activity tests, fore- and hindlimb grip strength, hindlimb landing foot splay and neurohistopathology with perfusion fixation, there were no effects on the nervous system at the highest concentration tested (80 ppm). Based on these studies, it is concluded that the nervous system is not uniquely sensitive to sulfuryl fluoride as the NOECs for neurotoxic effects were as high as or higher than the NOECs for general toxicity.

Carcinogenicity potentials

No carcinogenic effects were observed in the 18 month mouse study or the 24 month rat study. Sulfuryl fluoride showed no genotoxic potential in *in vitro* tests for bacterial cell mutation or unscheduled DNA synthesis in mammalian cells. The *in vitro* tests for mutagenicity and clastogenicity in mammalian cells (mouse lymphoma $TK^{+/-}$ and rat lymphocytes) were positive, consistent with the database on fluoride ion genotoxicity. An *in vivo* micronucleus test with sulfuryl fluoride was negative. As sulfuryl fluoride is a highly reactive compound, exposures would be predominantly to fluoride ion. It is generally recognised that fluoride does not represent an *in vivo* genotoxic risk to humans. Therefore, in view of the negative *in vivo* genotoxicity data and the absence of carcinogenicity in mice and rats, it is concluded that sulfuryl fluoride is unlikely to pose a carcinogenic risk to humans.

Antidote potentials

Since there is no known antidote available for sulfuryl fluoride poisoning and a study was performed to investigate the protective and therapeutic effectiveness of calcium gluconate (the recommended antidote for fluoride toxicity) and three anticonvulsants (phenobarbital, diazepam or diphenylhydantoin) in rats exposed to lethal concentration of sulfuryl fluoride. This study showed that calcium gluconate and phenobarbital, given before or after exposure to sulfuryl fluoride, appeared to ameliorate the acute toxic effects of sulfuryl fluoride in rats, at 4,000 ppm but not at 10,000 ppm. Treatment with diazepam followed by exposure to sulfuryl fluoride was relatively effective.

Human exposure

Manufacturing plant health surveillance examinations revealed no significant sulfuryl fluoride-related health problems among the employees during its use for about 40 years. Since 1993, 335 reports of alleged human health effects associated with Vikane use have been reported to the U.S. EPA by Dow AgroSciences. Most of the human deaths have resulted from unauthorised entry into the tented fumigated structures. However, lethal concentrations resulting into theses deaths have not been determined. Incidents of non-lethal, adverse effects had symptoms of irritation of eyes and respiratory tract, headache, nausea, fever and diarrhoea. As chloropicrin (a stenching agent) was also used, it is possible that some of these affects might be due to exposure to chloropicrin rather than sulfuryl fluoride. In two epidemiological investigations of sulfuryl fluoride and methyl bromide fumigators, there were no clear effects that could be attributed to

the use of sulfuryl fluoride. However, biomonitoring was not conducted in these studies to assess exposure to sulfuryl fluoride.

3.7 DOSE LEVELS RELEVANT FOR DIETARY RISK ASSESSMENT

To convert sulfuryl fluoride concentrations in air (mg/m^3) to a systemic dose (mg/kg bw/d), account was taken of the daily respiratory volume of the laboratory animals (rats 0.96 m^3/kg bw; rabbits 0.54 m^3/kg bw; mice 1.8 m^3/kg bw and dogs 0.39 m^3/kg bw; Zielhuis & vanderKreek, 1979), the duration of exposure (hours/day and days/week) and the proportion (10%) of the inspired dose that was absorbed (based on the toxicokinetic study of Mendrala et al, 2002).

3.8.1 Acceptable Daily Intake (ADI)

To determine the appropriate NOEL for the establishment of an ADI, a summary of the NOELs determined in those studies deemed adequate for regulatory purposes is shown in the Table below.

Summary of NOELs relevant for risk assessment

Species	Study	Effect	NOEC	LOEC	Reference
Rabbit	90 day (6 h/day, 5 days/week), whole body exposure	Toxicity	30 ppm (1.4 mg/kg bw/d)	100 ppm (4.1 mg/kg bw/d)	Nitschke, K.D. Zimmer, M. A., and Eisenbrandt, D.L. (1987)
Dog	1 year (6 h/day, 5 days/week), whole body exposure	Toxicity & mortality	20 ppm (0.6 mg/kg bw/d)	80 ppm (2.3 mg/kg bw/d)	Quast, J.F., Beckman, M.J., Nitschke, K.D. (1993)
Mouse	18 month (6h/day, 5 days/week) whole body exposure	Toxicity	20 ppm (3.0 mg/kg bw/d)	80 ppm (12 mg/kg bw/d)	Quast, J.F., Bradley, G.J., Nitschke, K.D. (1993)
		Carcinogenicity	80 ppm[a] (12 mg/kg bw/d)	-	
Rat	2 year (6 h/day, 5 days/week) whole body exposure	Toxicity	20 ppm (1.4 mg/kg bw/)	80 ppm (5.6 mg/kg bw/d)	Quast, J.F., Bradley, G.J., Nitschke, K.D. (1993)
		Carcinogenicity	80 ppm[a] (5.6 mg/kg bw/)	-	
	2-generation reproductive toxicity (6 h/day, 5 days/week) whole body exposure	Reproduction	150 ppm[a] (10.8 mg/kg bw/d)	-	Breslin, W.J., Liberacki, A.B., Kirk, H.D., Bradley, G.J., Crissman, J.W. (1992)
		Offspring	20 ppm (1.4 mg/kg bw/d)	80 ppm (5.6 mg/kg bw/d)	
		Parental	5 ppm (0.4 mg/kg bw/d)	20 ppm (1.4 mg/kg/d)	
	Developmental toxicity (6 h/day, 5 days/week) whole body exposure	Maternal	225 ppm[a] (16 mg/kg bw/d)	-	Hanley, T.R., Jr., Calhoun, L.L., Kociba, R.J., Cobel-Geard, S.R., Hayes, W.C., Ouellette, J.H., Scherbarth, L. M., Sutter, B. N., John, J.A. (1981).
		Developmental	225 ppm[a] (16 mg/kg bw/d)	-	
Rabbit	Developmental toxicity study (6 h/day, 5 days/week), whole body exposure	Maternal	75 ppm (4.3 mg/kg bw/d)	225 ppm (13 mg/kg bw/d)	Hanley, T.R., Jr., Calhoun, L.L., Kociba, R.J., Cobel-Geard, S.R., Hayes, W.C., Ouellette, J.H., Scherbarth, L. M., Sutter, B. N., John, J.A. (1981).
		Developmental	75 ppm (4.3 mg/kg bw/d)	225 ppm (13 mg/kg bw/d)	

[a] - Highest level tested

The critical toxicity studies with sulfuryl fluoride used inhalation exposures and whilst this would result in a significant systemic dose of fluoride, it was impossible to separate reliably the effects due to systemic exposure to fluoride with those due to gaseous sulfuryl fluoride. The lowest NOEC was obtained in a 24-month study of rats exposed to sulfuryl fluoride by inhalation, based on effects on the kidney, brain, bone and survival at 80 ppm. It is noted that some of the endpoints in the rat chronic study, such as kidney toxicity, were consistent with the data on fluoride toxicity. The slight dental fluorosis observed at the NOEC was not considered to be a toxicologically significant finding. Increase in fluoride levels in tissue and blood are considered to be a marker of exposure and not an adverse effect *per se*.

An ADI of 0.01 mg/kg bw/d, based on a NOEC of 20 ppm (approximately equivalent to 1.4 mg/kg bw/d systemic exposure) can be established by applying a 100-fold safety factor to the NOEC of 1.4 mg/kg bw/d. A 100-fold safety factor was chosen to account for interspecies extrapolation and intraspecies variability and the adequacy of the toxicological database.

Whilst it is recognised that that any residues in food resulting from the use of sulfuryl fluoride fumigation would primarily be in the form of fluoride. There were no studies submitted that would enable the establishment of a reference value for fluoride. Any consideration of the dietary fluoride intake associated with the use of sulfuryl fluoride as a fumigant should be included in an overall assessment of fluoride from all sources.

3.8.2 Acute reference dose (ARfD)

Since the acute oral LD_{50} was reported to be *ca* 100 mg/kg bw there is a need to derive an ARfD. The only appropriate study in the database for deriving an ARfD was the acute neurotoxicity study in rats. It was recognised that the use of this study was likely to result in a conservative assessment and was probably not relevant to dietary intake of residue, which will probably be in the form of fluoride ion. There was no clear evidence for any acute systemic toxicity due to sulfuryl fluoride exposure *per se* rather than the fluoride ion. The critical endpoint of brain vacuolation, which had not been evaluated in the acute neurotoxicity study, was considered unlikely to be an acute effect. An ARfD of 0.3 mg/kg bw for sulfuryl fluoride, was established on the basis of a NOEC of 300 ppm (1251 mg/m^3) (approximately equivalent to 31 mg/kg bw per day systemic exposure) and a 100-fold safety factor. The concentration of 300 ppm (1251 mg/m^3) was the highest tested in a short-term (2 days) neurotoxicity study in rats (Albee et al, 1993).

3.9 SELECTION OF A NOEL FOR OHS RISK ASSESSMENT PURPOSES

As the product will only be available for use by PCOs, a chronic exposure NOEC is appropriate for the risk assessment. Therefore, a NOEC of 20 ppm, observed in a 2-year rat study is used for fumigators and aerators (Quast et al., 1993b).

For bystander and re-entry risk where inhalational exposure is expected to be transient, a NOEC of 300 ppm is appropriate. This value was observed in a short-term (2-days) inhalational neurotoxicity study in rats (Albee et al., 1993).

3.10 POISONS SCHEDULE CONSIDERATIONS

Sulfuryl fluoride
Sulfuryl fluoride is currently registered as Vikane Gas Fumigant for non-food use in the USA, Germany, Sweden and Norway, Puerto Rico, Indonesia and Japan and as Profume Gas Fumigant for food use in the USA, UK, Germany and Switzerland. Accidental high levels of exposure during the long-term and extensive usage of Vikane Gas Fumigant in North America over 40 years have resulted from unauthorised entry into fumigated structures.

Acute toxicity:

- Moderate oral toxicity in rats (LD_{50}~100 mg/kg bw; sulfuryl fluoride bubbled into corn oil). However, this study was difficult to interpret due to the very high volume of corn oil administered (40 mL/kg bw).
- No data submitted on standard dermal toxicity study due to the nature of the active constituent (gas).
- The inhalation LC_{50} was 4130 mg/m^3 in rats and between 1668 and 2502 mg/m^3 in mice.

- No skin irritation when exposed to vapours of sulfuryl fluoride in a whole body exposure (head out).
- No data submitted on eye irritation and skin sensitisation due to the nature of the active constituent (gas). However, lacrimation and rapid blinking were observed prior to death in animals exposed to ≥ 6 mg/l in an acute inhalation study and whole body exposures and experience in humans over a period of 40 years of use indicate that sulfuryl fluoride is not a significant eye irritant, nor a skin sensitizer.

Repeat dose studies:

- In repeat dose inhalation studies, the principal effects in rats were reduced survival, brain vacuolation, and chronic progressive glomerular nephrosis. In mice, the principal effects were reduced survival and slight vacuolation in the cerebrum. In dog, the principal effects were reduced survival and respiratory changes (inflammation).

Carcinogenic potential:

- No carcinogenic effects were observed in long-term inhalation studies in mouse (18 month) or in rat (24 month).

Reproduction:

- No effect on reproductive parameters when inhaled by rats in a 2-generation reproduction study at concentrations up to and including 150 ppm (625.5 mg/m^3) (approximately equivalent to 11 mg/kg bw per day systemic exposure). Reduced bodyweight gain in F1 and F2 pups during the lactation period was observed at 150 ppm (625.5 mg/m^3).

Developmental effects:

- No teratogenicity was observed in rat and rabbit inhalation studies. In rats, there was no evidence of maternal toxicity, embryolethality, or fetotoxicity at exposure levels up to 225 ppm (938.25 mg/m^3) (approximately equivalent to 16.2 mg/kg bw/d systemic exposure), the highest dose tested. In rabbits, there was slight toxicity to dams and offspring at 225 ppm (938.25 mg/m^3) (approximately equivalent to 13 mg/kg bw/d systemic exposure), which was manifested by reduced bodyweights and lower foetal weights.

Genotoxic potential:

- A battery of tests found no evidence that sulfuryl fluoride has genotoxic potential.

At its 47th meeting, in June 2006, the NDPSC agreed that, based upon its moderate acute toxicity, low to moderate inhalation toxicity, and intended APVMA classification as a Restricted Chemical Product, sulfuryl fluoride be included in Schedule 6 of the SUSDP.

4 EVALUATION OF SUBMITTED STUDIES

4.1 TOXICOKINETICS AND METABOLISM

Oral Route:

No data were submitted.

Inhalation route:

1. Mendrala, AL, et al (2002): Sulfuryl Fluoride: Pharmacokinetics and metabolism in Fischer 344 rats. Dow AgroSciences LLC. Report No. DECO HET K-016399-059. Unpublished. Report date: 22 May 2002.

Test Compound:	Sulfuryl fluoride (99.8% purity for non-radiolabelled test compound and 100% radiochemical purity for radiolabelled test compound (^{35}S labelled)-specific activity 0.22 – 0.25 mCi/mmol)
Batch No:	OC16160101 (non-radiolabelled), 901-059-010 (radiolabelled)
Test Species:	Rat, Fisher, male, 197-242 g bw, jugular vein cannulated rats from Hilltop Lab Animals Inc (Scottsdale, Pennsylvania) and non-cannulated rats from Charles River Laboratories (Raleigh, North Carolina)
Study Duration:	Study started on 26 March 2001 & completed on 22 May 2002
Laboratory:	Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan 48674
GLP& QA:	Yes
Guidelines:	USEPA (OPPTS 870.7485, 1998); OECD (Guideline 417, 1984); EEC (Part B.36, 87/302/EEC, 1986)

***Study design*:**

Animals were exposed to sulfuryl fluoride gas (SO_2F_2) via inhalation (nose-only chamber) at targeted time-weighted average (TWA) concentrations of 30 ppm (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) (see table below). These exposure concentrations were selected based on the 4-h LC_{50} value for rats of 991-1122 ppm (4130-4680 mg/m^3) (Miller *et al*., 1980).

Non-cannulated animals exposed to radiolabelled fluoride were housed one per cage in glass Roth-type metabolism cages during exposure. Non-cannulated animals exposed to non-radiolabelled fluoride were housed one per cage in stainless steel cages. Cannulated animals were housed in plastic tubs with corncob bedding for the duration of blood collection. Animals were provided with LabDiet Certified Diet in pelleted form. Analysis of the feed was performed to confirm that the diet provided adequate nutrition and to quantify the levels of selected contaminants.

Animals were assigned to the treatment groups and specimens were collected as shown in the table below.

Summary of experimental design

Target dose level	Number of animals		Specimen collection
	Jugular vein cannulated	Non-cannulated	
30 ppm (125.10 mg/m^3) ^{35}sulfuryl fluoride [specific activity 0.26 µCi/litre]	4	4	Venous blood samples were collected via jugular cannulae at 0.25, 0.5, 1, 2, 3 and 4 h during the inhalation exposure and at 0.5, 1, 2, 4, 6, 12, 24, 36, 48, 72, 96, 120, 144 and 168-h post-exposure. The sampling times are designated in the text and tables as –3.75, -3.5, -3, -2, -1, and 0 h for the 0.25, 0.5, 1, 2, 3 and 4 h, respectively, for the samples collected during exposure. When the animals were killed, blood was obtained via cardiac puncture. Excreta was collected in dry-ice cooled traps - urine: 0 h (end of exposure) and at 6, 12, 24, 48, 72, 96, 120, 144 and 168-h post-exposure; faeces: 0 h and at 24, 48, 72, 96, 120, 144 and 168-h post-exposure. Selected tissues (brain, gastrointestinal tract, kidneys, liver, lungs, perirenal fat, residual carcass, respiratory turbinates, olfactory turbinates, skin, spleen) were collected 7-days post exposure and analysed for radioactivity. Blood, urine, and faeces were analysed for radioactivity including ^{35}S-labelled fluorosulphate, sulphate and fluoride (urine and faeces only).
300 ppm (1251 mg/m^3) ^{35}sulfuryl fluoride [specific activity 2.8 µCi/litre]	4	4	As above
30 ppm (125.10 mg/m^3) non-radiolabelled sulfuryl fluoride	0	18	Groups of three rats were sacrificed at -2 h (during exposure), at 0 h (end of exposure), and at 2, 4, 8 and 20 h post-exposure. When the animals were killed, blood was obtained via cardiac puncture and the brain and kidney tissues were collected and analysed for fluoride ion.
300 ppm (1251 mg/m^3) non-radiolabelled sulfuryl fluoride	0	18	As above
0 ppm (control group)	0	8	Groups of two rats were killed at -4, 0, 4 and 8 h. Blood was obtained when the animals were killed via cardiac puncture. Brain and kidney tissues were also collected for analyses.

Chamber concentrations of 30 ppm (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) ppm were generated using a pump, which delivered the test substance at a set rate to the inlet of the chamber, where the gas was mixed with the appropriate amount of dry, compressed air. The jugular vein cannulated animals were used only during the radiolabelled portion of the study for blood sampling during and post-exposure. All other specimens were collected from non-cannulated animals. Chamber concentration of the test material was checked at least three times during exposure by drawing a sample of air from the breathing zone of the chamber through a closed gas-sampling loop.

The radioactivity of ^{35}S was quantified by liquid scintillation counting (LSC). The concentration of fluoride ion in the urine of rats exposed to both concentrations of ^{35}S-sulfuryl fluoride was determined using an ion selective electrode (ISE). In addition, ISE determination of the fluoride

ion concentration in the plasma, and the brain and kidney tissue homogenates, of rats exposed to both concentrations of non-radiolabelled sulfuryl fluoride was conducted. Selected samples of urine and faeces were pooled and underwent radiochemical profile analysis for possible metabolite identification.

Results:

The target exposure concentration of 30 ppm (125.10 mg/m^3) ^{35}S-sulfuryl fluoride had an actual TWA of 28.4 ppm (118.43 mg/m^3) during the 4 h exposure period and that for the non-radiolabelled 30 ppm (125.10 mg/m^3) group was 31.2 ppm (130.10 mg/m^3). The targeted exposure concentration of 300 ppm (1251 mg/m^3) ^{35}S-sulfuryl fluoride had an actual TWA of 274 ppm (1142.58 mg/m^3) during the 4 h exposure period, whilst the non-radiolabelled 300 ppm (1251 mg/m^3) exposure had a TWA of 312 ppm (1301 mg/m^3). No radioactivity was detected in the 0-24 h post-dosing charcoal traps following the 300 ppm (1251 mg/m^3) exposure. Therefore, expired air was not collected during the remainder of the 300 ppm (1251 mg/m^3) sample collection period nor in the case of the 30 ppm (125.10 mg/m^3) exposure group.

There were no mortalities during the study.

Absorption

Plasma radioactivity: In the case of a dose level of 30 ppm (125.10 mg/m^3), plasma radioactivity levels were increased during the exposure period and reached the maximum concentration of 5.2 µg equivalent/g (µg-eq/g) at the end of the exposure period (see table below). Plasma levels of radioactivity never reached steady-state conditions during the exposure. At a dose level of 300 ppm (1251 mg/m^3), plasma levels rapidly increased throughout the exposure period and reached the maximum concentration of 37.7 µg equivalent/g (µg-eq/g) at 15 minutes after termination of exposure. Plasma levels of radioactivity increased throughout the exposure period and similar to the 30 ppm (125.10 mg/m^3), exposure, never reached steady-state conditions.

Red blood cell (RBC) radioactivity: Following the 30 ppm (125.10 mg/m^3) exposure, peak RBC radioactivity of 4.7 µg-eq/g RBC was noted at the end of the exposure period (see table below). Following the 300 ppm exposure, peak RBC radioactivity of 40.3 µg-eq/g RBC was also noted at the end of the exposure period. Therefore, test substance concentrations in RBCs were similar to that in plasma. Radioactivity remained at measurable, albeit small, concentrations until sacrifice at 168 h post exposure in the 30 ppm (125.10 mg/m^3) grup and relatively high in 300 ppm (1251 mg/m^3) group.

Radioactivity in plasma and RBC during and following nose-only exposure to 30 or 300 ppm sulfuryl fluoride for 4 h

Sampling time	Dose group			
	30 ppm (125.10 mg/m^3)		300 ppm (1251 mg/m^3)	
	Concentration (µg-eq/g)			
	Plasma*	RBC*	Plasma*	RBC*
During exposure (h)				
-4.00	NQ (<0.37)	NQ (<1.13)	NS	NS
-3.75	NQ (<0.33)	NQ (<0.61)	11.33	7.96
-3.50	1.01	NQ (<0.63)	16.01	12.72
-3.00	1.89	1.32	22.09	19.28
-2.00	3.31	2.48	29.51	27.53
-1.00	4.44	3.67	28.40	28.78
0.00	5.18	4.67	37.52	40.32
Post-exposure period (h)				
0.50	4.717	4.16	37.65	38.00
1.00	4.435	3.74	33.21	47.90
2.00	3.039	3.39	25.03	32.67
4.00	1.901	2.87	16.02	24.53
6.00	1.512	2.47	12.53	25.80
12.00	0.949	2.50	7.94	24.99
24.00	0.529	2.26	4.98	22.85
36.00	0.422	1.77	4.34	20.93
48.00	0.346	1.61	3.29	20.78
72.00	0.197	1.38	2.51	16.54
96.00**	0.157	1.39	1.94	15.36
120.00	0.242	1.40	1.45	12.20
144.00	<0.140	1.07	1.15	11.99
168.00	NQ (<0.158)	1.85	0.84	12.90

*Mean of four animals; **96 h sample collected at 95 h post exposure for 300 ppm exposure group
NQ = Not quantifiable (limit of quantitation); NS=No sample

Plasma kinetics: Following the 30 ppm (125.10 mg/m^3) exposure, the plasma radioactivity decreased rapidly with an initial (α phase) half-life of 2.6 h and a secondary half life (β phase) of 82.7 h being observed from about 24 h post exposure (see table below). Following the 300 ppm (1251 mg/m^3) exposure, plasma radioactivity also decreased rapidly, with an initial phase half-life of 2.4 h and a secondary half-life of 56.2 h.

RBC kinetics: Following the 30 ppm (125.10 mg/m^3) exposure, an initial half-life of 2.5 h was calculated for clearance from RBCs and a secondary half live was estimated to be about 222 h. Following the 300 ppm (1251 mg/m^3) exposure, an initial half-life of 1.1 h was calculated for clearance from RBCs and the secondary half-life was estimated to be about 139 h. In both treatment groups, the initial half-life in RBCs was somewhat similar to that observed for plasma, but there was a longer secondary half-life in the case of the RBCs.

RBC kinetics were similar to that of plasma in uptake and initial distribution phases but a longer terminal–half life for the elimination of RBC radioactivity was observed. It appears that initially the test material was evenly distributed between the two compartments (RBCs & plasma). The authors have suggested an aggrebale explanation for the longer secondary half-lives in the case of the RBCs. It is proposed that this may have been as a result of either non-specific incorporation of the ^{35}S radiolabel as the radiolabel became available through the sulfate pool and was transformed into amino acids and incorporated into tissues, including the RBCs, or it may have been a result of the binding of some unknown ^{35}S-containing component to RBCs.

Half-lives (h) and AUC $_{(-4\ h-\infty)}$ values (µg-h mL^{-1}) in plasma and RBCs during and following nose-only exposure to 30 or 300 ppm sulfuryl fluoride for 4 h

Dose group (ppm)											
30 (125.10 mg/m^3)						300 (1251 mg/m^3)					
Plasma			RBC			Plasma			RBC		
α-phase	β-phase	AUC	α-phase	β-phase	AUC	α-phase	β-phase	AUC	α-phase	β-phase	AUC
2.6	82.7	96.7	2.5	222	863	2.4	56.2	756.3	1.1	139	5492

*α phase refers to the initial phase while β phase refers to the second phase beginning at about 24 h post-exposure.

Total Absorption: Summation of the recovered radioactivity in the urine, faeces and tissues gives an estimate of the total absorbed radioactivity (see table under excretion section). The total absorbed radioactivity can be used as an estimate of the amount of sulfuryl fluoride that became systemically available during the 4 h exposures.

Following the 30 ppm (125.10 mg/m^3) exposure, 581, 73, and 35 µg-eq sulfuryl fluoride (5.7, 0.7, and 0.34 µmole-eq) were recovered in the urine, faeces and tissues, respectively. Therefore, about 688 µg-eq sulfuryl fluoride (~6.7 µmole-eq) was absorbed during the 4-h exposure to 30 ppm. Following the 300 ppm (1251 mg/m^3) exposure, 4618, 777, and 298 µg-eq sulfuryl fluoride (45, 7.6, and 2.9 µmole-eq) were recovered in the urine, faeces, and tissues, respectively. Therefore, about 5690 µg-eq sulfuryl fluoride (~55 µmole-eq) was absorbed during exposure to 300 ppm (1251 mg/m^3). The authors suggest that the approximately 5% of the ^{35}S radiolabel that was recovered from tissues 7 days after exposure was likely to have resulted from incorporation of the ^{35}S radiolabel into amino acids and their incorporation into tissues.

As exposures were via inhalation of a test atmosphere, the actual 'dose received' (total systemic dose) could be estimated by addition of the total recovered radioactivity from urine, faeces and tissues. Using a breathing rate of 0.96 m^3/kg/day for rats (Zielhuis and vanderKreek, 1979) and a figure for bodyweight of 250 g, it can be calculated that the proportion of the dose absorbed was 14% at 30 ppm and 11% at 300 ppm (1251 mg/m^3).

Distribution

Tissue distribution: Following both the 30 (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) exposure, the highest concentration of radioactivity was detected in tissues at the site of first exposure to the gas (lungs) (see table below). With 30 ppm (125.10 mg/m^3) exposure, the lung radioactivity concentration was followed by spleen, kidneys, nasal turbinates (respiratory & olfactory), brain, skin, carcass, liver, GI tract, and fat. The rank-order following exposure to 300 ppm (1251 mg/m^3) was similar to that obtained with 30 ppm (125.10 mg/m^3) exposure except that the respiratory and olfactory turbinates followed the lungs in the relative concentration of radioactivity in the tissues. In general, the concentrations of radioactivity in the tissues were 7-to 11-fold higher following the 300 ppm (1251 mg/m^3) exposure than following the 30 ppm (125.10 mg/m^3) exposure.

Radioactivity in tissues (µg-eq SO_2F_2/g tissue, mean of four animals) at 168 h following nose-only exposure to 30 or 300 ppm sulfuryl fluoride for 4 h

Tissue	Dose group	
	30 ppm (125.10 mg/m^3)	300 ppm (1251 mg/m^3)
Carcass	0.162	1.484
Kidneys	0.368	2.756
Liver	0.127	0.915
Skin	0.169	1.556
Brain	0.225	1.913
Fat	0.031	0.457
GI tract	0.099	0.779
Lungs	0.774	6.298
Spleen	0.394	3.075
Olfactory Turbinates	0.285	3.233
Respiratory Turbinates	0.312	3.491

Fluoride analysis:

Urine fluoride analysis: Non-exposed rats had a concentration of fluoride ion of approximately 2.5 µg/g urine (see table below). By the end of the 4 h 30 ppm (125.10 mg/m^3) exposure, the urine levels of fluoride ion reached a maximum concentration of 9.3 µg/g urine. This concentration was observed during the first 6 h post-exposure. By 12 h post-exposure, the concentration had decreased to near background levels (2.7 µg/g urine). Likewise, by the end of the 4 h 300 ppm (1251 mg/m^3) exposure, the urine levels of fluoride ion reached a concentration of 76 µg/g urine, which was about 8-fold greater than that seen at 30 ppm (125.10 mg/m^3). But this concentration was decreased during the first 6 h post-exposure to 32 µg/g urine and by 24 h post-exposure to 5.0 µg/g urine. The overall shape of the three curves for urine HPLC and ISE data during and following the sulfuryl fluoride exposures were similar. Based on these, the authors suggest that the kinetics of formation and elimination of the three metabolites (urinary sulfate, fluorosulfate and fluoride) were similar or interrelated.

Concentration (µg fluoride ion/g urine) of fluoride ion in urine during and following nose-only exposure to 30 ppm or 300 ppm sulfuryl fluoride for 4 h

Sampling time	Dose group (ppm)	
	30 (125.10 mg/m^3)	300 (1251 mg/m^3)
Non-exposed	2.33	2.55
During exposure (h)		
-4 to 0	9.33	76.25
Post-exposure (h)		
0 to 6	9.21	31.90
6 to 12	2.71	6.34
12 to 24	-	5.04

- indicates not determined.

Plasma fluoride analysis: An apparent elevation of plasma fluoride above control levels was noted during the 30 ppm (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) exposures that had returned closer to control levels by about 2 h after the exposure period (see tbale below). Plasma fluoride was about 1.6- and 5.4-fold higher than the control values at the end of exposure to 30 (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) sulfuryl fluoride exposures, respectively. The maximum concentration of plasma fluoride measured at the termination of the 4-h 30 ppm (125.10 mg/m^3) sulfuryl fluoride exposure is similar to that at the 30 ppm (125.10 mg/m^3)

sulfuryl fluoride exposure level in a 13 week inhalational study (Eisenbrandt and Nitschke 1989; cited by the authors), although considerable variation was reported between the two studies. However, the plasma concentration reported at the 300 ppm (1251 mg/m^3) exposure level in the present study was almost twice as large as that reported in the 13 week inhalational study (Eisenbrandt and Nitschke 1989; cited by the author), at this level. The authors of the present study suggested that the rapid clearance of fluoride from the plasma and return to background levels by roughly 2 h after the end of exposure in the present study indicates that a delay in sacrificing the animals after exposure in the 13 week study may have resulted in fluoride measurements that were below peak levels. As in the case of the metabolites in urine, the three curves during and following the sulfuryl fluoride exposures were found to be similar for the 3 metabolites (urinary sulfate, fluorosulfate and fluoride), suggesting that the formation and elimination from the plasma of the three metabolites (sulfate, fluorosulfate and fluoride) was similar and interrelated.

Tissues fluoride analysis: Fluoride levels in kidney tissues during and after exposure to 30 (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) sulfuryl fluoride were approximately 2- to 2.5-fold greater than control levels at all collection times (see table below). Control rats had mean fluoride levels of around 2.2 µg/g (0.12 µmole/g) kidney tissue, while both 30 (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) exposure levels resulted in concentrations of approximately 5µg/g (0.26 µmole/g) kidney tissue. These levels were reached by the second hour of exposure and maintained for at least 4 h post-exposure.

Some elevation in fluoride levels in brain tissue relative to control levels was observed during and after exposure to 30 ppm (125.10 mg/m^3) sulfuryl fluoride. This effect was more pronounced at the 300 ppm (1251 mg/m^3) dose level.

Mean concentration (µg fluoride ion/g plasma or tissues) of fluoride ion in plasma, brain and kidney during and following nose-only exposure to 30 ppm (125.10 mg/m^3) or 300 ppm (1251 mg/m^3) sulfuryl fluoride for 4 h

Sampling time	Plasma			Brain			Kidney		
	Control	30 ppm	300 ppm	Control	30 ppm	300 ppm	Control	30 ppm	300 ppm
Pre-exposure (h)									
-4	0.63	-	-	0.46	-	-	2.25	-	-
During exposure (h)									
-2	-	0.87	2.51	-	1.11	1.48	-	4.82	5.34
End of exposure (h)									
0	0.46	0.76*	2.51*	0.60	0.79	2.27	2.25	5.38*	5.54*
Post-exposure (h)									
2	-	0.56	0.86	-	0.78	1.32	-	5.38	4.88
4	0.44	0.53*	0.71*	0.46	0.80	0.98	2.46	5.69*	5.04*
8	1.24	0.38*	0.55*	0.76	-	-	1.91	-	-
20	0.56	0.47	0.52	-	-	-	-	-	-

* Significant difference from control at the indicated sacrifice time; alpha = 0.05
- indicates not determined.

Metabolism

Whole blood metabolites: Blood extract samples showed only two radiolabelled components, tentatively identified as sulfate and fluorosulfate (see table below). The authors have stated that analysis was not performed for the parent compound, as it had been shown (*in vitro*) that sulfuryl fluoride was rapidly removed ($t_{1/2}$<3 min) from rat blood fortified with high concentrations of

sulfuryl fluoride (Waecher, 1991; cited in this study). The identification of fluorosulfate was confirmed by ^{19}F NMR spectroscopy. The amount of fluorosulfate was generally higher than that of sulfate during and after exposure to sulfuryl fluoride, except 4 h after the end of the 300 ppm (1251 mg/m^3) exposure at which time only a small amount of fluorosulfate was detected. At all sample times, sulfate and fluorosulfate levels were approximately 3- to 5-fold higher during and after the 300 ppm (1251 mg/m^3) exposure than in the case of the 30 ppm (125.10 mg/m^3) exposure. Based on the limited amount of data available, a half-life for fluorosulfate elimination from whole blood was calculated to be 48 to 73 minutes while the half-life for sulfate elimination from whole blood was calculated to be 50 to 64 minutes.

Urine metabolites: Two radioactive peaks were detected in urine (identified as sulfate and fluorosulfate) (see table below). The authors did not perform analysis for parent sulfuryl fluoride in urine, as it has been shown previously that sulfuryl fluoride is rapidly hydrolysed in aqueous solutions ($t_{1/2}$<18 min at pH 8.07; Cady and Misra, 1974; Bailey 1992; cited in the study). During the exposure period, the amount of fluorosulfate eliminated in urine was about 3- to 3.5-fold greater than the amount of sulfate (see table below). However, during the post-exposure period the amount of sulfate recovered in urine was greater than the amount of fluorosulfate. By 12 h post-exposure, about 5- to 7-fold more sulfate was recovered in urine than fluorosulfate. The total µmoles of sulfate plus fluorosulfate recovered in the urine as determined by high performance liquid chromatography/radioactivity monitor (HPLC/RAM) compares well with the µmole-eq sulfuryl fluoride in the urine plus rinse as determined from the radiolabelled portion of this study. Conversion of sulfate and fluorosulfate urine concentrations to rate estimates to correct for unequal collection intervals allowed calculation of half-lives for the elimination of sulfate and fluorosulfate in urine. Sulfate was eliminated in the urine with a half-life of 2.2 and 3.8 h for the 30 (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) exposure groups, respectively. Fluorosulfate was eliminated slightly faster with a half-life estimate of 1.2 and 2.4 h for the 30 (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) exposure groups, respectively.

Concentration (nmole metabolite/mL whole blood or µmole metabolite/mL urine) of sulfate and fluorosulfate in whole blood and urine during and after nose-only exposure to 30 ppm or 300 ppm sulfuryl fluoride for 4 h

Sampling time	Dose group							
	30 ppm (125.10 mg/m^3)				300 ppm (1251 mg/m^3)			
	Sulfate		Flurosulfate		Sulfate		Flurosulfate	
	Whole blood	Urine	Whole blood	Urine	Whole blood	Urine	Whole blood	Urine
During exposure (h)								
-3.5		-	-	-	14	-	90.7	-
-2.0	9.7	-	27.3	-	50.3	-	118.7	-
-4 to 0	-	0.15	-	0.44	-	2.34	-	8.24
End of exposure (h)								
0	21.0	0-	34.4	-	62.2	-	134.5	-
Post-exposure (h)								
1	9.1	-	19.5	-	32.4	-	74.8	-
4	-	-	-	-	18.7	-	4.5	-
0 to 6	-	0.76		0.55	-	3.83	-	2.82
6 to 12	-	0.12		0.02	-	0.70	-	0.16
12 to 24	-	-	-	-	-	0.23	-	0.04

- indicates not determined.

Mean µmole metabolite recovered in urine per rat during and following nose-only exposure to 30 ppm or 300 ppm sulfuryl fluoride for 4 h

Sampling time	Dose group			
	30 ppm (125.10 mg/m^3)		300 ppm (1251 mg/m^3)	
	Sulfate	Flurosulfate	Sulfate	Flurosulfate
During exposure (h)				
-4 to 0	0.58	1.68	6.35	22.36
Post-exposure (h)				
0 to 6	0.64	0.46	5.38	3.96
6 to 12	0.37	0.06	2.59	0.59
12 to 24	-	-	1.43	0.22
Total	**1.59**	**2.2**	**15.75**	**27.13**

- indicates not determined.

Excretion

Urine: Once absorbed, the ^{35}S-sulfuryl fluoride-derived radioactivity rapidly appeared in the urine and faeces (see table below). Inhaled sulfuryl fluoride was excreted during the exposure, with the majority of the radioactivity being recovered in urine during this period (-4 to 0 h). These urine samples contained 273 and 2766 µg-eq or about 47 and 60% of the total urinary radioactivity at 30 ppm (125.10 mg/m^3) and 300 ppm (1251 mg/m^3), respectively. The 0 to 6 h interval urine samples collected after the exposure period contained 167 and 936 µg-eq or an additional 29 and 20% of the total urinary radioactivity at 30 ppm (125.10 mg/m^3) and 300 ppm (1251 mg/m^3), respectively. Radioactivity remained detectable in the urine for 7 days after exposure, accounting for about 80-83% of the total excreted radioactivity during this period. An initial urinary half-life for ^{35}S-sulfuryl fluoride-derived radioactivity was estimated as approximately 4 h at both exposure concentrations. This was followed by a second urinary elimination phase with a half-life of approximately 40 h. The existence of the second phase perhaps being due to radiolabeled sulphur becoming incorporated into amino acids, via the sulphate pool, as mentioned above.

Faeces: Up to 48 h post-exposure, 64 and 704 µg-eq sulfuryl fluoride were recovered from the faeces of animals at 30 ppm (125.10 mg/m^3) and 300 ppm (1251 mg/m^3), respectively, representing 88-91% of the total amount of radioactivity recovered in the faeces. Totals of 73 and 777 µg-eq sulfuryl fluoride, respectively, were recovered in the faeces from the 30 ppm (125.10 mg/m^3) and 300 ppm (1251 mg/m^3) exposure groups.

Radioactivity in urine and faeces during and following nose-only exposure to 30 or 300 ppm sulfuryl fluoride for 4 h

Sampling time	Dose group			
	30 ppm (125.10 mg/m^3)		300 ppm (1251 mg/m^3)	
	Urine (+rinse)* (µg-eq. sulfuryl fluoride)	Faeces* (µg-eq. sulfuryl fluoride)	Urine (+rinse)* (µg-eq. sulfuryl fluoride)	Faeces* (µg-eq. sulfuryl fluoride)
Exposure period (h)				
-4-0 h	272.94	9.56	2765.98	324.74
Post-Exposure period (h)				
0-6 h	167.41	-	935.61	-
6-12 h	54.24	-	429.36	-
0-24 h	-	32.43	-	221.62
12-24 h	43.23	-	198.89	-
24-48 h	20.13	21.84	123.51	158.04
48-72 h	8.55	5.81	55.74	38.28
72-96 h	5.27	2.10	39.25	19.43
96-120 h	3.93	1.10	34.72	9.38
120-144 h	2.92	0	21.38	0.59
144-168 h	2.02	0	13.62	4.43
Total	**580.64**	**72.74**	**4618.05**	**776.51**

*Mean of four animals
- indicates not determined

Conclusions and discussion

Radiolabelled sulfuryl fluoride was rapidly absorbed via inhalational exposure, reaching maximum concentrations in the plasma and RBCs near the end of the 4 h exposure period. Radioactivity was rapidly cleared from plasma and red blood cells (RBCs) with initial half-lives of ~2.5 h following the 30 ppm (125.10 mg/m^3) exposure and 1-2.5 h following 300 ppm (1251 mg/m^3) exposure. However, the secondary half-life of radioactivity was ~2.5 fold longer in RBCs than plasma. Radioactivity associated with the RBCs remained elevated at 7 days post-exposure, which may explain why highly perfused tissues such as the spleen and kidneys had higher levels of radioactivity than other non-respiratory tissues, probably due to the radioactivity in the blood. The ^{35}S was rapidly excreted, primarily via the urine (>80%), with a large portion of the absorbed ^{35}S being excreted in the urine during the 4 h exposure period. Seven days post-exposure, the ^{35}S was widely distributed among the tissues, consistent with its incorporation as sulfur into amino acids.

The identification of fluorosulfate and sulfate in blood and urine suggests that sulfuryl fluoride (SO_2F_2) may be first hydrolysed to fluorosulfate (SO_3F) with release of fluoride, followed by further hydrolysis to sulfate (SO_4) and release of the remaining fluoride. This is consistent with the increases in fluoride detected in the plasma and urine following exposure of rats to sulfuryl fluoride.

4.2 PERCUTANEOUS ABSORPTION

Percutaneous absorptions studies were not submitted.

4.4 TOXICOLOGICAL STUDIES

Sulfuryl fluoride is a gas with a boiling point of minus 55^0C (218K), which makes the performance of oral toxicity studies difficult. Therefore, all but three of the studies described in this monograph have involved exposure to atmospheres containing sulfuryl fluoride vapour. To convert from air concentrations to a systemic dose in mg/kg bw/day, account was taken of the respiratory rate and volume of the animals(rats 0.96 m^3/kg bw; rabbits 0.54 m^3/kg bw; mice 1.8 m^3/kg bw and dogs 0.39 m^3/kg bw; Zielhuis & vanderKreek, 1979), the duration of exposure (hours/day and days/week) and the proportion (10%) of the inspired dose that was absorbed (based on the toxicokinetic study of Mendrala et al, 2002). Furthermore, 1 ppm of sulfuryl fluoride is equivalent to 4.17 mg/m^3, or 0.00417 mg/L.

All the toxicology studies submitted were performed on a formulated product 'Vikane Gas Fumigant' (synonyms-Profume Gas Fumigant), which contains approximately 99.8% sulfuryl fluoride, the active constituent.

4.4.1 Acute Studies

Because sulfuryl fluoride is a gas, the oral and dermal acute toxicity studies were performed in a non-standard manner. The acute toxicity via inhalation has been extensively investigated in several studies.

Summary of acute toxicity studies conducted with sulfuryl fluoride

Study type	Species	Purity (%)	Vehicle	Dose levels	Result	Reference
Inhalation: (4h, whole body)	Mouse (B6C3F1)	99.6	None	400, 600, 1000 ppm	LC_{50} 1668-2502 mg/m^3 (400-600 ppm) (M&F)	Nitschke & Lomax., 1989
Inhalation: (4h, whole body)	Mouse (CD-1)	99.6	None	596, 692, 806 ppm	LC_{50} 2750 mg/m^3 (M; 660 ppm), 2680 mg/m^3 (F; 642 ppm)	Nitschke & Quast., 1990
Oral/gavage	Rat (strain not stated)	NA	Corn oil	50, 100, 200, 400 mg/kg bw (M); 40, 80, 160 mg/kg /bw (F)	LD_{50} ca. 100 mg/kg bw (M&F)	Anon., 1959a
Oral/gavage	Guinea pigs (strain not stated)	NA	Corn oil	50, 100, 200, 400 mg/kg bw	LD_{50} ca. 100 mg/kg bw (F)	Anon., 1959a
Dermal/vapour* (4h)	Rat (Fisher F344)	99.7	None	987, 1013, 9599 ppm	LD_{50} 40315 mg/m^3/4 h (9599 ppm in air). No adverse effects were noted at this dose.	Bradley et al., 1990
Inhalation (4h, whole body?)	Rats (Wistar)	99.7	None	1000, 2000, 4000, 8000, 15,000 ppm	LC_{50} ca. 4700 mg/m^3 (1000 ppm)	Anon., 1959b
Inhalation (4h, whole body)	Rat (Fisher F344)	99.7	None	500, 1000, 1500, 2000 ppm	LC_{50} 4680 mg/m^3 (M; 1122 ppm), 4130 mg/ m^3 (F; 991 ppm)	Miller et al., 1980
Dermal irritation	No studies.					
Eye irritation/ skin sensitisation	No studies.					

NA – not available – solution prepared by bubbling 'Vikane' into the corn oil
*By exposure to gas; head in fresh air

1. Nitschke, K.D. and Lomax, L.G. (1989): Sulfuryl Fluoride: Acute LC_{50} study with B6C3F1 Mice. Study No: Unspecified, Report No: K-9016399-028,-028A and –028B, Unpublished, Report date: 3 March, 1989.

Test Compound:	Sulfuryl fluoride (99.6% pure)
Batch:	880329 752
Test Species:	Mice (B6C3F1); age and source are not stated; 5 mice/sex/exposure
Study Duration:	Study began on 8 September 1988 & completed on 22 March 1989.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 81-3, 40 CFR 158.135 Deviation from EC guideline Method B.2 Acute Toxicity (Inhalation): None.

Clinical findings: All animals died within 90 minutes following exposure to 1000 ppm sulfuryl fluoride and within 5 days following exposure to 600 ppm. Body tremors were observed in several female mice shortly after exposure to 600 ppm and animals surviving after the exposure period were lethargic prior to their death. Body weights for most mice exposed to 600 ppm sulfuryl fluoride, which survived one day post-exposure, were decreased from pre-exposure values. Mice exposed to 400 ppm sulfuryl fluoride survived until the scheduled sacrifice. There were no body weight effects noted in male and female mice exposed to 400 ppm.

Necropsy findings: There were no exposure-related gross pathologic effects noted in male and female mice exposed to 400, 600 or 1000 ppm sulfuryl fluoride.

Conclusions: The 4-h LC_{50} of sulfuryl fluoride is between 400 & 600 ppm (1668 and 2502 mg/m^3) for both male and female mice.

2. Nitschke, K.D. and Quast J.F. (1990): Sulfuryl Fluoride: Acute LC_{50} study with CD-1 Mice. Study No: Unspecified, Report No: K-016399-031,-031A and –031B, Unpublished, Report date: 12 December, 1990.

Test Compound:	Sulfuryl fluoride (99.6% pure)
Batch:	880329 752
Test Species:	Mice (CD-1); age and source are not stated; 5 mice/sex/exposure
Study Duration:	Study began on 8 November 1988 & completed on 21 December 1990.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 81-1 Deviation from EC guideline Method B.2 Acute Toxicity (Inhalation): None.

Clinical findings: Seven of ten mice exposed to 806 ppm sulfuryl fluoride and eight of ten mice exposed to 692 ppm died either during the 4–hr exposure period or within the two-week post-exposure period. Body tremors and/or lethargy were observed in several mice shortly after exposure to 692 or 806 ppm. All animals exposed to 596 ppm survived with no clinically visible effects noted.

Necropsy findings: There were no exposure-related gross pathologic effects observed in male or female mice exposed to sulfuryl fluoride. However, animals which died on the day of exposure as well as those dying during the post-exposure period interval had visceral congestion. The visceral

congestion in animals dying during the post-exposure period was accompanied by evidence that these animals were not eating.

Conclusions: The approximate LC_{50} (4-h) values are 660 & 642 ppm sulfuryl fluoride for male and female CD-1 mice, respectively. This corresponds to 2750 mg/m^3 and 2680 mg/m^3 for males and females, respectively.

3. Anonymous (1959a): The Acute Oral Toxicity of Vikane, Administration of Single Doses to Male Rats, Female Rats and Guinea Pigs. Study No: Unspecified, Unpublished, Report date: 22 October, 1959.

Test Compound:	Test material: Not specified in report available. The dosing solutions were prepared by bubbling the gas through chilled corn oil so that about 1% became Vikane to 99% oil. The volume administered, of necessity, were very large and possibly leading to physiological effects.
Batch:	Not stated
Test Species:	Rat and Guinea Pig. Strain and source is not stated.
Study Duration:	Not stated.
Laboratory:	Biochemical Research Laboratory, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	No-This study pre-dates GLP Compliance Programme. QA: Not stated.
Guidelines:	No-This study is pre-guideline. Deviations from EC guideline Method B.1. Acute Toxicity (Oral): There is not enough detail in this report to enumerate differences from guideline.

Findings: Mortality was observed at 100 mg/kg bw and higher, as shown in the Table below.

Summary of study design and findings

Species	Sex	Dose (mg/kg)	Mortality (No Dying/No Fed)	Observations
Rat	F	40	0/4	Nothing remarkable. Pathology very slight-possibly some in liver and lung.
Rat	M	50	0/4	
Guinea Pig	F	50	0/4	
Rat	F	80	0/4	Only diarrhoea, dehydration. Slight liver and lung congestion, appreciable gastritis, and cloudy swelling in kidneys.
Rat	M	100	2/4	
Guinea Pig	F	100	2/4	
Rat	F	160	4/4	Deaths in a matter of hours. Mechanism not determined.
Rat	M	200	4/4	
Guinea Pig	F	200	4/4	
Rat	M	400	4/4	Death in 2 hours.
Guinea Pig	F	400	4/4	
Rat	F	40 cc of corn oil	0/2	No serious effects.
Guinea Pig	F	40 cc of corn oil	2/4	All sick. Recovery slow. Oily diarrhoea. Loss of hair.

Conclusions: The LD_{50} for rats and guinea pigs was estimated to be about 100 mg/kg bw.

4. Anonymous (1959b): The Acute Vapour Toxicity of Vikane as determined on Male and Female Rats, Single Exposures of Groups of Rats to High Concentrations of Vikane in Air. Study No: Unspecified, Unpublished, Report date: 22 October, 1959.

Test Compound:	Vikane (not otherwise specified).
Batch:	Not stated.
Test Species:	Rat (Wistar), age and source are not stated.
Study Duration:	Not stated.
Laboratory:	Biochemical Research Laboratory, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	No-This study pre-dates GLP Compliance Programme. QA: Not stated.
Guidelines:	This study is pre-guideline. Deviation from EC guideline Method B.2 Acute Toxicity (Inhalation): This study used more animals than the guideline, more concentrations than required, more times of exposures, no body weights reported. It is also stated by the applicant that the report was too sketch to determine a full comparison.

Study: Single exposures to Vikane were conducted in a 160 L glass 'Monel' chamber using groups of 8-20 rats of each sex. The concentration of Vikane was maintained by pumping the gas from a Saran bag by means of a Dual Syringe Feeder Pump. The air-flow through the chamber was continuous and ranged from 4-19 L/ minute.

The concentrations during part of the exposures were monitored by means of a Recording IR with 4.5 m cell. The concentrations were within 10% of the calculated levels. During the exposures of male rats to 1000 ppm, the chamber atmosphere was analysed for Vikane by taking grab samples, hydrolysing the fluoride with caustic and determining the liberated fluoride by a Thorium-Alizarin method. The amount of fluoride recorded agreed closely with the theoretical value for 1000 ppm of sulfuryl fluoride.

Findings: Findings are summarised below in a table below.

Summary of exposure of rats to Vikane

Conc. (ppm)	lbs/1000 ft^2	Exposure Duration (hrs)	Sex	No. Died/No. Exposed	Response - Remarks
15,000	3.9	0.2	M	18/18	Very quiet during the last half exposure. Drowsy and laboured breathing when removed. Tremors shortly after removal. Convulsing about 48 minutes after exposure. Convulsions similar to strychnine. All dead after 3 hrs.
			F	9/10	
15,000	3.9	0.1	M	1/18	Very little response during exposure. Slow moving on removal. Two hrs after exposure, one rat started convulsions and subsequently died.
			F	0/10	
8000	2.1	0.5	M	18/18	Tremors started after about 8 minutes of exposure. Rats were still able to crawl around after 15 minutes of exposure. All became convulsant and died in less than 2.5 hrs after exposure.
			F	10/10	
8000	2.1	0.2	M	1/18	Slight weight loss. Rapid recovery.
			F	1/10	
4000	1.05	1	M	19/20	All animals were weak on removal but appeared to be conscious. Half were dead in less than 2 hrs. Three rats died before morning. One rat died 4 days after exposure.
			F	10/10	
4000	1.05	0.5	M	5/20	Essentially no weight loss.
			F	7/10	
2000	0.52	2.0	M	12/18	All alive but drowsy on removal. Two hrs after exposure, rats were very sick, slow moving and had slight tremors. One rat died 2 hrs after exposure. Recovered appreciably in 2 days.
			F	10/10	
2000	0.52	1.0	M	1/18	Rats were only slightly affected including only a slight weight loss.
			F	0/10	
1000	0.26	6.0	M	4/8	No unusual response 1.5 hrs after exposure started. After 4 hrs of exposure, tremors and slight convulsions occurred. The tremors and convulsions increased in frequency and intensity during the remainder of the exposure. The first death occurred after 5 hrs of exposure. Four rats were dead at the end of the exposure. Survivors were sick and trembling but lost only a small amount of weight.
		5.6	M	2/10	
		5.6	F	2/10	
		4.0	M	4/10	
		4.0	F	2/10	
1000	0.26	3.0	M	0/8	Possibly slight tremors after exposure. Only slight weight loss occurred.
		2.0	M	0/10	
		2.0	F	1/10	

Conclusions: The 4 hr LC_{50} for rats was ca. 1000 ppm (4700 mg/m^3).

5. Bradley, G.J., Landry, T.D., Battjes, J.E., Quast, J. F. (1990): Sulfuryl Fluoride: Four-Hour Dermal Vapour Exposure in Fischer 344 Rats. Study No: Unspecified, Report No: K-016399-036, -036A, -036B, Unpublished, Report date: 16 November, 1990.

Test Compound:	Sulfuryl fluoride (99.67% pure)
Batch:	880329 752
Test Species:	Rat (Fischer 344); age and source are not stated.
Study Duration:	Study began on 20 February 1990 & completed on 16 November 1990.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 81-5. Deviation from EC guideline Method B.3 Acute Toxicity (Dermal): There were no untreated control rats and the test material was vapour.

Study: Groups of 5 rats were exposed dermally to sulfuryl fluoride vapours of 987 ppm (4.145 mg/L) and 1013 ppm (4.254 mg/L), respectively, for a single 4-hour period. Since no effects were noted from this exposure, another group of 5 rats/sex was dermally exposed to 9599 ppm (40.315 mg/L) for a similar 4-hr period.

The dorsal skin on the rats was shaved prior to exposure to maximise any effect. Surviving animals were weighed on days 1, 2, 4, 8, 11, and 15. Necropsies took place on day 15. The rats were observed during exposure and on test days 1 to 14 post-exposure. Sections of brain and skin were examined histologically. No other tissues were examined microscopically since no gross pathologic observations were noted.

Chamber concentrations were analysed using a Miran 1A infrared spectrophotometer and atmospheres were generated using a J-tube mixer with Saran bag delivering the test material. The chamber was modified in such a way that heads of the rats protruded through an elastic dental dam, which served as a barrier between the test material and the breathing air for the rats. The breathing air contained <20 ppm sulfuryl fluoride.

Findings: All animals survived 4-hr exposure and 14 day post-exposure period with no clinically visible effects. In all exposure groups, the average body weight on day 2 was decreased slightly (3%) from pre-exposure values. This was thought to be due to the stress of handling and restrain, rather than due to sulfuryl fluoride exposure. By day 4, body weight values were greater than pre-exposure values, and the animals continued to gain weight. There were no grossly visible lesions noted in animals necropsies at the end of the 14-day post-exposure period. Histopathologic examination of brain and skin samples taken from animals exposed to 9599 ppm revealed no treatment-related effects.

Conclusions: Results of this study indicate no acute toxicological hazard on exposure to sulfuryl fluoride via the skin were observed with exposures up to 40315 mg/m^3 (9600 ppm).

6. Miller, R.R., Calhoun, L.L., Keyes, D.G., Kociba, R. J. (1980): Sulfuryl Fluoride (Vikane Fumigant): An LC_{50} Determination. Study No: Unspecified, Report No: K-016399-013, Unpublished, Report date: 25 August, 1980.

Test Compound:	Sulfuryl fluoride (99.7% pure)
Batch:	141
Test Species:	Rat (Fischer 344); age and source are not stated; 10 rats/sex/exposure
Study Duration:	Study began on 8 May 1979 & completed on 25 August 1980.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 81-3. Deviation from EC guideline Method B.2 Acute Toxicity (Inhalation): None.

Clinical findings: An inhibition of growth was apparent for groups of animals which survived exposure to a concentration of approximately 750 ppm or higher. If recovery occurred, it was generally apparent within the first few days after exposure and no spontaneous mortalities occurred after 6 days post-exposure.

It was also suggested that a generalised sedation, possibly via central nervous system depression, should be anticipated within 20-40 minutes of exposure to high concentration (e.g. greater than 1500-2000 ppm) of VIKANE. Continued exposure following sedation results in convulsions and adverse effects on the respiratory system, liver and kidneys, followed by death within 3-4 hrs. Exposure concentrations below the LC_{50} (e.g. 700 ppm) may have had some slight short-term effect as evidenced by the decreased growth of rodents during the first few days after exposure. However, there were no discernible treatment-related effects after 14 days of recovery in animals exposed to concentrations lower than 1000 ppm.

Necropsy findings: Histopathology was conducted on rats from the control and 1250 ppm (male) and 1200 ppm (female) exposure groups. The liver, kidneys, brain, lungs and testes were weighted at necropsy. Organ weights from animals, which survived until the end of the 14 day observation period, revealed no clear treatment-related abnormalities. Gross pathologic examination revealed lesions primarily in the upper and lower respiratory tract. Histopathologic examination of animals, which died as a result of exposure to 1200-2500 ppm, revealed clear treatment effects in the liver and kidneys and possible effects in lung, heart and spleen. Kidney effects, which were considered to be regenerative responses subsequent to previous toxicity, were noted in animals, which survived for two weeks following the exposure to 1200-1250 ppm.

Conclusions: The LC_{50} values for male and female rat in this study were 1122 ppm (4680 mg/m^3) and 991 ppm (4130 mg/m^3), respectively.

4.4.2. Short-term Studies

There were no short-term oral toxicity studies of a standard length (28 days) submitted on sulfuryl fluoride.

1. Anonymous (1959c): Short Term Dietary Feeding Study of Commercial Laboratory Diet Fumigated with Vikane. Study No: Unspecified, Report No: K-16399-005, Unpublished, Report date: 22 October, 1959.

Test Compound:	Vikane. No additional details were provided.
Batch:	Not stated.
Test Species:	Wistar rat; at least 50 days of age when the study began; source is not stated; 10/sex/dose, also 2/sex/dose for necropsy at day 30.
Study Duration:	Not stated.
Laboratory:	Biochemical Research Laboratory, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	This study pre-dates the GLP Compliance Program.
Guidelines:	This study is pre-guideline. Deviation from EC guideline Method B.7 Repeated Dose (28 days) Toxicity (Oral). This study was not conducted in the usual manner. The duration was 66 days. It was conducted to test whether fumigation of feed with Vikane would cause the feed to become toxic. It is stated that the food consumption data was not reported; body weight data not tabulated; no clinical blood chemistry; and no routine urinalysis. Although tissues and urine were tested for fluoride content, tissues histologically examined did not necessarily reflect those with effects (bone/teeth not done). Teeth were also examined for fluorosis. The applicant also states that the report was sketchy.

Study: Groups of 10 rats/sex/dose (diet) were maintained for 66 days on the diets fumigated with 0, 2, 10, 100 and 200 pounds/1000 cu ft of Vikane. Samples of feed from each of the diets were analysed for fluoride (see table below). Two extra rats of each sex were set up at each dietary level for necropsy after 30 days. The rats were weighed twice weekly for 28 days and then weekly. They were observed 'frequently' for gross changes in appearance and behaviour. The teeth of all rats were checked for any visual evidence of fluorosis. Food consumption was recorded for the first month. Samples of urine were obtained prior to termination from all males for fluoride analysis; terminal haematology values were obtained from 5 female rats on the 0, 2 and 10 lbs diets and from 2 males from each dietary level. At necropsy, the lungs, heart, liver, kidneys, spleen, and testes were weighed. Portions of these organs as well as pancreas and adrenals were examined histologically. Samples of blood, urine (male), kidney, lung, liver and bones were collected and analysed for fluoride from the rats killed at 30 days.

Fluoride (ppm) in Diets Fumigated with Vikane

Rate of Fumigation with Vikane (lbs/1000 cu. ft)	Average ppm Fluorides*	
	Total	**Net****
Control Diet (no fumigation)	36	-
2	55	19
10	89	53
100	386	350
200	740	704

*The identity of the 'fluoride' in the diet was not given. ** i.e. minus control

Mortality: No mortality was reported.

Clinical Findings: No clinical signs were reported. Growth was retarded in a dose-related manner in all but the lowest dose (19 ppm fluoride) group in males and at the highest dose group in females (see table below). There is no food consumption data or statement about it in the results. Opthalmic observations were not undertaken.

Final bodyweights, liver and testes weights in rats fed diets treated with 'Vikane'

Diet (net ppm fluoride)	No. of Rats	Body Weight (g)	Liver		Testes	
			g	g/100g	g	g/100g
Males						
0	8	306	8.72	2.86	3.02	0.99
19	9	285	8.43	2.96	2.86	1.01
53	10	275*	8.36	3.03*	2.78	1.01
350	9	247**	7.31	2.96	2.80	1.09*
704	10	207**	6.23	3.00*	2.72	1.33*
Females						
0	9	173	5.40	3.12	-	-
19	10	185	5.66	3.06	-	-
53	10	171	5.40	3.15	-	-
350	9	169	5.28	3.12	-	-
704	10	145**	4.52	3.12	-	-

*P = 0.01 to 0.05 (statistical test not specified)
**P = <0.01 (statistical test not specified)

Haematology, Clinical Chemistry, and Urinalysis: No treatment related effects were reported on haematology. Clinical chemistry was not conducted. Although a full urine analysis was not conducted, fluoride levels were measured in the urine of males, as well as in some tissues of males and females (see table below). Fluoride content in urine and bone increased in a dose-dependent manner. In tissue other than bone, fluoride content could not be correlated with dose.

Urinary and tissue fluoride content (mean; ppm) in rats fed on 'Vikane' treated diets for 30 days

Diet (net ppm fluoride)	Blood	Urine	Kidney	Lung	Liver	Bone
Males						
0	0.0	9.9	0.9	13.5	0.0	260
19	2.7	11.9	2.4	5.0	0.0	408
53	0.4	13.3	10.3	1.0	0.3	413
350	0.4	85.6	2.3	17.6	0.0	1615
704	6.2	174.4	2.3	6.0	8.4	1920
Females						
0	4.4	-	1.3	20.3	1.6	276
19	3.0	-	1.3	13.0	2.0	339
53	0.0	-	9.6	20.4	2.0	339
350	0.6	-	0.0	17.2	0.0	1875
704	2.9	-	5.7	25.3	0.3	3445

Pathology: Lowered liver and testes weights appeared to be associated with lower body weights (see table above). Teeth were noted to have fluorosis banding, altered pigmentation and staining at 53 ppm and above. Histopathology findings included ‘glomerular’ involvement of the kidneys, no dose levels being specified.

Conclusions: The study was not conducted as per guidelines and limited details were provided from which to derive a NOEL for this 66 day oral study in rats. However, a tentative value of 19 ppm (net amount of fluoride above the control diet value of 36 ppm fluoride in the fumigated diet; equivalent to a total fluoride intake of 2.5 mg/kg bw/d) can be proposed based on overt fluorosis of the teeth in both sexes and reduced bodyweight gain in males at 53 ppm (equivalent to a total fluoride intake of 4.5 mg/kg bw/d).

2. Nitschke, K.D. and Quast, J.F. (2002): Sulfuryl fluoride: Two-Week-Inhalation Toxicity Study in CD-1 Mice. Study No: Unspecified, Report No: DECE HET K-016399-029, Unpublished, Report date: 11 February, 2002.

Test Compound:	Sulfuryl fluoride (99.6% purity)
Batch:	WP 880329 752
Test Species:	CD-1 mice; age and source are not stated; 10/dose (5 males & 5 females)
Study Duration:	Study started on 10 October 1988 & completed on 11 February 2002. Laboratory: Toxicology and Environmental Research and Consulting, The Dow Chemical Company., Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	OECD 412 (19), 84/449/EEC, Method B8 (1984) Deviation from EC guideline Method B.8. Repeated Dose (28 days) Toxicity (Inhalation). None, except that this was a 2-week study.

Study: Groups of 5 male and 5 female mice were exposed (inhalation-whole body) to 0, 30, 100, or 300 ppm (0, 125.10, 417, 1251 mg/m^3, respectively) sulfuryl fluoride for 6 hrs/d, 5 days/week for 9 expsoures during a two-week period. Test article intake was approximately equivalent to 0, 4.1, 13, 39 mg/kg bw/d for 0, 30, 100 or 300 ppm group, respectively.

All animals were observed daily for overt signs of toxicity or changes in demeanor. These observations included an evaluation of the fur, eyes, mucous membranes, and respiration. Behavior pattern and nervous system activity were assessed by specific observations for lethargy, tremors, convulsions, salivation, lacrimation, diarrhea, or other signs of altered central nervous system functions. All animals were weighed on test days 1, 3, 5, 8, and 11. Blood samples were collected by orbital sinus puncture from anaesthetised mice prior to necropsy. The following haematologic parameters were evaluated for each animal: haematocrit (HCT), haemoglobin concentration (HCB), and erythrocyte (RBC), total leukocyte (WBC) and platelet (PLAT) counts. The following clinical chemistry parameters were measured: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and urea nitrogen (UN).

All surviving animals were necropsied the day following the last exposure to the test material. Weights of the brain, heart, liver, kidneys and testes (males) were recorded. All animals were examined for gross pathological alterations. A complete set of tissues was collected from each animal and preserved in neutral phosphate-buffered 10% formalin. The lungs were infused with buffered formalin to their approximate normal inspiratory volume and the nasal cavity was flushed with formalin via the pharyngeal duct to ensure rapid fixation. The necropsy included *in situ* examination of the eyes by a glass-slide technique with fluorescent illumination. Histopathologic examination of brain, liver, kidney and respiratory tract (nasal tissue, trachea, larynx, and lungs) was conducted on all animals.

Mortality: At 300 ppm (1251 mg/m^3), all male and 4/5 female mice died during the second week of the study.

Clinical Findings: Decedents were thin and many had roughened haircoat and exhibited body tremors (males only). All animals exposed to lower concentrations (<300 ppm) survived to the end of the study with no overt signs of toxicity or changes to the demeanor. Bodyweights of mice exposed to 300 ppm (1251 mg/m^3) were significantly decreased from control values (see table below). Mean body weights of male and female mice exposed to 30 ppm (125.10 mg/m^3)

or 100 ppm (417 mg/m^3) were comparable to control values. Food consumption was not assessed. Ophthalmic observations were not conducted post-exposure.

Mean body weights (g) in mice exposed to sulfuryl fluoride for 2 weeks

Test Day	Concentration			
	0	30 ppm (125.10 mg/m^3)	100 ppm (417 mg/m^3)	300 ppm* (1251 mg/m^3)
Males				
1	33.2	32.1	31.2	32.8
3	30.3	31.8	30.5	30.2
5	32.8	32.9	31.5	27.9
8	34.2	33.4	31.9	24.4
11	33.7	32.8	31.1	20.5
Females				
1	25.3	25.2	25.4	24.5
3	25.2	23.4	26.1	22.2
5	25.9	25.9	26.8	20.2
8	26.5	26.2	27.2	20.7
11	26.7	26.3	26.6	20.2

*Time-dose interaction was highly statistically significant for males and females at the high dose, alpha= 0.05

Haematology, Clinical Chemistry & Urinalysis: RBC counts in male mice and haemoglobin concentrations in male and female mice were elevated (statistically significantly) only in mice exposed to 100 ppm (417 mg/m^3) sulfuryl fluoride and not at other doses. However, these values were within the range of the historical control data from this laboratory. All remaining haematological parameters in male and female mice exposed to 30 (125.10 mg/m^3) or 100 (417 mg/m^3) ppm were comparable to control values. All clinical chemistry parameters measured in mice exposed to sulfuryl fluoride were comparable to control values. Urinalysis was not conducted.

Pathology: The terminal body weights and absolute and relative organ weights of male and female mice exposed to 30 (125.10 mg/m^3) or 100 ppm (417 mg/m^3) sulfuryl fluoride were comparable to control values. Due to the decreased bodyweight in the sole surviving female mouse exposed to 300 ppm (1251 mg/m^3), several absolute and/or relative organ weight values, while not statistically significant, were different from control values. These differences included an increase in relative brain, heart and kidney weights and a decrease in absolute liver weights. There were no effects on organ weights at 30 ppm (125.10 mg/m^3) or at 100 ppm (417 mg/m^3).

Several gross pathological changes were observed in male and female mice exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride that died prior to scheduled necropsy. These changes included decreased amounts of ingesta in the digestive tract, decreased fat and erosions of the stomach. There were no effects at 30 ppm (125.10 mg/m^3) or at 100 ppm (417 mg/m^3).

Exposure-related histopathological effects were observed in the cerebrum and medulla of the brain of mice exposed to 100 ppm (417 mg/m^3) and 300 ppm (1251 mg/m^3) sulfuryl fluoride (see table below). Multifocal vacuoles, which were very slight in degree, were observed in the cerebrum of 4 male and 2 female mice exposed to 100 ppm (417 mg/m^3). More severe vacuoles graded as moderate were observed in the cerebrum of the majority of mice exposed to 300 ppm. In addition, 4 male mice and 1 female mouse exposed to 300 ppm (1251 mg/m^3) had vacuoles in the medulla, which were very slight or moderate in severity. There were no histopathologic

changes in the medulla of mice exposed to 100 ppm (417 mg/m^3) sulfuryl fluoride and no lesions noted in the cerebrum or cerebellum of mice exposed to 30 ppm (125.10 mg/m^3).

Nine of ten mice exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride had hepatocellular and lacrimal gland atrophy, which were considered to be secondary to inanition and the moribund condition of these animals. There were no histopathological effects at 100 ppm (417 mg/m^3) or below. All other microscopic changes in mice were considered to be incidental findings unrelated to exposure to sulfuryl fluoride. There were no exposure related effects on the kidney.

Summary of histopathological findings

Sex			**Males**				**Females**			
Dose			**0**	**30**	**100**	**300**	**0**	**30**	**100**	**300**
Number of mice examined			5			(5)	5			1 (4)
Brain	No. examined/within normal limits		5/5		5/1	(5)/0	5/5		5/3	1(4)/1(1)
	Cerebrum: Vacuolation, bilateral, multifocal	very slight	0		4	(1)	0		2	0
		moderate	0			(4)	0			(3)
	Medulla: Vacuolation, bilateral, multifocal	very slight	0			(2)	0			(1)
		moderate	0			(2)	0			0
Liver	No. examined/within normal limits		5/3	5/2	5/3	(5)/0	5/2	5/4	5/2	1(4)/1
	Aggregates(s) of reticuloendothelial cells		2	3	2	0	3	1	3	0
	Atrophy, secondary to inanition		0			(5)	0			(4)
Kidney	No. examined/within normal limits		5/4	5/5		(5)/(5)	5/3			1(4)/1(4)
	Atrophy, tubule, unilateral, focal,	very slight	1	0	0	0	1	2	0	0
	Atrophy, tubule, unilateral, multifocal	very slight	0			0	0		1	0
	Atrophy, tubule, bilateral, focal	very slight	0			0	1	0	1	0
Lacrimal/ Harderian Gland	No. examined		0			(5)	0		0	(4)
	Atrophy					(5)				(4)

( ) denotes decedent animals

Conclusions: In this 14-day inhalation study in CD-1 mice, there was no effect in males and females at 30 ppm (125.10 mg/m^3) (approximately equivalent to 4.1 mg/kg bw/d systemic exposure). However, very slight vacuolation in the cerebrum of male and female mice was observed at 100 ppm (417 mg/m^3) (approximately equivalent to 13 mg/kg bw/d systemic exposure)**.**

3. Eisenbrandt, D.L., Nitschke, K.D., Streeter, C.M. and Wolfe, E.L. (1985): Sulfuryl Fluoride (Vikane gas Fumigant): 2-Week Inhalation Toxicity Probe with Rats and Rabbits. Study No: Unspecified, Report No: K-16399-022, Unpublished, Report date: 2 April, 1985.

Test Compound:	Vikane gas fumigant (99.8% sulfuryl fluoride)
Batch:	TWP 830919-408
Test Species:	Fischer 344 rat; age and source are not stated; 5/sex/dose
Study Duration:	Study began on 27 November 1983 & completed on 2 April 1985
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	None cited. This study was conducted as 'probe' for a 13week study. Deviation from EC guideline Method B.8. Repeated Dose (28 days) Toxicity (Inhalation). Although this is a 14-day study, the applicant states that it meets the guidelines for a 28-day study.

Rats

Study: Groups of 5 male and 5 female rats were exposed (inhalation-nose only) to 0, 100, 300 or 600 ppm (0, 417, 1251, 2502 mg/m^3, respectively) sulfuryl fluoride for 6 hrs/d, 5 days/week for 9 expsoures during a two-week period. Test article intake was approximately equivalent to 0, 7.2, 22, 44 mg/kg bw/d for 0, 100, 300, 600 ppm group, respectively.

Animals were observed daily and bodyweights were recorded several times throughout the study. Prior to the 9th exposure, blood samples were collected from rats for haematology (PCV, Hgb, RBC, WBC & differential counts, MCV, MCH, MCHC, and platelets) and urine samples were collected for urinalysis (bilirubin, glucose, ketones, blood, pH, protein, urobilinogen and specific gravity). Serum samples were collected for clinical chemistry (UN, SGPT, SGOT, AP, glucose, total protein, albumin and globulins) and organs (brain, heart, liver, kidneys, thymus and testes) were weighed at the terminal sacrifice. A complete necropsy was performed on all animals and extensive histopathology was completed on controls and high dose groups (300 & 600 ppm animals). Otherwise, examination of tissues from the intermediate group (100 ppm) was confined to target organs (kidney, lungs, trachea, nasal tissues, larynx) and several other tissues. Special stains were used on brain, lung, kidney, heart and stomach from top dose rats in order to accurately evaluate effects.

Mortality: All males and 4 of 5 females at 600 ppm (2502 mg/m^3) died or were moribund between the second and sixth exposures. No other rats died in this study.

Clinical Findings: Clinical signs are not specified in the report. Bodyweights were statistically reduced at the top dose group (600 ppm-2502 mg/m^3) for most of the study (see table below). Food and water consumption observations were not conducted in this study. Opthalmic observations were also not undertaken. However, eyes were examined at necropsy and histopathology.

Mean body weights (g) in rats exposed to sulfuryl fluoride

Experimental Day	Concentration			
	0	100 ppm (417 mg/m^3)	300 ppm (1251 mg/m^3)	600 ppm (2502 mg/m^3)
Males				
1	170.5	165.5	170.5	167.9
5	179.3	174.2	182.4	120.7*
8	190.1	184.1	193.0	-
11	194.5	188.9	194.3	-
Females				
1	115.0	113.5	112.6	112.0
5	121.2	118.0	117.3	85.9*
8	127.8	125.4	123.8	89.3*
11	129.9	126.8	123.6	80.3*

*Statistically significant difference from control mean by Dunnett's test, alpha = 0.05

Haematology, Clinical Chemistry & Urinalysis: WBC count was elevated at all doses in both sexes and red blood cell parameters were elevated in high dose females (see table below). There were some statistically significant alterations in the surviving female rat at the top dose (see table below). With urinalysis, no changes were identified in survivors.

Summary of haematology results

Dose	No.	RBC x 10^6/mm^3	HGB g/dL	PCV %	WBC x 10^6/mm^3
Males					
0	5	-	-	-	6.7
100 ppm (417 mg/m^3)	5	-	-	-	7.4
300 ppm (1251 mg/m^3)	5	-	-	-	8.8*
600 ppm (2502 mg/m^3)	0	-	-	-	-
Females					
0	5	7.78	17.0	48.0	5.3
100 ppm (417 mg/m^3)	5	7.87	17.0	48.4	6.6*
300 ppm (1251 mg/m^3)	5	7.80	17.0	48.0	7.9*
600 ppm (2502 mg/m^3)	1	8.76*	19.2*	53.0*	11.6*

*Statistically significant difference from control mean by Dunnett's test, alpha = 0.05.
- Values not stated in the report.

Summary of clinical chemistry results in females only exposed to sulfuryl fluoride

Dose	No.	UN (mg/dl)	SGPT (mU/mL)	Glucose (mg/dL)	Albumin (g/dL)	Globulin (g/dL)
0	5	19	37	123	3.5	1.6
100 ppm (417 mg/m^3)	5	21	39	115	3.4	1.7
300 ppm (1251 mg/m^3)	5	17	41	126	3.3*	2.0
600 ppm (2502 mg/m^3)	1	213*	132*	1483*	2.9*	2.3*

*Statistically significant difference from control mean by Dunnett's test, alpha = 0.05.

Pathology: There were some slight increases (<10%) in male rat kidney weight at the 300 ppm (1251 mg/m^3) dose level and a statistically significant increase in relative kidney weight in female rats at the top two doses (see table below). The relative heart weight was elevated for females at 300 ppm (1251 mg/m^3) and 600 (2502 mg/m^3) ppm although the absolute weight was significantly reduced for the surviving female at 600 ppm (2502 mg/m^3).

Summary of organ weights

Dose (ppm)	No.	Terminal Bodyweight (G)	Heart		Kidney	
			(g)	(g/100g)	(g)	(g/100g)
	MALES					
0	5	173.7	0.617	0.355	1.452	0.834
100 ppm (417 mg/m^3)	5	167.7	0.637	0.380*	1.443	0.861
300 ppm (1251 mg/m^3)	5	172.3	0.614	0.356	1.545	0.896
600 ppm (2502 mg/m^3)	0	-	-	-	-	-
	FEMALES					
0	5	112.2	0.459	0.409	1.071	0.955
100 ppm (417 mg/m^3)	5	109.4	0.467	0.427	1.123	1.028
300 ppm (1251 mg/m^3)	5	107.6	0.471	0.438*	1.155	1.075*
600 ppm (2502 mg/m^3)	1	67.6*	0.313*	0.463*	0.961	1.422*

*Statistically significant difference from control mean by Dunnett's test, alpha = 0.05.

Histopathologically, decedents had severe microscopic kidney lesions that included papillary necrosis as well as degeneration and regeneration of collecting tubules and proximal tubules. Numerous microscopic pathologic observations in these rats were considered secondary to the renal effects or terminal changes. The single female rat that survived until termination has moderate degenerative and regenerative changes in renal collecting tubules, hyperplasia of renal papillary epithelium and basophilic epithelial cells in the proximal tubules. This rat also had severe inflammation of nasal mucosa and slight bronchioalveolar inflammation. In addition, it was in poor condition and had a variety of secondary changes. Five of 10 rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride had minimal renal changes. There were no renal effects at 100 ppm (417 mg/m^3).

Summary of histopathological findings

Sex			**Males**				**Females**			
Dose			**0**	**100**	**300**	**600**	**0**	**100**	**300**	**600**
Number of mice examined			5			(5)	5			5 (4)
Kidney	No. examined/within normal limits		5/2	5/3	5/2	(5)/(0)	5/1	5/4	5/0	5(4)/0(0)
	Altered tinctorial properties – increased basophilia, proximal tubule(s):	very slight	0		2	(0)	0		1	0(0)
		slight	0			(0)	0			1(0)
	Hyperplasia-collecting ducts	very slight	0		1	(0)	0		2	0(0)
		slight	0		1	(0)	0		1	0(0)
	Hyperplasia-epithelial, papilla(e)	slight	0		1	(0)	0		1	0(0)
		moderate	0			(5)	0			5(4)
	Necrosis-papilla(e)-	slight	0			(0)	0			1(1)

	Degeneration/ regeneration, collecting ducts	moderate	0			(0)	0				3(3)
		severe	0			(5)	0				4(4)
	Necrosis-papilla(e)-Degeneration/ regeneration, proximal tubule(s): moderate		0			(5)	0				4(4)
	Atrophy, individual nephrons(s):		0			(0)	1	0			0(0)
	Cyst, unilateral, multifocal:		0	1	0	(0)	0				0(0)
	Mineralisation	very slight	2	1	0	(0	2	0			0(0)
		slight	1	0	1	(1)	1		3		3(2)
Lung	No. examined/within normal limits		5/2	5/3	5/2	(5)/(1)	5/4		5/3		5(4)/0(0)
	Alveolar histiocytosis, focal:		1	1	0	(0)	0		1		0(0)
	Atrophy, secondary to inanition		0			(1)	0				2(2)
	Oedema: slight		0			(1)	0				2(2)
	Fibrin, alveoli, multifocal: slight		0			(0)	0				1(1)
	Fibrin, alveoli, diffuse: moderate		0			(1)	0				0(0)
	Haemorrhage: slight		0			(0)	0				1(1)
	Inflammation-subacute, pleura: slight		0			(3)	0				2(2)
	Inflammation-subacute, bronchoalveolar, multifocal: slight		0			(0)	0				1(0)
	Mineralisation, alveoli	slight	0			(0)	0				1(0)
		moderate	0			(1)	0				0(0)
	Thrombus-acute or recent, capillaries	Very slight	0			(1)	0				1(1)
		moderate	0			(1)	0				0(0)
	Inflammation-subacute to chronic, interstitium: very slight or slight		2	1	3	(1)	1				1(0)
Trachea	No. examined/within normal limits		5/5			(5)/(4)	5/5				5(4)/4(4)
	Mineralosation, mucosa: slight		0			(1)	0				0(0)
	Necrosis-individual cell(s), respiratory epithelium		0			(0)	0				1(0)
Nasal Tissues	No. examined/within normal limits		5/5			(5)/(0)	5/4				5(4)/4(4)
	Degeneration, olfactory epithelium, focal:		0			(0)	0		1		0(0)
	Degeneration, respiratory epithelium, focal:		0			(0)	0	1	0		0(0)
	Inflammation-subacute, mucosa, diffuse, with multifocal ulceration and mucopurulent exudates-severe		0			0(0)	0				1(0)
	Inflamamtion-subcuate, olfactory, epithelium, focal: very slight		0			(0)	2	0	0		0(0)
	Necrosis-individual cells(s), olfactory epithelium		0			(5)	0				0(0)
Larynx	No. examined/within normal limits		5/5	5/4	5/4	(5)/(4)	5/4	5/5	5/5		5(4)/3(3)
	Inflamamtion-subacute, mucosa	slight	0	1	0	(0)	0				0(0)
	Mineralisation-mucosa	slight	0		1	(1)	1	0			2(1)
	Necrosis-individual cell(s), respiratory epithelium	slight	0			(0)	0				1(0)

( ) denotes decedent animals

Conclusions: In this 14 day inhalational toxicity study in F344 rats, there was no effect was at 100 ppm (417 mg/m^3) (approximately equivalent to 7.2 mg/kg bw/d systemic expsoure). However, very slight or slight renal hyperplasia was observed in rats at 300 ppm (1251 mg/m^3) (approximately equivalent to 22 mg/kg bw/d systemic exposure)**.** Changes in WBC counts in females at 100 ppm (417 mg/m^3) were not considered toxicologically significant as they were not reproduced in the 13 week study.

Rabbits

Test Compound:	Vikane gas fumigant (99.8% sulfuryl fluoride)
Batch:	TWP 830919-408
Test Species:	NZW rabbit; age and source are not stated; 3/sex/dose
Study Duration:	Study began on 27 November 19983. Completion date not stated.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	None cited. This study was conducted as 'probe' for a 13week study. Deviation from EC guideline Method B.8. Repeated Dose (28 days) Toxicity (Inhalation). This was a 2-week study. The rabbit groups were only 3/sex/dose, otherwise it meets the guideline.

Study: Groups of 3 male and 3 female rabbits were exposed (inhalation-nose only) to 0, 100, 300 or 600 ppm (0, 417, 1251, 2502 mg/m^3, respectively) sulfuryl fluoride for 6 hrs/d, 5 days/week for 9 expsoures during a two-week period. Test article intake was approximately equivalent to 0, 4.1, 13, 25 mg/kg bw/d for 0, 100, 300, 600 ppm group, respectively.

Animals were observed daily and bodyweights were recorded several times throughout the study. Prior to the 9th exposure, blood samples were collected from rabbits for haematology (PCV, Hgb, RBC, WBC & differential counts, MCV, MCH, MCHC, and platelets). Serum samples were collected for clinical chemistry (UN, SGPT, SGOT, AP, glucose, total protein, albumin and globulins) and organs (brain, heart, liver, kidneys, thymus and testes) were weighed at the terminal sacrifice. A complete necropsy was performed on all animals and extensive histopathology was completed on controls and high dose groups (300 & 600 ppm animals). Otherwise, examination of tissues from the intermediate group (100 ppm) was confined to target organs and several other tissues.

Mortality: Two 600 ppm (2502 mg/m^3) dose female rabbits died during the study: one had a fractured tibia subsequent to convulsions after the fifth exposure and the other had a fractured vertebrum after the sixth exposure but convulsions were not observed.

Clinical Findings: One top dose rabbit had convulsions after the fifth exposure. Most rabbits exposed to 300 ppm (1251 mg/m^3) or 600 ppm (2502 mg/m^3) had moderate nasal exudate, probably indicative of chronic inflammation due to exposure. Male and female rabbits that survived exposure to 600 ppm (2502 mg/m^3) were slightly hyperactive compared to control animals. There were no statistically significant effects on body weight. Food and water consumption were not measured. Ophthalmic observations were not undertaken, although eyes were examined at necropsy and histopathology.

Haematology: Clinical Chemistry & Urinalysis: No effects were attributed to treatment other than an elevated WBC in one high dose male rabbit that had pneumonia, which might have been secondary to treatment. No notable effects were noted in clinical chemistry apart from a slightly

reduced (non-significant) serum albumin in some rabbits at 300 ppm (1251 mg/m^3) and 600 ppm (2502 mg/m^3) which was related to altered nutritional status. Urinalysis was not performed.

Pathology: Terminal bodyweights were slightly decreased at 300 ppm (1251 mg/m^3) and 600 ppm (2502 mg/m^3). Some of these rabbits also had decreased liver weights at termination. However, the increased liver weight at 100 ppm (417 mg/m^3) in females is considered to be a chance finding. The heart weight of the surviving female at 600 ppm (2502 mg/m^3) appeared to be raised.

Summary of organ weights

Dose (ppm)	No.	Terminal Bodyweight (g)	Brain		Heart		Liver	
			(g)	(g/100g)	(g)	(g/100g)	(g)	(g/100g)
	Males							
0	3	3250.2	9.74	0.30	6.69	0.21	114.51	3.51
100 ppm (417 mg/m^3)	3	3212.3	9.27	0.29	6.97	0.22	117.89	3.68
300 ppm (1251 mg/m^3)	3	3061.7	9.90	0.32	5.82	0.19	91.66	2.99
600 ppm (2502 mg/m^3)	3	2917.8*	9.04*	0.31	5.86	0.20	84.15	2.89
	Females							
0	3	3503.1	9.29	0.27	6.58	0.19	96.69	2.77
100 ppm (417 mg/m^3)	3	3593.7	9.87	0.28	6.70	0.19	137.21*	3.83*
300 ppm (1251 mg/m^3)	3	3384.4	9.69	0.29	6.36	0.19	97.68	2.86
600 ppm (2502 mg/m^3)	1	3315.7	10.29	0.31	8.47*	0.26*	88.95	2.68

*Statistically significant difference from control mean by Dunnett's test, alpha = 0.05.

Other than the fractures observed for the prematurely decedent rabbits, there were no significant gross pathological findings.

Histopathology revealed treatment-related, focal malacia (necrosis) in the cerebrum of all rabbits exposed to 600 ppm (2502 mg/m^3) sulfuryl fluoride as well as one male and one female exposed to 300 ppm (1251 mg/m^3). Also, the same part of the cerebrum was vacuolated in all rabbits that were exposed to 300 ppm (1251 mg/m^3) or 600 ppm (2502 mg/m^3). Most rabbits exposed to 300 ppm (1251 mg/m^3) or 600 ppm (2502 mg/m^3) sulfuryl fluoride had moderate inflammation of the nasal tissues. Some of these rabbits also had acute inflammation of the trachea and one female had inflammation of the bronchi and bronchioles. A variable haematopoietic response was associated with the inflammation in the respiratory system of some rabbits. Alterations included lymphoid hyperplasia in the mediastinal lymph nodes and spleen. There were no histopathological changes at 100 ppm (417 mg/m^3).

Conclusions: In this 14-day inhalational toxicity study in rabbits, there was no effect at 100 ppm (417 mg/m^3) (approximately equivalent to 4.1 mg/kg bw/d systemic exposure). However, focal malacia (necrosis) and vacuolation in the cerebrum and inflammation of the respiratory tract was noted at 300 ppm (1251 mg/m^3) (approximately equivalent to 13 mg/kg bw/d systemic exposure)**.**

4. Nitschke, K.D. and Quast, J.F. (1991): Sulfuryl fluoride: Two-Week-Inhalation Toxicity Study in Beagle Dogs. Study No: Unspecified, Report No: K-016399-038, Unpublished, Report date: 30 April 1991.

Test Compound:	Sulfuryl fluoride (99.6% purity)
Batch:	880329 752 MAR/88
Test Species:	Beagle dog; age and source are not stated; 1/sex/dose (1 male & 1 female)
Study Duration:	Study started on 26 March 1990 & completed on 30 April 1991.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 82-4, Supplemental. Deviation from EC guideline Method B.8. Repeated Dose (28 days) Toxicity (Inhalation). The study was conducted in dogs and it was a probe study using only one dog/sex/dose level. Histologic examination of likely target tissues was conducted on all dogs rather than a wider range of tissues on control and high dose.

Study: Groups of 1 male and 1 female dog were exposed (inhalation) to 0, 30, 100 or 300 ppm (0, 125.1, 417, 1251 mg/m^3, respectively) sulfuryl fluoride for 6 hrs/d, 5 days/week for 9 expsoures during a two-week period. Test article intake was approximately equivalent to 0, 0.9, 2.9, 5.8 mg/kg bw/d for 0, 30, 100, 300 ppm group, respectively.

Whole-body inhalation exposures were conducted under dynamic airflow conditions. Animals were observed daily and weighed on test days –7, -5, -3, 1, 3, 5, 8 and 11. Animals were necropsied on the day after the last exposure. Blood samples were obtained from each animal at least twice prior to the initial exposure to sulfuryl fluoride and again at necropsy for haematology (HCT, Hgb, RBC, WBC/differential count, and platelets) and clinical chemistry (AP, AST, ALT, CK, UN, creatinine, total protein, albumin, globulin, glucose, cholesterol, triglycerides, total bilirubin, Na, K, P, Cl, Ca and F). Urinalysis (pH, bilirubin, glucose, proteins, ketones, occult blood, urobilinogen and specific gravity) was conducted on samples obtained from the urinary bladders at necropsy. An ophthalmologic examination was conducted prior to the study and after the last exposure. Major organs were weighed and selected tissues examined histopathologically.

Mortality: All dogs survived the nine exposures.

Clinical Findings: Due to the large bodyweight variations in the dogs used in this study, each dog served its own control. Bodyweights were obtained several times prior to the first exposure. The bodyweight on day 11 of the female dog exposed to 300 ppm (1251 mg/m^3) was decreased (not statistically significant) by approximately 500 g from pre-exposure values (mean of pre-exposure values-9337 g). Body weights for the male dog exposed to 300 ppm (1251 mg/m^3) and the male and female dogs exposed to 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3) were comparable to pre-exposure values.

At 300 ppm (1251 mg/m^3), infrequent intermittent episodes of tremors and tetany were observed in both dogs beginning with the 5th exposure. On day 9, during the 7th exposure, the tremors and tetany were severe enough that the exposure was terminated after approximately 5.5 hours. Within thirty minutes after terminating the exposure, both dogs appeared to be normal. Similar clinical effects were noted during subsequent exposure periods and were rapidly reversible even during the exposure period. There were no exposure-related effects noted in dogs exposed to 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3) sulfuryl fluoride. Food and water consumption were not assessed. No treatment related effects were noted in ophthalmic observations in the report.

Haematology, Clinical Chemistry and Urinalysis: Haematology values for dogs exposed up to the highest concentrations (300 ppm-1251 mg/m^3) were comparable to pre-exposure values. Serum fluoride levels of dogs exposed to 100 ppm (417 mg/m^3) or 300 ppm (1251 mg/m^3) were elevated to 2-4 fold higher than control values. Serum fluoride levels of dogs exposed to 30 ppm (125.1 mg/m^3) and all other clinical chemistry values were comparable with control and/or pre-exposure values. Urinalysis values for male and female dogs exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride were comparable to control values. The specific gravity for the male dog exposed to 100 ppm (417 mg/m^3) was lower than for the control or the 300 ppm (1251 mg/m^3) exposed dog. This was not considered to be exposure-related, since there was no apparent dose-response relationship.

Serum samples were collected shortly after exposure on days 5 and 9 to measure calcium levels in an attempt to determine if the tremors and tetany observed during exposure at 300 ppm (1251 mg/m^3) were due to an electrolyte imbalance. At the time the blood samples were drawn, the animals appeared clinically normal. While the tremors and tetany noted may be due to a localised electrolyte imbalance, total serum calcium levels were comparable to control values. No attempt was made to measure ionic versus non-ionic calcium levels in the serum.

Pathology: There were no apparent exposure-related effects noted on organ weights and in gross pathology (including teeth). Minimal microscopic inflammatory changes were observed in the nasal turbinates of the male and female dog and trachea of the female dog exposed to 300 ppm (1251 mg/m^3). Although numerous microscopic sections were examined from the cerebral cortex, brain stem, cerebellum and medulla oblongata, there were no changes detected in dogs exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride. There were no exposure-related effects noted in dogs exposed to 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3) sulfuryl fluoride.

Conclusions: In this 14-day exploratory inhalation study in Beagle dogs, there was no effect at 100 ppm (417 mg/m^3) (approximately equivalent to 2.9 mg/kg bw/d systemic exposure). However, tremors and tetany were noted beginning with the 5th exposure at 300 ppm (1251 mg/m^3) (approximately equivalent to 8.7 mg/kg bw/d systemic exposure). There were no serum electrolyte or histologic CNS changes found to explain this effect. Also at 300 ppm (1251 mg/m^3), the upper respiratory tract showed histological signs of inflammatory changes**.**

4.4.3 Subchronic Studies

There were no subchronic oral toxicity studies submitted. All studies of this length were inhalational.

1. Nitschke, K.D. and Quast, J.F. (1993): Sulfuryl fluoride: Thirteen-Week Inhalation Toxicity Study in CD-1 Mice. Study No: Unspecified, Report No: K-016399-032, Unpublished, Report date: 28 December 1993.

Test Compound:	Sulfuryl fluoride (99.6% purity)
Batch:	WP 880329 752 MAR/88
Test Species:	CD-1 mice; age and source are not stated; 10/sex/dose main study; 4/sex /dose nervous system investigation.
Study Duration:	Study started on 29 November 1988. Completion date not stated.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 82-4, OECD 412, 84/449/EEC Method B8, MAFF Guideline: Subchronic Inhalation Toxicity Deviation from EC guideline Method B.29.Sub-Chronic Inhalation Toxicity Study: 90-Day Repeated Inhalation Dose Study Using Rodent Species. This study, with its extra groups for evaluation of brain pathology and serum fluoride, exceeds requirements of the guideline. Although the eyes were not examined after exposure using an ophthalmoscope, they were histologically examined in two separate groups using separate methods for fixing tissues.

Study: Groups of 14 CD-1 mice/sex were exposed to 0, 10, 30 or 100 ppm (0, 41.7, 125.1 or 417 mg/m^3, respectively) sulfuryl fluoride via inhalation (whole body exposure) for 6 hour/day, 5 days/week for 13 weeks. Test article intake was approximately equivalent to 0, 1.4, 4.1 or 13 mg/kg bw/d for 0, 10, 30 or 100 ppm sulfuryl fluoride, respectively.

Parameters examined were daily clinical observations; weekly detailed clinical examination; functional observational battery (FOB) on all mice after 4, 8 and 12 weeks of exposure; weekly bodyweights; haematology (HCT, Hgb, RBC, WBC/differential, platelets) of 10 mice/sex/dose prior to necropsy; clinical chemistry (ALT, AST, AP, UN, creatinine, total protein, albumin, globulin, glucose, cholesterol, triglycerides, total bilirubin, Ca, P and F) on 10 mice/sex/dose at necropsy; gross pathologic examinations of 10/sex/dose; histopathologic examination of a wide range of tissues from the control and 100 ppm (417 mg/m^3) groups; histologic examination of nasal tissues, trachea, lungs, brain, thyroid, heart, liver, kidneys, salivary glands and testes from mice in the 10 ppm (41.7 mg/m^3) and 30 ppm (125.1 mg/m^3) groups.

The remaining animals, 4/sex/dose level, were used to measure serum fluoride levels. In addition, tissues from these animals were perfused with glutaraldehyde/formaldehyde fixative and neural tissues (cerebellum, cerebrum, medulla oblongata, thalamus/hypothalamus, spinal cord, dorsal root ganglia, trigeminal ganglia, peripheral nerves, including sciatic, tibial and sural nerves) as well as the head, liver, kidneys and lung were examined histopathologically. Chamber concentrations were measured using a Miran 1A IR and were exactly the same as target concentrations.

Mortality: Three mice died during the study: one control female due to inanition (tongue abscess) and the other two due to accidental handling trauma.

Clinical Findings: There were no exposure-related cageside, clinical or functional observational effects in any of the exposure groups. In general, mean bodyweights of male and female mice exposed to 100 ppm (417 mg/m^3) were statistically significantly decreased from control values from day 25 to the end of the study. By the end of the study, the mean bodyweights for male and female mice exposed to 100 ppm (417 mg/m^3) sulfuryl fluoride were 89 and 91% of control values, respectively. Mean body weights of male and female mice exposed to 10 ppm (41.7

mg/m^3) or 30 ppm (125.1 mg/m^3) were comparable to control values. Food and water consumption was not assessed. Ophthalmic observations were not assessed following treatment.

Summary of Body Weights (g)

	Males				Females			
Conc.	**0**	**10 ppm (41.7 mg/m^3)**	**30 ppm (125.1 mg/m^3)**	**100 ppm (417 mg/m^3)**	**0**	**10 ppm (41.7 mg/m^3)**	**30 ppm (125.1 mg/m^3)**	**100 ppm (417 mg/m^3)**
Days on Test								
1	33.1	32.4	32.4	32.8	24.9	24.2	24.9	24.1
25	35.9	35.5	35.3	33.9	27.5	27.2	28.2	25.5*
93	39.6	38.8	38.9	35.3*	30.3	30.7	31.2	27.6**

*Statistically different from control mean by Dunnett's test, alpha= 0.05
**Statistically different from control mean by Wilcoxon's test, alpha= 0.05

FOB: The auditory brainstem response in about half of the CD-1 mice from several different purchase orders had been shown to be poor; thus the startle response, typically measured in FOBs, was not measured in this study. FOB results were similar in treated and control groups.

Haematology, Clinical Chemistry and Urinalysis: There was no evidence of an exposure related effect on haematology. Serum fluoride levels in male and female mice exposed to 100 ppm (417 mg/m^3) and female mice exposed to 30 ppm were statistically significantly elevated above controls in an exposure-related manner. Alkaline phosphatase activity and triglyceride levels in male mice exposed to 100 ppm (417 mg/m^3) were slightly but statistically significantly increased from control values. The authors have postulated that this change may be a secondary effect associated with an altered nutritional status and the body eight decrease. All remaining clinical chemistry and electrolyte parameters for mice exposed to 10 ppm (41.7 mg/m^3), 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3) were comparable to control values. Urinalysis was not conducted.

Clinical Chemical results

Conc.	**Males**			**Females**
	AP (mu/mL)	Triglyceride (mg/dL)	Serum Fluoride (ppm, n=4)	Serum Fluoride (ppm, n=4)
0	43	91	0.107	0.090
10 ppm (41.7 mg/m^3)	42	83	0.112	0.088
30 ppm (125.1 mg/m^3)	47	89	0.156	0.132*
100 ppm (417 mg/m^3)	57*	143*	0.259*	0.233*

*Statistically different from control mean by Dunnett's test, alpha = 0.05.

Pathology: There were no exposure-related gross pathologic changes noted at any dose. Several absolute organ weight values in males and females exposed to 100 ppm (417 mg/m^3) were different from control values. These differences included a statistically significant decrease in absolute brain, heart and liver weights for male and female mice and absolute kidney weights in male mice (see table below). These absolute organ weight changes were not accompanied by significant histopathologic changes and the relative organ weights for these animals were comparable to control values. The terminal body weight in male and female mice exposed to 100

ppm (417 mg/m^3) was statistically significantly decreased. Thus, the decrease in absolute organ weights was considered to be a secondary reflection of the body weight decrease. Terminal body weight and absolute and relative organ weights of male and female mice exposed to 10 ppm (41.7 mg/m^3) or 30 ppm (125.1 mg/m^3) sulfuryl fluoride were comparable to control values.

Summary of organ weights

Conc. (ppm)	Final Bodyweight (g)	Brain		Heart		Kidneys		Liver	
		(g)	(g/100g)	(g)	(g/100g)	(g)	(g/100g)	(g)	(g/100g)
Males									
0	38.9	0.502	1.294	0.170	0.436	0.625	1.604	2.212	5.682
10	37.5	0.493	1.321	0.166	0.444	0.614	1.645	2.146	5.770
30	37.5	0.479	1.288	0.164	0.439	0.638	1.703	2.163	5.779
100	34.3*	0.471*	1.377	0.147*	0.428	0.490*	1.427	1.861*	5.411
Females									
0	29.7	0.511	1.721	0.134	0.451			1.621	5.460
10	31.1	0.504	1.619	0.141	0.453			1.650	5.300
30	30.6	0.504	1.647	0.139	0.454			1.673	5.463
100	27.5*	0.482*	1.760	0.125*	0.454			1.477*	5.373

*Statistically different from control mean by Dunnett's test, alpha = 0.05.

There were a number of microscopic observations in mice from the various groups, which were primarily related to the three mice which died during the study and one mouse with a liver abscess. These observations were not considered exposure-related. However, target organ effects were observed in the brain and thyroid gland of 100 ppm (417 mg/m^3) exposed mice (see table below).

Summary of histopathological findings in the main study

Sex			**Males**				**Females**			
Dose			**0**	**10**	**30**	**100**	**0**	**10**	**30**	**100**
Number of mice examined			10				10			
Brain-Cerebellum	No. examined/within normal limits		10/10				10/10			
Brain-Cerebrum	No. examined/within normal limits		10/10			10/1	10/10			10/0
	Vacuolation, caudate putamen, bilateral, focal	very slight	0			7	0			3
		slight	0			2	0			5
	Vacuolation, external capsule, bilateral, focal	very slight	0			7	0			6
		slight	0			2	0			4
Brain-Medulla oblongata	No. examined/within normal limits		10/10				10/10			
Brain-Olfactory lobe	No. examined/within normal limits		10/10				10/10			
Brain-Thalamus/hypothalamus	No. examined/within normal limits		10/10			10/1	10/10			10/0
	Vacuolation, external capsule, bilateral, focal: very slight		0			9	0			10
Salivary Glands	No. examined/within normal limits		10/9	10/10	10/9	10/0	10/9	9/9	10/10	
	Missing		0				0	1	0	
	Decreased secretory material: very slight		1	0	1	10	1	0		
Thyroid Gland	No. examined/within normal limits		10/8	10/10		10/1	10/10			10/4
	Cystic dilation, follicles(s), focal:		1	0			0			
	Degeneration – fibrinoid, blood vessels, focal:		1	0			0			
	Hypertrophy, follicles(s): very slight		0			9	0			6

Nervous System/Special Process: Tissues were examined from the nervous systems of the mice which had been subjected to whole-body perfusion. To maximise the detection of possible changes in the perfusion fixed tissue, in contrast to the immersion fixed tissue, a total of nine sections of brain were prepared from each mouse from regions 3, 4 and 7. Region 3 (section 3) represented corpus callosum, caudate putamen, globus pallidus, optic chiasm, cortex (frontal & parietal), lateral ventricles; Region 4 (section 4) represented hippocampus, thalamus, hypothalamus, cortex (parietal & temporal), third ventricle; and region 5 (section 5) represented cerebellum, inferior colliculus, V nerve, pyramidal tract, nucleus trapezoid body.

Despite the additional evaluation of extra brain sections, the microvacuoles in the various affected regions appeared less prevalent in the perfusion fixed than in the immersion fixed tissue. Whether this was an artefact or due to fewer mice being evaluated was undetermined. There were no other nervous system tissues affected in the perfusion fixed mice, and these findings were consistent with the absence of observed effects in other parts of the nervous system following immersion fixation.

Conclusions: In this 13-week inhalation study in CD-1 mice, the NOEC was 30 ppm (125.1 mg/m^3) (approximately equivalent to 4.1 mg/kg bw/d systemic exposure) primarily based on

reduced bodyweight (ca. 10%) and vacuolation in the brain at 100 ppm (417 mg/m^3) (approximately equivalent to 13 mg/kg bw/d systemic exposure).

2. Nitschke, K.D. Dittenber, D. A., and Eisenbrandt, D.L. (1987a): Sulfuryl fluoride (Vikane Gas Fumigant): 13-Week-Inhalation Toxicity Study with Rats. Study No: Unspecified, Report No: K-016399-025R, Unpublished, Report date: 16 November 1987.

Test Compound:	Sulfuryl fluoride (99.8% purity)
Batch:	TWP 830919-408
Test Species:	Fischer 344 Rats; age and source are not stated; 10/sex/dose
Study Duration:	Study started on 11 September 1984 & completed on 16 November 1987.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 82-4 (19) Deviation from EC guideline Method B.29.Sub-Chronic Inhalation Toxicity Study: 90-Day Repeated Inhalation Dose Study Using Rodent Species. There was no ophthalmologic examination. All other aspects of the guideline have been met.

Study: Groups of 10 rats/sex were exposed to 0, 30, 100 or 300 ppm (0, 125.1, 417, 1251 mg/m^3, respectively) sulfuryl fluoride via inhalation (whole body exposure) for 6 hour/day, 5 days/week for 13 weeks. Test article intake was approximately equivalent to 0, 2.2, 7.2, 22 mg/kg bw/d, respectively.

Observations included daily clinical observations; weekly bodyweights; haematology (PCV, Hgb, RBC, MCV, MCH, MCHC, WBC differential count, platelets) on the day of necropsy; clinical chemistry (Ca, P, creatinine, UN, ALT, AST, AP, glucose, total protein, albumin, globulins, F) at terminal sacrifice; urinalysis (bilirubin, glucose, ketones, blood, pH, protein, urobilinogen, specific gravity) after 11 weeks of exposure; organ weights (brain, heart, liver, kidneys, thymus, testes) for all animals; gross pathology for all animals; complete histopathologic examination of a wide range of tissues of control and top dose rats; histopathological examination of brains, kidneys, nasal tissues, trachea and lungs of rats in the 30 and 100 ppm groups; and special staining of brain sections from 3 rats/sex from the top dose. Electron microscopy of top dose rat brain sections was attempted but failed due to numerous artifacts (tissues had been previously fixed for light microscopy). Chamber concentrations (29.8, 100, 297 ppm) were very close to the target (30, 100, 300 ppm) concentrations, as measured with a Miran 1A IR

Mortality: No rat died during the study.

Clinical Findings: There were no clinically observed effects which were considered to be exposure-related. Bodyweights of males and females in the 300 ppm (1251 mg/m^3) groups were statistically significantly decreased from control values after 24 and 45 days, respectively. Overall, the body weights of rats exposed to 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3) were comparable to control values throughout the 13-week exposure period. Food consumption and ophthalmology were not addressed.

Haematology, Clinical Chemistry and Urinalysis: RBC counts for male rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride were statistically significantly decreased from control values; RBC counts of female rats exposed at 300 ppm (1251 mg/m^3) were slightly decreased from

control values (see table below). Platelet counts for male rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride were statistically significantly increased from control values. Since the RBC and the platelet counts were within the range of historical control values, these effects were not considered to be toxicologically significant. The WBC counts of rats exposed to concentrations as high as 300 ppm (1251 mg/m^3) sulfuryl fluoride were not significantly elevated from control values. However, a slight increase in the percentage of segmented neutrophils and a slight decrease in the percentage of lymphocytes was observed in male rats and to a lesser extent in female rats exposed to 300 ppm (1251 mg/m^3). No other haematologic parameters were affected in rats exposed to sulfuryl fluoride.

Several clinical chemistry values from rats exposed to 100 ppm (417 mg/m^3) or 300 ppm (1251 mg/m^3) sulfuryl fluoride were statistically significantly different from control values (see table below). The authors have stated that a slight but statistically significant increase in urea nitrogen and decrease in calcium levels in female rats exposed to 300 ppm (1251 mg/m^3) were not considered to be toxicologically significant even though they may be due to the test material The authors have not given any reason for this conclusion. Furthermore, the observed increases in AP activity and globulin values and decreases in ALT activity, total protein and albumin at 300 ppm (1251 mg/m^3) were either within or very close to the range of historical control values and were not considered to be toxicologically significant. No other clinical chemistry parameters were affected in rats exposed to sulfuryl fluoride. Serum fluoride levels were unaffected in male rats exposed to 300 ppm (1251 mg/m^3) or male and female rats exposed to 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3). Serum fluoride levels of female rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride were slightly above control values. The specific gravity of urine from male rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride was statistically significantly decreased from control values. No other urinary parameters were affected in rats exposed to sulfuryl fluoride.

Haematology, clinical chemistry and urinalysis results in the rat 13 week inhalational toxicity study with sulfuryl fluoride

Conc (ppm)	RBC (10^6/cu .mm)	Plat (10^3/cu .mm)	ALT (mU /ml)	AP (mU /ml)	UN (mg/dl)	Globulin (g/dl)	Total protein (g/dl)	Albumin (g/dl)	Calcium (mg/dl)	Fluoride (ug/ml)	Urinary specific gravity
Males											
0	9.07	502	65	65		2.5				1.00	1.063
30	9.05	516	62	67		2.5				0.72	1.061
100	9.08	548	52**	72		2.7				0.89	1.062
300	8.64*	565*	62**	85*		2.9*				1.15	1.050*
Females											
0	8.63	582		48	16		6.0	3.7	11.0	0.61	1.049
30	8.73	565		51	16		5.9	3.6	10.8	.074	1.049
100	8.74	599		53	17		5.9	3.6	10.8	0.58	1.050
300	8.28	619		72*	21**		5.6*	3.4*	10.7*	1.37	1.040

*Statistically different from control mean by Dunnett's test, alpha = 0.05.

**Statistically different from control mean by Wilcoxon's test, alpha = 0.05.

Pathology: Many of the absolute and relative organ weights of rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride were statistically significantly different from the respective control values. These changes were considered to be a secondary reflection of the decreased bodyweights. The final body weights of rats exposed to lower concentrations of sulfuryl fluoride were comparable to control values. The absolute brain weight of female rats exposed to 100 ppm (417 mg/m^3) sulfuryl fluoride was statistically significantly decreased from control values. Since

the relative brain weight was comparable to control values, this decrease in absolute weight was considered to be due to slightly decreased body weight and to be of no toxicological significance. All other absolute and relative organ weights of rats exposed to 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3) sulfuryl fluoride were comparable to control values.

At necropsy, gross examination of rats exposed to 100 ppm (417 mg/m^3) or 300 ppm (1251 mg/m^3) sulfuryl fluoride revealed mottled upper and lower incisors. In addition, pale foci were observed on the lung surface of most rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride.

Summary of organ weights

Conc. (ppm)	Final body weight (g)	Brain		Heart		Kidneys		Liver		Testes		Thymus	
		(g)	(g/100g	(g)	(g/100g)	(g)	(g/100g)	(g)	(g/100g)	(g)	(g/100g)	(g)	(g/100g)
Males													
0	285.0	1.90	0.67	0.86	0.30	2.05	0.72	7.47	2.62	3.05	1.07	0.22	0.08
30	289.3	1.92	0.67	0.91	0.31	2.13	0.74	7.39	2.55	3.11	1.08	0.22	0.08
100	292.6	1.93	0.66	0.90	0.31	2.10	0.72	7.34	2.51	3.06	1.05	0.23	0.08
300	238.1*	1.83	0.77**	0.78	0.33*	1.85	0.78*	6.03*	2.54	2.98	1.26*	0.17*	0.07
Females													
0	163.5	1.82	1.11	0.59	0.36	1.31	0.80	4.56	2.79			0.21	0.126
30	159.3	1.78	1.12	0.56	0.35	1.31	0.82	4.34	2.72			0.21	0.133
100	157.4	1.75*	1.11	0.57	0.36	1.31	0.83	4.34	2.75			0.21	0.132
300	141.9*	1.72*	1.22*	0.52	0.37	1.25	0.88*	3.69*	2.60*			0.17*	0.117*

*Statistically different from control mean by Dunnett's test, alpha = 0.05.

**Statistically different from control mean by Wilcoxon's test, alpha = 0.05.

A summary of histopathology is presented in the table below. Subacute inflammation was detected histopathologically in the nasal tissues of all male and female rats exposed to 300 ppm sulfuryl fluoride. All females and most males had minimal inflammation in the nasal tissue. A few males had more severe inflammation in the respiratory and olfactory mucosa with mucopurulent exudate in the nasal passages. The more extensive inflammation was accompanied by degeneration and reactive changes in the mucosa. Slight, subpleural histiocytosis was observed in the lungs of rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride

Microscopic vacuolation was observed in the brains of all rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride. The minimal vacuolation was in the area of the caudate-putamen nuclei and was more prominent in the white fibre tracts of the internal capsule than in the adjacent neuropil. Special stains of the brain with LFB-PAS or Sevier Munger stain did not reveal any additional effects.

A slight decrease in protein droplet formation was observed in the renal cortical tubules of male rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride and was likely to be secondary to the decreased bodyweight. Most female rats exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride had

very slight hyperplasia of the renal collecting ducts which was most apparent in the outer portion of the inner zone of the medulla.

There was no histopathologic correlate to the mottled teeth, which were observed at necropsy. All other histopathological changes observed were considered to be spontaneous changes typical of Fischer 344 rats and unrelated to exposure to sulfuryl fluoride.

Summary of histopathological findings

Sex			**Males**				**Females**			
Dose			**0**	**30**	**100**	**300**	**0**	**30**	**100**	**300**
Number of rats examined			10				10			
Brain	No. examined/within normal limits		10/10			10/0	10/10			10/0
	Vacuolation, cerebrum, bilateral, focal	slight	0			10	0			10
Kidneys	No. examined/within normal limits		10/0	10/3	10/2	10/0	10/1	10/7	10/8	10/1
	Aggregate(s) of reticuloendothelial cells		0				1		0	1
	Atrophy, individual nephron	very slight	9	7	8	3	4	0	1	2
	Cyst, medulla, focal		0		1	0	0			
	Hyperplasia, collecting ducts	very slight	0				0			9
	Mineralisation, tubule(s), multifocal	slight	6	2	3		4	0	1	2
	Decreased protein droplets, cortex	very slight				10	0			
	Dilated with proteinaceous cats, tubule(s), focal:		0				2		0	
Lungs	No. examined/within normal limits		10/10	10/9	10/10	10/0	10/8	10/9	10/8	10/0
	Alveolar histiocytosis, subpleural, focal:	very slight	0	1	0		2	1	2	0
		slight	0			10	0			10
Nasal Turbinates	No. examined/within normal limits		10/10	10/8	10/9	10/0	10/6	10/6	10/4	10/0
	Cyst, focal		0				0		1	0
	Inflammation–subacute, mucosa, diffuse	Very slight	0			4	0	1	0	9
		slight	0			3	0			1
		moderate	0			1	0			
		sever	0			2	0			
	Inflammation–subacute to chronic, respiratory, multifocal	Very slight	0				2			0
		slight	0	2	1	0	2	1	4	0

Conclusions: In this 13-week inhalation study in F344 rats, the NOEC was 30 ppm (125.1 mg/m^3) (approximately equivalent to 2.2 mg/kg bw/d systemic exposure), based decreased brain weight in females at exposures levels at 100 ppm (417 mg/m^3) (approximately equivalent to 7.2 mg/kg bw per day). Dental fluoris (mottled teeth), observed at 100 ppm (417 mg/m^3) (approximately equivalent to 7.2 mg/kg bw per day), was not considered an adverse effect. Increase in fluoride levels in tissue and blood are considered to be a marker of exposure and not an adverse effect *per se*.

3. Nitschke, K.D. Zimmer, M. A., & Eisenbrandt, D.L. (1987b): Sulfuryl fluoride (Vikane Gas Fumigant): 13-Week-Inhalation Toxicity Study with Rabbits. Study No: Unspecified, Report No: K-016399-025B, Unpublished, Report date: 16 November 1987.

Test Compound:	Sulfuryl fluoride (99.8% purity)
Batch:	TWP 830919-408
Test Species:	NZW rabbit; age and source are not stated; 7/sex/dose
Study Duration:	Study started on 11 September 1984 & completed on 16 November 1987.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 82-4 Deviation from EC guideline: There is not guideline for a Non-Rodent 90-Day Inhalation study.

Study: Groups of 7 rabbits/sex were scheduled for exposure to 0, 30, 100 or 600 ppm (0, 125.1, 417, 2502 mg/m^3, respectively) sulfuryl fluoride via inhalation (whole body exposure) for 6 hour/day, 5 days/week for 13 weeks. After 9 exposures to 600 ppm (2502 mg/m^3) rabbits were exposed to 300 ppm (1251 mg/m^3) for the remainder of the study. Test article intake was approximately equivalent to 0, 1.4, 4.1 or 13 mg/kg bw/d for 0, 30, 100 or 600/300 ppm, respectively.

Observations included daily clinical observations; weekly body weights; haematology (HCT, Hgb, RBC, MCV, MCH, MCHC, WBC differential count, platelets) at the end of the study; clinical chemistry (Ca, P, creatinine, UN, ALT, AST, AP, glucose, total protein, albumin, globulins, F) at the end of the study; gross pathology for all animals; weights of brain, heart, liver, kidneys and testes; complete histopathologic examination of control and top dose animals' tissues; histopathology of the brain, kidneys, liver, nasal tissues, oral tissues, trachea and lungs of low and middle dose rabbits; and special staining techniques and light microscopy of sections of the brain from one female rabbit exposed to 100 ppm and 3 males and 4 females from the top dose group. Chamber concentrations were very close (29.8, 100, 337 ppm including initial 9 exposures at 600 ppm to the target (30, 100, 300, 600 ppm) concentrations, as measured by a Miran 1A IR. The highest concentration was reduced to 300 ppm after 9 exposures following a death and convulsions in two other animals.

Mortality: One female rabbit was euthanised following the 8th exposure to 600 ppm (2502 mg/m^3) as the animals was not using one of its hind limbs.

Clinical Findings: Convulsions were observed in one male and one female rabbit following the ninth exposure to 600 ppm (2502 mg/m^3) sulfuryl fluoride. A second female rabbit did not use one of its hind limbs following the 8th exposure to 600 ppm (2502 mg/m^3) and was euthanised. There were no clinically visible effects in rabbits exposed to 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3) for 13 weeks or 300 ppm (1251 mg/m^3) for 11 weeks. Food consumption measurement and ophthalmology examination were not undertaken.

The body weights of male rabbits exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride were statistically significantly decreased from control values from days 11 to 60 and remained slightly decreased until termination. The body weights of females at this dose level were slightly decreased on days 25 and 88. Body weights of male and female rabbits exposed to 100 ppm (417 mg/m^3) sulfuryl fluoride were slightly decreased from control values at the end of the 13-week

exposure period. Body weights of rabbits exposed to 30 ppm (125.1 mg/m^3) sulfuryl fluoride were comparable to control values throughout the 13-week exposure period.

Summary of Body Weights (g)

	Males				Females			
Conc. (ppm)	**0**	**30**	**100**	**600/300**	**0**	**30**	**100**	**600/300**
Days on Test								
-1	3318	3329	3322	3334	3255	3273	3301	3333
4	3338	3358	3329	3346	3275	3283	3351	3363
11	3481	3499	3408	3254*	3368	3408	3476	3378
25	3712	3714	3674	3323*	3646	3662	3699	3555
88	4139	4109	3963	3823	4564	4591	4383	4301

*Statistically different from control mean by Dunnett's test, alpha = 0.05.

Haematology, Clinical Chemistry and Urinalysis: The WBC counts for male rabbits in the 300 ppm (1251 mg/m^3) group were statistical significantly increased from control values (9.9 vs 7.6 WBC 10^3/mm^3, Dunnett's t test, alpha = 0.05). The differential counts for these animals were normal. All other haematologic parameters were unaffected in rabbits exposed to sulfuryl fluoride. Urinalysis was not performed.

Several clinical chemistry values from rabbits exposed to 30 ppm (125.1 mg/m^3), 100 ppm (417 mg/m^3) or 300 ppm (1251 mg/m^3) sulfuryl fluoride were statistically significantly different from control values (see table below). The statistically significant decreases in total protein, albumin and globulin observed in males exposed to 300 ppm (1251 mg/m^3) is most likely due to decreased nutritional status. The remaining statistically significant differences in parameters did not occur in a concentration-related manner and/or were observed in only one sex. Thus, they were considered to be due to normal variation and not a result of exposure to sulfuryl fluoride. No other clinical chemistry parameters were affected in rabbits exposed to sulfuryl fluoride. Serum fluoride levels of male and female rabbits exposed to 30 ppm (125.1 mg/m^3), 100 ppm (417 mg/m^3) or 300 ppm (1251 mg/m^3) sulfuryl fluoride were significantly increased from controls.

Clinical chemistry results in the rabbit 13 week inhalational toxicity study with sulfuryl fluoride

Conc. (ppm)	Males							Females	
	Glucose (mg/dl)	**Total protein (g/dl)**	**Albumin (g/dl)**	**Globulin (g/dl)**	**Ca (mg/dl)**	**P (mg/dl)**	**Fluoride (µg/ml)**	**UN (mg/dl)**	**Fluoride (µg/ml)**
0	176	6.3	4.4	1.9	15.3	6.2	0.065	20	0.56
30	194	5.7*	4.1*	1.6*	14.5*	6.1	0.17**	21	0.697*
100	219*	6.4	4.4	2.0	14.8	7.2*	0.408**	21	0.829*
300	199	5.7*	4.1*	1.5*	14.7	6.1	0.621**	24*	1.003*

*Statistically different from control mean by Dunnett's test, alpha = 0.05.
**Statistically different from control mean by Wilcoxon's test, alpha = 0.05.

Pathology: Absolute liver weights of male rabbits exposed to 100 ppm (417 mg/m^3) and absolute and relative liver weights of female rabbits exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride were statistically significantly decreased from control values (see table below). The absolute liver weight of male rabbits exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride was also slightly decreased from control values. Due to the lack of a dose-response relationship in male rabbit liver weights following exposure to 100 ppm (417 mg/m^3) or 300 ppm (1251 mg/m^3), these values are probably related to decreased body weight. Although the absolute and

relative liver weights of female rabbits exposed to 300 ppm (1251 mg/m^3) sulfuryl fluoride were either close to or within the range of historical control values, the decrease in liver weight values was considered to be exposure-related and most likely secondary to decreased body weight. All other absolute and relative organ weight values for rabbits exposed to 30 ppm (125.1 mg/m^3), 100 ppm (417 mg/m^3) or 300 ppm (1251 mg/m^3) sulfuryl fluoride were comparable to control values.

Summary of organ (liver) weight

Conc.	Liver			
	Males		Females	
	(g)	(g/100g)	(g)	(g/100g)
0	130.27	3.15	143.37	3.15
30 ppm (125.1 mg/m^3)	129.29	3.13	137.74	3.00
100 ppm (417 mg/m^3)	99.43*	2.60	113.61	2.57
300 ppm (1251 mg/m^3)	110.92	2.87	103.59*	2.40*

*Statistically different from control mean by Dunnett's test, alpha = 0.05.

One female rabbit, which was exposed to 600 ppm and was euthanised as it had lost the use of one of its hind limbs, had a fractured vertebra. There were no gross pathological findings in animals surviving to the end of the study.

Microscopic changes were observed in the nasal tissues of most male and female rabbits exposed to 600/300 ppm and one male exposed to 100 ppm (417 mg/m^3) sulfuryl fluoride. The changes consisted of varying degree of purulent nasal exudates, olfactory epithelial degeneration, and hyperplasia and hypertrophy of the respiratory epithelium. The most prominent features were the luminal exudates and hyperplasia and hypertrophy of the respiratory epithelium. The affected respiratory epithelium was primarily located on the nasal turbinates and consisted of goblet cells and pseudostrafied epithelial cells.

Microscopic changes were observed in the brain of most male and female rabbits exposed to 600/300 ppm and one female rabbit exposed to 100 ppm (417 mg/m^3) sulfuryl fluoride. The changes ranged from vacuolation of the white matter following exposure to 100 ppm (417 mg/m^3), to malacia of the internal and external capsules, putamen and globus pallidus following exposure to 300 ppm (1251 mg/m^3). In addition, some animals exposed to 300 ppm (1251 mg/m^3) had gliosis and/or hypertrophy of vascular endothelial cells in the same location. Special stains of the brain with LFB-PAS or Sevier Munger stain did not reveal any additional effects. All other histopathologic changes observed were considered to be spontaneous changes typical of rabbits of this age and strain and unrelated to exposure to the test substance

Summary of histopathological findings

Sex			**Males**				**Females**			
Dose			**0**	**30**	**100**	**300**	**0**	**30**	**100**	**300**
Number of rats examined			7				7			
Brain	No. examined/within normal limits		7/7			7/1	7/7		7/6	7/1
	Gliosis, cerebrum, focal:	slight	0				0			2
	Hypertrophy, endothelium, focal:	very slight	0				0			2
	Inflammatory changes consistent with encephalitozoonosis, multifocal:	slight	0				0			1
	Malacia, cerebrum, focal	severe	0			3	0			1
	Vacuolation, cerebrum, focal	very slight	0			3	0			3
		slight	0				0			2
		moderate	0				0		1	0
Nasal Tissues	No. examined/within normal limits		7/2	7/1	7/1	7/0	7/1	7/0	7/2	7/0
	Degenerative, olfactory epithelium, multifocal	slight	0			1	0			2
	Degenerative, olfactory epithelium, diffuse	slight	0			0	0			1
		moderate	0			1	0			
	Dilated, blood vessels, diffuse	severe	0				0			1
	Inflammation–chronic, submucosa, focal	very slight	0	1	0		1	0	2	1
	Inflammation–chronic, submucosa, multifocal	very slight	4	5	3	2	4	5	3	3
		slight	1	0	1	0	1	2	0	1
	Inflammation–chronic, submucosa, diffuse	Severe	0			2	0			
	Inflammation–chronic active, submucosa, multifocal	very slight	0		1	0	0			1
		slight	0				0			1
		moderate	0			2	0			
	Inflammation–suppurative, submucosa, focal	very slight	0		1	0	0			
		moderate	1	0			0			
	Inflammation–suppurative, submucosa, multifocal	very slight	0		1	0	0			
	Inflammation–suppurative, submucosa, diffuse	slight	0			1	0			
	Necrosis–respiratory epithelium, multifocal	very slight	0				0			1
	Exudate, lumen, diffuse	very slight	0		1		2	1	0	1
		slight	1	0		3	0			2
		moderate	0		1	1	0			1
		severe	0			2	0			2
	Hyperplasia and hypertrophy, respiratory epithelium, diffuse	very slight	0			1	0			
		slight	0			2	0			3
		moderate	0			2	0			
		severe	0			2	0			3

Conclusions: : In this 13-week inhalation study in NZW rabbits, the NOEC was 30 ppm (125.1 mg/m^3) (approximately equivalent to 1.4 mg/kg bw/d systemic exposure), based on changes in the upper respiratory tract in one male animal and changes in brain, comprising moderate vacuolation in the cerebrum, in one female animal at 100 ppm (417 mg/m^3). At 300 ppm (1251 mg/m^3) (partially 600 ppm), all rabbits had respiratory tract changes and most had brain changes.

4. Nitschke, K.D., Beckman, M. J., and Quast, J.F. (1992): Sulfuryl fluoride: 13-Week-Inhalation Toxicity Study in Beagle Dogs. Study No: Unspecified, Report No: K-016399-041 and 041A, Unpublished, Report date: 24 February 1992.

Test Compound:	Sulfuryl fluoride (96.26% purity)
Batch:	WP880329 752 and WP901011 907
Test Species:	Beagle dog; age and source are not stated; 4/sex/dose
Study Duration:	Study started on 26 March 1990. Completion date not stated.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	California SB-950, US EPA 82-1 and 82-4R, OECD 409 and 413, EEC Method No. L 133/3 pages 12 and 20 Deviations from EC guideline: There is no guideline for a Non-Rodent 90-Day Inhalation Study.

Study: Groups of 4 dogs/sex were exposed to 0, 30, 100 or 200 ppm (0, 125.1, 417, 834 mg/m^3, respectively) sulfuryl fluoride via inhalation (whole body exposure) for 6 hour/day, 5 days/week for 13 weeks. Test article intake was approximately equivalent to 0, 0.9, 2.9 or 5.8 mg/kg bw/d for 0, 30, 100 or 200 ppm sulfuryl fluoride, respectively.

The study included daily clinical observations; weekly body weights; haematology (HCT, Hgb, RBC, WBC/differential, platelets) on 3 occasions: prior to exposure/midway/week 12; clinical chemistry (AP, AST, ALT, CK, UN, creatinine, total protein. albumin, globulin, glucose, cholesterol, triglycerides, total bilirubin, Na, K. P, Cl and Ca) on 3 occasions: prior to exposure/midway/week 12; ophthalmology prior to start of study and within 1 week of scheduled necropsy; urinalysis (pH, bilirubin, glucose, proteins, ketones, occult blood and urobilinogen, colour, appearance, specific gravity) at time of necropsy; gross pathology of all animals; weights of brain, heart, lung, liver, kidneys, thyroid with parathyroid, pituitary adrenals, ovaries and testes; microscopic pathology of a wide range of tissues on all animals; additional immunohistochemical staining of brain sections to demonstrate glial fibrillary acidic protein (GFAP). Chamber concentrations were very close (29.9, 99.0, 197.6 ppm) to the target (30, 100, 200 ppm) concentrations, as measured with a Miran 1A IR.

Mortality: All animals survived to the end of the study.

Clinical Findings: One male exhibited lateral recumbency, tetany, tremors, salivation and incoordination 75 minutes after exposure to 200 ppm (834 mg/m^3) on day 19. An hour later, during the weekly clinical examination, the activity of this animal was decreased relative to controls but was otherwise normal. Food consumption measurements were not conducted. No effects were reported during ophthalmic observations.

Pre-exposure (average of day -4 and1 values) mean body weight values of male and female dogs exposed to 200 ppm (834 mg/m^3) sulfuryl fluoride were 94 and 99% of control values, respectively. Since there were no statistical time-sex-dose interactions, body weight values for male and female dogs within a group were combined to increase statistical power. Thus, mean body weight values of male and female dogs exposed to 200 ppm (834 mg/m^3) sulfuryl fluoride were statistically significantly decreased from control values (see table below). By the end of the study, mean body weight values of male and female dogs exposed to 200 ppm (834 mg/m^3) sulfuryl fluoride were 88% and 96%, respectively, of control values. Male dogs appeared to be slightly more affected than female dogs. Mean body weight values for male and female dogs exposed to lower concentrations of sulfuryl fluoride were comparable to control values.

Summary of Body Weights (g)

	Males				Females			
Conc. (ppm)	**0**	**30**	**100**	**200***	**0**	**30**	**100**	**200***
Days on Test								
-4	10714	10686	10245	10166	9835	9530	9633	9558
5	10912	10825	10325	10208	9737	9323	9689	9370
12	11320	11320	10680	10569	10018	9663	10102	9563
26	11766	11718	11087	10862	10023	10085	10675	9817
94	12680	13522	12584	12095	11186	11882	11621	9757

*Time-dose interaction statistically significant for combined sex, alpha = 0.05.

Haematology, Clinical Chemistry and Urinalysis: There were no exposure-related effects noted in haematology. AST activity and albumin levels in male and female dogs exposed to 200 ppm (834 mg/m^3) sulfuryl fluoride were statistically significantly decreased from control values. However, the decreases were very slight and were considered to be of no toxicological significance, due the variation in these values between groups. All remaining clinical chemistry values for male and female dogs exposed to sulfuryl fluoride were comparable to control values. Urinalysis values were also comparable to control values.

Pathology: There were no grossly visible exposure-related lesions. Mean absolute and relative organ weights were comparable to control values at all exposure levels.

Exposure-related histopathological effects were observed in the midbrain region of one male and one female dog exposed to 200 ppm (834 mg/m^3) sulfuryl fluoride. In these two dogs, there was a single, small bilatera1ly symmetrical focal microscopic change noted in the putamen of the midbrain. This focal change was characterised microscopically by vacuolation, gliosis (microglial gitter cells), perivascular cuffing, hypertrophy of endothelial cells and individual cells showing nuclear pyknosis and karyorrhexis. The size of the lesion was extremely small and barely recognisable microscopically. The focal reaction was slightly more prominent in the affected male dog compared with the female. Examination of these brain sections with GFAP immunohistochemistry did not reveal any reaction. This was consistent with the absence of any gliosis noted in haematoxylin and eosin sections, with the exception of the microglial gitter cell reaction.

Conclusions: In this 13-week inhalation study in Beagle dogs, the NOEC was 100 ppm (417 mg/m^3) (approximately equivalent to 2.9 mg/kg bw/d systemic exposure), based on slightly reduced body weights and histopathological changes in the brain at 200 ppm (834 mg/m^3). These comprised very slight, small, bilateral focal vacuolation and gliosis in the putamen region of two of eight dogs at 200 ppm (834 mg/m^3) (the male dog exhibited transient tremors and tetany some time after exposure ended on day 19 but appeared normal at all other times).

4.4.3 Chronic Studies

1. Quast, J.F., Bradley, G.J., Nitschke, K.D. (1993a) Sulfuryl fluoride: 18-Month Inhalation Oncogenicity Study in CD-1 Mice. Study No: Unspecified, Report No: DECO-HET K-016399-044, Unpublished, Report date: 19 August 1993.

Test Compound:	Sulfuryl fluoride (93.6 - 99.7% purity)
Batch:	WP 880329-752, WP 901011- 907, WP 910321-918 and WP 910826-929
Test Species:	Mouse, CD-1; age and source are not stated; Main study-50/sex/dose; One year sacrifice study: 10/sex/dose
Study Duration:	Study started on 24 July 1990 & completed on 19 August 1993.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA: GLP-Guidelines:	Yes. QA-not stated. US EPA 83-2, OECD 451, 87/302/EEC: Chronic Toxicity Test, MAFF Guideline: Oncogenicity Test Deviations from EC test guideline B.32. Carcinogenicity Test: None, except no food consumption measured, as this was not a dietary study. This study meets and exceeds the guideline requirements. This study actually meets the guidelines for a combined Carcinogenicity and Chronic Toxicity study, B. 33., except that there was no urinalysis conducted, but that is more difficult, and not frequent, in mice

Study: Groups of 50 mice/sex were exposed to targeted concentrations of 0, 5, 20 or 80 ppm (0, 20.85 mg/m^3, 83.4 mg/m^3 or 333.6 mg/m^3) (0, 0.7, 3.0, 12 mg/kg bw/d) sulfuryl fluoride for 6 hours/day, 5 days/week for up to 18 months. Ten additional mice/sex/exposure levels were randomly designated at the beginning of the study as a satellite group. The satellite group of rats were necropsied after approximately 12 months of exposure to evaluate chronic general toxicity and chronic neurotoxicity of sulfuryl fluoride, prior to the onset of confounding geriatric changes.

Since sulfuryl fluoride is a gas at room temperature and pressure, the study was conducted using whole-body exposures under dynamic airflow conditions. Animals were observed daily for assessment of exposure-related effects. Individual body weights were determined weekly for the first 13 weeks and monthly thereafter. Blood samples were obtained for haematology (HCT, Hgb, RBC, WBC/diff, platelets) and clinical chemistry (AP, AST, ALT, UN, creatinine, total protein, albumin, globulin, glucose, cholesterol, triglycerides, total bilirubin, Na, K, P, Cl and Ca) from 10 animals/sex/exposure level when necropsied at 12 months and from 20 animals/sex/exposure level at the 18-month terminal necropsy. Palpation for masses was conducted during a weekly clinical examination

At each scheduled necropsy, a wide range of tissues was collected and major organs (brain, heart, liver, kidney, testes) were weighed. Lungs were weighed only at 18 months. In general, all tissues, including gross lesions from control and 80 ppm (333.6 mg/m^3) exposed mice, were examined microscopically. Grossly visible lesions from all dose groups and target tissues from mice in the lower exposure groups were examined microscopically.

Animals were exposed in 14.5 m^3 stainless steel and glass chambers. Sulfuryl fluoride concentrations were generated using the I-tube method and analysed using a Miran IA IR. The chambers ran at target measurements. Analytical concentrations were 5.1, 20.1 and 79.7 ppm average.

Findings:

Mortality: In the satellite group, a few male mice and a single female mouse scheduled for the 12-month necropsy were removed from the study due to morbidity or death. The cause of these premature deaths was considered to be unrelated to treatment. In the main study, male and female mice from all groups were removed from the study when they became moribund or were found dead.

During the first year of exposure, a slightly earlier onset of cases of mortality was observed in the 80 ppm (333.6 mg/m^3) males, however mortality at the end of 18 months of exposure was not statistically significantly increased in any of the sulfuryl fluoride exposed groups of males. The female mortality rate during the first year of exposure was comparable in all groups. During days 455 to 545, the 80 ppm (333.6 mg/m^3) exposed females became moribund or died at an increasing rate when compared to other exposure groups and controls. The increased mortality rate in the 80 ppm (333.6 mg/m^3) exposure group of females was statistically significant at the end of 18 months. Overall, the survival rate was considered adequate for assessing carcinogenic potential.

Summary of Percentage Cumulative Mortality-18 Month Study

	Males				**Females**			
Conc.	**0**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)	**0**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)
Test Days								
155-161	4	4	4	4	6	0	0	0
204-210	4	6	6	10	10	6	2	0
260-266	4	8	6	12	10	8	4	2
323-329	8	8	8	16	10	8	8	6
365-371	8	8	8	16	14	10	8	10
379-385	8	8	12	16	14	10	8	16
421-427	12	12	16	24	18	10	10	24
470-476	22	24	32	38	26	12	18	50
512-518	42	34	40	50	34	18	26	64
540-546	44	38	46	64	35	22	38	68
554-555(males) 554-557 (females)	46	40	50	64	36	24	40	72*

*Statistically different from control mean by Gehan-Wilcoxon test, alpha = 0.05.

Clinical Findings: No clinical signs that could be attributed to treatment were observed. Prior to necropsy at 12 and 18 months, the mean bodyweight of 80 ppm (333.6 mg/m^3) male mice had decreased by approximately 12% and 14%, respectively, and that of female mice by approximately 8% and 15%, respectively, when compared to controls. Food consumption and ophthalmology examinations were not conducted.

Summary of Mean Body Weights (g)

	Males				Females			
Conc.	**0 ppm**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)	**0 ppm**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)
Days on Test								
-5	26.5	26.5	26.5	26.5	20.2	20.3	20.3	20.2
34	34.6	34.2	34.6	32.8*	26.9	26.6	26.4	25.8*
90	37.4	37.2	37.7	34.8*	29.4	28.6	29.2	28.3*
369	41.9	42.1	41.6	36.9**	34.5	33.2	34.1	31.8*
551	41.0	41.6	40.8	35.3**	34.9	34.1	35.0	29.8*

*Statistically different from control mean by Dunnett's test, alpha = 0.05.
**Statistically different from control mean by Wilcoxon's test, alpha = 0.05.

Haematology: In males, a statistically significant increased platelet count was noted in the mice exposed to 80 ppm (333.6 mg/m^3) at 12 months, but not at 18 months. The erythrocyte count in the 80 ppm (333.6 mg/m^3) exposed group at 18 months was slightly increased and this was statistically significant. In females, a statistically significant increased platelet count was observed in the mice exposed at all concentrations at 12 months; however, they were normal at 18 months. Evaluation of individual mouse differential counts and morphology of blood smears did not reveal any exposure-related effects. The absence of an exposure-related effect on the peripheral blood of male and female mice at 12 and 18 months was consistent with the normal appearance of bone marrow sections evaluated histopathologically.

Clinical Chemistry: In males, a low serum potassium level was noted in 80 ppm (333.6 mg/m^3) group at 12 months, however it was not evident at 18 months (see table below). The serum glucose levels in the 80 ppm (333.6 mg/m^3) group males and the serum albumin in the 5 ppm group males were also statistically significantly decreased in mice at 18 months. These identified differences in clinical chemistry parameters lacked a consistent dose-response pattern and are not considered to be an adverse effect of exposure to sulfuryl fluoride.

At 12 months in females, there was a statistically significantly increased serum urea nitrogen value in the 80 ppm (333.6 mg/m^3) group. However this value is well within the normal physiological range and it was not associated with an increase in creatinine that would suggest a renal effect. Furthermore, the alteration did not progress with longer exposure duration.

Summary of clinical chemistry findings

Conc.	**Males**				**Females**			
	Glucose (mg/dl)		**K (mmol/L)**		**UN (mg/dl)**		**Creatinine (mg/dl)**	
	12-Month	18-Month	12-Month	18-Month	12-Month	18-Month	12-Month	18-Month
0 ppm	199	149	5.8	6.0	21	27	0.4	0.5
5 ppm (20.85 mg/m^3)	188	129	5.2	6.0	22	32	0.4	0.4
20 ppm (83.4 mg/m^3)	164	159	5.5	5.9	20	34	0.4	0.5
80 ppm (333.6 mg/m^3)	169	112*	4.9**	6.0	27*	37	0.4	0.5

*Statistically different from control mean by Dunnett's test, alpha = 0.05.
*Statistically different from control mean by Wilcoxon's test, alpha = 0.05.

Urinalysis: Urinalysis was not conducted.

Pathology:
Organ weights: There were a number of organ weight changes in the 80 ppm (333.6 mg/m^3) group. These changes were considered to be reflective of decreased bodyweights and none were interpreted as indicative of a target organ effect due to exposure.

Gross pathology:
12 Month Study (satellite group): There were no gross observations indicative of a target organ effect at any exposure concentration.
18 Month Study (main group): In all exposed groups of male mice, but especially in the 80 ppm (333.6 mg/m^3) group, the numbers with dilated kidney pelves were considerably decreased. There were no other exposure-related kidney findings in male mice. Based upon the gross necropsy findings, there were no target organs of toxicity identified in the mice after 18 months. The observed changes were those generally expected in mice of this age.

Histopathology (non-neoplastic changes):
12 months (satellite group): In 80 ppm (333.6 mg/m^3) exposed male and female mice, the brain and the thyroid gland were the target tissues affected by exposure. These were the only tissues microscopically affected by sulfuryl fluoride exposure at 12 months, and they had previously been identified as target organs in the subchronic study (see table below). There were no microscopic effects in the lung.

18 months (main group)
There was a variety of statistically significant effects at 18 months, which are tabulated below. The brain and thyroid gland were again identified as target organs, having been previously identified as target organs at 12-months and in the subchronic study. Exposure-related effects in these tissues were confined to mice in the 80 ppm (333.6 mg/m^3) group.

Brain: Microscopic vacuolation in the external capsule of the brain of mice from the 18-month study was only observed in mice exposed at 80 ppm (333.6 mg/m^3). The extent of involvement of the brain was less at 18 months than at 12 months, and less than in mice from the subchronic (13 weeks) study exposed to 100 ppm sulfuryl fluoride. In the brains of mice examined microscopically at 12 months, 10/10 males and 9/10 females were affected, in contrast to 13/50 males and 12/50 females at 18 months. In the brain sections from the region of the thalamus and hypothalamus, there was a statistically significantly decreased incidence of focal mineralisation at 18 months in the 80 ppm (333.6 mg/m^3) group of males and females and in the 20 ppm (83.4 mg/m^3) females. The exposure-related microscopic changes in the brain were not associated with an increased incidence of nervous system tumours.

Thyroid: The microscopic changes were identical to those previously observed (13 week study) and were characterised primarily by hypertrophy of follicular epithelial cells. The colloid within the follicles was decreased in amount and stained less intensely eosinophilic. There were no degenerative or inflammatory changes present in the affected thyroids. The incidence of mice affected at 18 months was considerably decreased when compared to 12 months. At both time intervals, the changes were present in a greater number of males than females. The decreased incidence of mice with affected thyroids at the end of the 18 - month study paralleled the decreased incidence of microvacuolation in the brains of the mice at this time. The reason for

these observations is unknown. The microscopic thyroid changes were not associated with development of follicular cell tumours in either sex.

Other/Amyloidosis: Although other tissues in the 80 ppm (333.6 mg/m^3) exposed mice showed statistically increased incidences of histopathological effects, some of these were not considered to be due to sulfuryl fluoride exposure

One of the most common microscopic findings in various tissues was amyloid deposition (see table below). The authors noted that amyloidosis is a multisystemic disease process with a significant incidence in numerous tissues critical to the normal physiology and well-being of the mouse. They also noted that amyloid deposits are only observed in the ileum, jejunum, duodenum, mesenteric lymph nodes and ovaries of mice between 0-8 months of age, but with increasing age, the number of other tissues affected increases. A higher incidence of amyloidosis in females than males has been reported. The authors stated that the statistical increases in the occurrence of amyloid in some tissues in the 20 ppm (83.4 mg/m^3) and 80 ppm (333.6 mg/m^3) exposed females at 18 months was probably due to a lower than expected incidence in the control females rather than being a treatment related adverse effect.

Kidney amyloidosis: Renal amyloidosis was detected in the glomeruli of all female mice. More of the 80 ppm (333.6 mg/m^3) exposed males had very slight or slight amounts of amyloid deposited in their glomeruli, in contrast to the 80 ppm (333.6 mg/m^3) females, which typically had severe to very severe amounts present. The total number of male mice with the two most severe categories of glomerular amyloidosis combined, was decreased although not significantly so, in contrast to the increase in females.

Intestinal amyloidosis: Only in the ileum and jejunum were there statistically significant differences in the 20 ppm (83.4 mg/m^3) and 80 ppm (333.6 mg/m^3) groups of females. The study authors noted that amyloid deposits are only observed in the ileum, jejunum, duodenum, mesenteric lymph nodes and ovaries of mice between 0-8 months of age. With increasing age, the number of other tissues affected also increased. The test facility have only a limited number (n=2) of contemporary studies in CD-1 mice and only one of these uses a similar grading scheme for amyloidosis in the intestines, and this shows a very different (less extensive) pattern of amyloid deposition to the controls in the sulfuryl fluoride study. Taking into account the variable background rate, absence of deposition at other sites and lack of clear dose response (for severity or incidence) between 20 ppm (83.4 mg/m^3) and 80 ppm (333.6 mg/m^3) it is considered that the statistically significant findings at 20 ppm (83.4 mg/m^3) in females are not a treatment related adverse effect.

Heart/amyloidosis: In the 80 ppm (333.6 mg/m^3) exposed female mice, several other organ systems were secondarily involved in pathological processes that likely contributed to morbidity and/or mortality. The incidence of cardiac amyloidosis was not different from controls; however, more mice contained an atrial thrombus of relatively acute onset. The authors concluded that the formation of the atrial thrombus was considered secondary to the possible renal failure and systemic amyloidosis rather than a direct effect on the heart.

Liver/spleen: More of the 80 ppm (333.6 mg/m^3) exposed mice were found to have hepatic and splenic atrophy due to stress-related, generalised systemic amyloidosis, inanition and the associated debility. A statistically significant increase in the number of female mice with macrophages containing pigment was also observed.

Peripheral Nerve: Fewer mice in the 20 ppm (83.4 mg/m^3) and 80 ppm (333.6 mg/m^3) groups of males showed degenerative changes in their peripheral nerves. However, the authors of the study had only limited confidence in the quality of these observations.

Summary of histopathological findings

Sex			**Males**				**Females**			
Concentration (ppm)			**0**	**5**	**20**	**80**	**0**	**5**	**20**	**80**
12 Months										
Number of mice examined			10	10	10	10	10	10	10	10
Brain-cerebrum	Vacuolation, caudate putamen, bilateral, focal	very slight	0	0	0	1	0	0	0	0
	Vacuolation, external capsule, bilateral, focal	very slight	0	0	0	10	0	0	0	9
Brain Thalamus/ Hypothalamus	Mineralisation, unilateral, focal:		3	3	3	1	2	3	2	0
	Mineralisation, bilateral, focal:		3	3	1	0	9	2	0	0
	Mineralisation, any symmetry, focal: (combined)		6	6	4	1	2	5	2	0
Thyroid Gland	Amyloid, interstitium	very slight	1	2	2	2	4	3	3	3
		slight	0	2	4	2	-	1	4	1
		moderate	0	1	0	0	0	0	0	0
	Hypertrophy, epithelial cells	very slight	0	0	0	7*	0	0	0	4*
18 Months										
Number of mice examined			50	50	50	50	50	50	50	50
Brain Cerebrum	Within normal limits:		48	50	49	37	49	50	47	38
	Vacuolation, external capsule, bilateral, focal	very slight	0	0	0	13	0	0	0	12
Brain - Thalamus/ Hypothalamus	Within normal limits:		11	16	16	39	19	27	40	46
	Mineralisation, any symmetry, focal (combined)		39	34	33	11*^{T}	30	23	10*	2*^{T}
	Mineralisation, meninges, focal:		1	0	0	0	0	0	0	2
Heart	Within normal limits:		9	13	14	20	18	19	18	11
	Thrombus - acute or recent, atrium:		0	1	3	1	0	0	2	9*^{T}
	Thrombus-acute or recent and/or chronic or organised (combined)		2	3	5	2	4	1	5	14*^{T}
Ileum	Within normal limits:		21	22	20	29	25	25	14	16
	Amyloid	very slight	0	1	1	0	0	0	0	0
		slight	0	1	1	2	2	2	2	2
		moderate	16	10	14	13	14	16	24	23
		severe	11	15	14	6	9	7	10	9
		very severe	2	1	0	0	0	0	0	0
		any severity (combined)	29	28	30	21	25	25	36*	34^T
Jejunum	Within normal limits:		23	23	24	30	27	26	17	17
	Amyloid	very slight	3	3	5	5	1	2	7*	7*^{T}
		slight	15	13	13	9	7	11	8	15
		moderate	9	11	8	5	15	11	18	11
		severe	0	0	0	0	1	0	0	2
		combined	27	27	26	19	23	24	33*	33*^{T}
Kidneys	Within normal limits:		1	1	2	4	1	1	1	0
	Amyloid, glomerulus, bilateral, multifocal:	very slight	15	15	12	14	17	14	10	6*^{T}
		slight	4	3	5	12*^{T}	8	7	6	5
		moderate	5	1	4	4	3	1	3	6
		severe	4	5	8	5	6	5	8	8
		very severe	18	20	16	9	14	18	20	24
	Amyloid, interstitium	very slight	9	6	6	18^T	6	13	12	9
		slight	0	1	0	1	6	3	6	3

Sex			Males				Females			
Concentration (ppm)			**0**	**5**	**20**	**80**	**0**	**5**	**20**	**80**
		moderate	2	0	0	0	3	2	5	0
		very severe	0	0	0	0	1	0	0	0
		combined	11	7	6	19*T	16	18	23	12
Liver	Atrophy secondary to inanition, hepatocellular:		18	11	18	27	15	11	19	27*T
	Pigment-laden macrophages	very slight to moderate	3	4	2	2	10	13	4	38T
Lymph Node – Mediastinal	Atrophy:		0	0	1	4T	1	1	0	1
Peripheral Nerve	Within normal limits:		15	20	25	26	11	23	18	18
	Degeneration - individual nerve fibre(s):	very slight to moderate	35	30	25*	24*T	39	27	32	32
Thymus	Atrophy:		1	0	1	6*T	7	4	8	12
Thyroid gland	Amyloid, interstitium	very slight	5	3	1	4	3	7	8	4
		slight	10	8	11	8	6	8	13	18*T
		moderate to severe	13	16	14	8	14	9	10	9
	Hypertrophy, epithelial cells:	very slight	1	0	1	20*	1	1	1	6

*Statistically significant difference from control mean by Yate's Chi-Square Pairwise Test, alpha = 0.05.
TLinear trend by Cochran-Armitage Linear Trend test, alpha = 0.02, two-sided.

Tumour Incidence: No increases in tumour incidences were seen in mice exposed to sulfuryl fluoride. In addition to statistical analyses of the individual tumours, additional statistical procedures (Peto, 1974; McConnell et al, 1996) were carried out to take account of the reduced survival at the highest dose. These did not identify any increases in tumour incidences.

Conclusions: In the 1-year chronic inhalation toxicity study of sulfuryl fluoride in CD-1 mice, the NOEC was 20 ppm (83.4 mg/m^3) (approximately equivalent to 3 mg/kg bw/d), based on reduced body weights and microscopic changes in the brain and thyroid at 80 ppm (333.6 mg/m^3) (approximately equivalent to 12 mg/kg bw/d). The microscopic changes paralleled to some extent the observations made on mice in the subchronic study exposed to 100 ppm sulfuryl fluoride, although the changes in the caudate putamen were not seen in the present study.

In the 18-month inhalation oncogenicity study of sulfuryl fluoride in CD-1 mice, the NOEC was 20 ppm (83.4 mg/m^3) (approximately equivalent to 3 mg/kg bw/d), based primarily on reduced body weights and microscopic changes in the brain, thyroid, liver and heart at 80 ppm (333.6 mg/m^3) (approximately equivalent to 12 mg/kg bw/d).

There was no evidence of oncogenicity in either sex at any exposure concentration. The NOEC for carcinogenicity is 80 ppm (333.6 mg/m^3) (approximately equivalent to 12 mg/kg bw/d), the highest concentration tested.

2. Quast, J.F., Bradley, G.J., Nitschke, K.D. (1993b). Sulfuryl fluoride: 2-Year Inhalation Chronic Toxicity/Oncogenicity Study in Fischer 344 Rats. Study No: Unspecified, Report No: DECO-HET K-016399-040, Unpublished, Report date: 18 August 1993.

Test Compound:	Sulfuryl fluoride (93.6% to 99.7% purity)
Batch:	WP 880329-752, WP 901011-907, WP 910321-918, WP 910826-929 and WP 920131-940
Test Species:	Rat (Fischer 344); age and source are not stated; Main study: 50/sex/exposure level, 12 month satellite (sacrifice) group: 15/sex/exposure level
Study Duration:	Study started on 17 July 1990 & completed on 18 August 1993.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EP A 83-5, OECD 453, 87/302/EEC: Combined Chronic Toxicity/Oncogenicity Test, MAFF Guideline: Combined Chronic Toxicity/Oncogenicity Test Deviations from EC test guideline Method B.33. Combined Chronic Toxicity/Carcinogenicity Test: the satellite (sacrifice) groups had 15 rats instead of 20; food consumption was not studied as dosing was by inhalation; the high dose males reached 50% mortality at about 20 months, and females on the high dose reached this point at slightly over 20 months with both sexes reaching 100% mortality on the high dose at about 23 months (due to toxicity).

Study: Groups of 50 rats/sex/group were exposed to targeted concentrations of 0, 5, 20 or 80 ppm (0, 20.85 mg/m^3, 83.4 mg/m^3 or 333.6 mg/m^3) (0, 0.4, 1.4, 5.6 mg/kg bw/d) of sulfuryl fluoride for 6 hours/day, 5 days/week for up to 2 years. Fifteen additional rats/sex/exposure level were randomly designated at the beginning of the study as a satellite group. The satellite group of rats were necropsied after approximately 12 months of exposure to evaluate chronic general toxicity and chronic neurotoxicity of sulfuryl fluoride, prior to the onset of confounding geriatric changes.

Since sulfuryl fluoride is a gas at room temperature and pressure, the study was conducted using whole-body exposures under dynamic airflow conditions. Animals were observed daily for assessment of exposure-related effects and were palpated for masses during the weekly clinical examinations. Individual body weights were determined weekly for the first 13 weeks and monthly thereafter. Blood samples were obtained for haematology (HCT, Hgb, RBC, WBC/diff, platelets) and clinical chemistry (AP, ALT, creatine kinase, UN, creatinine, total protein, albumin, globulin, glucose, cholesterol, triglycerides, total bilirubin, Na, K, P, Cl and Ca) from 10 animals/sex/exposure level at approximately 6, 12, 19 and 21 months, and from 20 animals/sex/exposure level at the 24-month necropsy. Urinalysis (pH, bilirubin, glucose, proteins, ketones, occult blood, colour, appearance and specific gravity) was carried out on the same animals at approximately the same time intervals as for haematology and clinical chemistry.

At the scheduled necropsies, a full range of tissues was collected and major organs weighed. All tissues from control and 80 ppm (333.6 mg/m^3) exposed rats were examined histopathologically at the 12-month necropsy. Target tissues and grossly visible lesions were also examined from intermediate exposure levels. Because all of the 80 ppm (333.6 mg/m^3) exposed rats in the 2-year study were removed moribund or dead prior to study termination, a complete set of tissues from all groups was prepared and examined microscopically.

Animals were exposed in 14.5 m^3 stainless steel and glass chambers. Sulfuryl fluoride concentrations were generated using the I-tube method and analysed using a Miran IA IR. The chambers ran at target measurements. Analytical concentrations were 5.1, 20.2 and 79.6 ppm.

Findings:

Mortality: In males, the mortality rates in the 5 ppm (20.85 mg/m^3) and 20 ppm (83.4 mg/m^3) exposure groups did not differ from the control group. Increased morbidity and mortality was apparent from day 519 in the 80 ppm (333.6 mg/m^3) exposed rats (see table below). By day 665 only a single male rat was alive in this group and it was removed from the study by day 707. In females, it was not until day 560 that the mortality rate of the 80 ppm (333.6 mg/m^3) group reached that of the controls. However, during the remainder of the study, morbidity and mortality increased rapidly in the 80 ppm (333.6 mg/m^3) group in comparison to the other females. Only a single female was alive by day 665, and it was removed from study by day 701. At 20 ppm (83.4 mg/m^3), survival was similar to or better than controls.

The authors state that the expected disease conditions routinely observed in chronic toxicity/oncogenicity studies using Fischer 344 rats were noted in this study. However, 80 ppm (333.6 mg/m^3) exposed male and female rats were removed from the study primarily due to advanced chronic renal disease as a result of sulfuryl fluoride exposure. There were also many changes in other organs and measured parameters secondarily affected by renal failure. A spectrum of age-related external and internal neoplastic and non-neoplastic changes were also observed in rats that were removed from study. In the 5 ppm (20.85 mg/m^3) and 20 ppm (83.4 mg/m^3) exposed rats, there were no significant exposure-related effects on morbidity or mortality due to renal disease.

Summary of Percentage Cumulative Mortality-24 Month Study

	Males				**Females**			
Conc.	**0**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)	**0**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)
Test Days								
204-210	2	0	0	2	0	0	0	0
421-427	2	2	0	4	2	2	0	0
498-504	4	2	4	4	6	6	2	2
512-518	4	2	4	6	8	6	2	2
519-525	4	2	4	10	10	8	2	2
540-546	4	4	6	12	12	8	4	8
554-560	10	6	6	22	12	8	4	12
582-588	10	14	6	46	16	8	6	26
610-616	14	16	8	66	22	10	10	54
631-637	16	16	12	86	28	12	10	70
645-651	20	20	14	90	30	14	12	90
666-672	26	24	18	98	34	14	14	98
701-707	36	34	28	100*	46	20	22	100*
729-735	42	34	44	100*	50	26	24	100*
736-737 males/ 736-738 females	42	36	44	100*	50	26	24	100*

*Statistically different from control mean by Gehan-Wilcoxon test, alpha = 0.05.

Clinical Findings: No clinical signs that could be attributed to treatment were observed.

In males in the higher dose groups, slight sporadic effects on body weights throughout the first year of exposure were observed and were occasionally statistically significant. Because of the lower pre-exposure body weights in these groups, these effects were not necessarily exposure related. However, after one year, considerably lower body weights, which were statistically significant, were seen in the rats of the 80 ppm (333.6 mg/m^3) exposed group. The male rat body weights in the 5 ppm (20.85 mg/m^3) and 20 ppm (83.4 mg/m^3) groups were unaffected by exposure. In females in the 80 ppm exposed group, statistically significant decreased body weights were observed throughout the study. Food consumption was not studied. There were some ophthalmic observations in the 80 ppm (333.6 mg/m^3) group, which were considered to be secondary to kidney failure.

Summary of Mean Body Weights (g)

	Males				**Females**			
Conc.	**0**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)	**0**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)
Days on Test								
-1	98.1	97.7	95.8	96.1	84.4	84.9	84.7	83.9
5	121.8	120.7	119.3	120.4	100.4	100.4	99.3	98.5*
12	161.3	158.8	155.9*	156.9	120.6	120.5	119.3	115.4*
26	215.9	211.8	209.9*	211.1*	140.8	140.8	138.8	135.4**
89	314.6	307.9	307.3*	307.3*	180.3	180.3	177.6	171.7**
173	359.7	361.5	359.9	358.4	200.2	199.7	198.7	192.8*
369	414.2	414.2	416.7	407.0	222.8	220.0	220.8	216.5*
453	432.1	435.5	434.3	414.4*	237.0	231.8	232.3	225.3*
537	432.4	429.1	429.4	384.9*	254.4	245.9	245.3*	219.9*
621	435.9	430.4	427.1	347.5*	266.2	263.2	262.6	214.4*
649	424.7	422.8	421.0	333.1**	260.7	262.1	260.6	207.6*
677	424.4	417.8	413.4	374.6	262.2	264.5	260.2	247.9
706	411.8	407.5	400.1	-	257.4	265.7	259.2	-
734	401.7	388.7	378.7	-	255.9	265.4	258.4	-

*Statistically different from control mean by Dunnett's test, alpha = 0.05.
**Statistically different from control mean by Wilcoxon's test, alpha = 0.05.

Haematology: There were occasional statistically significant increased and decreased haematologic values observed at various times that were not considered to be exposure related. Most noteworthy of these were the decreased haematologic values (RBC counts, haemoglobin and haematocrit) observed at 19 and 21 months in the 80 ppm (333.6 mg/m^3) male group. However, these were not considered exposure-related because of high control male values at this time, when compared to their values at 6, 12 and 24 months, and also because of the absence of similar effects in females. Some of the parameters in females were also increased or decreased relative to controls and were occasionally statistically significant. However, none of these effects was consistent enough to be considered significant.

Clinical Chemistry: There were a number of treatment related effects at 80 ppm (333.6 mg/m^3) consistent with kidney disease (see table below), including increased urea nitrogen, decreased total protein, decreased albumin, raised cholesterol, raised triglycerides, raised creatinine, and raised phosphorus. Decreases in creatine kinase are not considered adverse in isolation from other findings and large variations seen in this study have also been observed historically in control rats and those receiving other test materials. The increase in AST in females was sporadic and not linked to any histopathological findings.

Summary of clinical chemistry findings in rats

Sex		Males				Females			
Conc.		**0**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)	**0**	**5 ppm** (20.85 mg/m^3)	**20 ppm** (83.4 mg/m^3)	**80 ppm** (333.6 mg/m^3)
Estimation	**Time (months)**								
Urea Nitrogen (mg/dl)	**6**	17	16	18	18	21	20	24*	20
	12	13	14	14	17*	15	14	14	17*
	19	18	20	20	62**	24	23	29**	69**
	21	16	18	20	78**	20	20	23	111**
	24	22	23	26	ND	22	20	21	ND
AST (mU/ml)	**6**	112	118	136	113	78	75	76	83
	12	109	153*	97	105	65	66	69	87**
	19	67	93	62	45**	90	66	69	91
	21	62	93	111	51**	75	58	70	67
	24	100	102	148	ND	108	95	86	ND
Total protein (g/dL)	**6**	9.0	8.8	8.9	8.9	8.5	8.7	8.7	8.9
	12	7.1	7.1	7.1	6.8*	7.4	7.4	7.4	7.6
	19	8.0	7.4	7.9	7.4**	9.1	8.9	8.4	7.8*
	21	7.8	7.9	7.7	7.1**	7.9	8.1	8.0	6.7*
	24	7.8	7.7	7.5	ND	8.2	8.4	8.0	ND
Albumin (g/dL)	**6**	4.2	4.1	4.2	4.1	4.3	4.2	4.3	4.3
	12	3.1	3.1	3.1	2.8*	3.6	3.5	3.6	3.6
	19	3.5	3.3	3.4	2.6*	3.9	4.1	3.9	2.9**
	21	3.4	3.4	3.1	2.6	3.6	3.8	3.8	2.6**
	24	3.1	3.2	3.1	ND	3.7	3.9**	3.8	ND
Cholesterol (mg/dL)	**6**	67	67	70	65	101	102	99	105
	12	76	78	75	102*	107	99	105	114
	19	139	125	152	319*	202	165	151	362**
	21	143	153	158	349*	193	156	148	310**
	24	206	221	218	ND	185	168	166	ND
Triglycerides (mg/dL)	**6**	65	61	63	63	42	46	44	46
	12	57	72**	52	99**	47	48	44	46
	19	131	164	157	396**	199	117	127	428
	21	125	148	198	432**	134	80	64	267
	24	169	192	224	ND	117	32	110	ND
Creatine Kinase (mU/ml)	**6**	121	67*	79	73*	158	114	122	109
	12	131	168	152	88	124	141	111	98
	19	143	91*	63*	47*	161	102**	77**	117**
	21	101	75	59*	53*	68	61	54	149
	24	204	187	130	ND	198	133**	101**	ND
Creatinine (mg/dl)	**6**	0.7	0.7	0.8*	0.8	0.7	0.8	0.7	0.7
	12	0.6	0.6	0.7	0.7*	0.6	0.6	0.6	0.6
	19	0.8	0.8	0.8	2.4**	0.9	0.8	0.8	1.9**
	21	0.7	0.7	0.8	2.8**	0.7	0.7	0.7	2.6**
	24	0.8	0.8	0.9	ND	0.7	0.6*	0.6*	ND
P (mg/dL)	**6**	7.4	7.6	7.3	10.9	6.2	6.6	6.9*	6.5
	12	6.6	6.5	6.5	7.0	6.3	6.1	6.1	6.3
	19	5.7	5.8	6.5	9.6**	5.3	4.9	5.6	9.2*
	21	5.7	5.6	5.9	11.8**	5.2	5.0	5.1	12.0*
	24	5.7	5.6	5.9	ND	5.9	5.6	5.8	ND
Cl$^-$ (mmol/L)	**6**	118	120	118	118	118	120	119	119
	12	107	107	107	105	108	107	107	107
	19	114	114	115	108	115	116	116	109**
	21	117	118	117	111*	109	109	110	102**
	24	113	114	114	ND	109	110	110	ND

* Statistically different from control mean by Dunnett's test, alpha = 0.05. ** Statistically different from control mean by Wilcoxon's test, alpha = 0.05. ND Not determined as all animals removed.

Urinalysis: The 6-month repeat urinalysis, which was performed approximately 2 weeks after the initial 6-month sample, did not confirm an increase in specific gravity and protein content seen at 6 months. In contrast to the absence of an effect in urinalyses during the first year, the specific gravity findings in male and female rats at 19 and 21 months clearly showed statistically significant biological effects of decreased urine specific gravity in males and females at each time interval in the 80 ppm (333.6 mg/m^3) exposed group. This was interpreted to be due to a loss of functional nephrons associated with progressive chronic renal disease. The findings of a slight increase in urinary blood may have been secondary to the renal histopathologic changes.

Pathology:
Organ weights:
12-Month Study: None of the absolute or relative organ weights of sulfuryl fluoride exposed females were statistically significantly different from the controls. The relative kidney and liver weights of 80 ppm (333.6 mg/m^3) exposed male rats were significantly higher than in controls. There were slight histopathological changes in the kidneys, but not in the liver of these rats. The slightly decreased body weight in the 80 ppm (333.6 mg/m^3) exposed males may have contributed to the observed relative organ weights.

24-Month Study: There were no biologically significant changes in organ weights.

Gross pathology:
12-Month Study:
Lungs: An exposure-related effect was observed in the lungs of both sexes in the 80 ppm (333.6 mg/m^3) group (see table below). The pulmonary changes were characterised by multiple, small pale coloured foci scattered sub-pleurally and located primarily in the diaphragmatic lobes.
Teeth: After formalin fixation of tissues, the labial surface of the incisor teeth of all 80 ppm (333.6 mg/m^3) exposed rats was found to be discoloured with repetitive pale and slightly darker coloured horizontal lines. None of the molar teeth was similarly affected after formalin fixation. The observations on the incisor teeth were only seen in the fixed tissue and were included in the gross pathology table.

24-Month Study:
Kidneys: The most significant gross observations in these rats were related to advanced chronic renal disease in the 80 ppm (333.6 mg/m^3) group. Due to renal failure, there were many other observations in numerous tissues (aorta, digestive tract, skin, eyes, heart, liver, lungs, oral tissues, parathyroid gland, pituitary gland, spleen, stomach, testes, uterus) which represent the spectrum of secondary uraemic changes.

Lungs and teeth: The lungs and incisor teeth were also grossly affected and their identification as target tissues was consistent with the 12-month necropsy observations.

Summary of gross pathologic observations

Sex		Males				Females			
Exposure concentration - ppm		**0**	**5** (20.85 mg/m^3)	**20** (83.4 mg/m^3)	**80** (333.6 mg/m^3)	**0**	**5** (20.85 mg/m^3)	**20** (83.4 mg/m^3)	**80** (333.6 mg/m^3)
		12 Month							
Number of Rats Examined		9	10	10	10	10	10	10	10
Lungs	Focus - pale, bilateral, multifocal: very slight	0	0	0	10	0	0	0	10
		24 Month							
Number of Rats Examined		50	50	50	50	50	50	50	50
Kidneys	Within normal limits	8	17	8	3	42	49	47	3
	Pale, bilateral	0	2	3	18	1	0	0	10
	Roughened surface, bilateral	33	28	31	45	4	0	1	40
Lungs	Within normal limits	39	38	30	1	43	44	45	0
	Firm	0	0	0	2	0	0	0	0
	Focus–pale, multifocal	0	1	8	46	0	0	1	46
	Dark–multifocal	2	1	3	3	2	3	1	14
Oral Tissues	Within normal limits	**49**	49	48	36	49	48	49	42
	Malocclusion, tooth	0	0	1	1	0	0	0	0
	Mottled, tooth	0	0	0	12	0	0	0	8
	Overgrown incisors, lower incisors	1	1	0	2	0	0	0	0

Histopathology (non-neoplastic):

12-Month Study (satellite group): Exposure-related effects were observed in kidneys, lungs and incisor teeth of males and females in the 80 ppm (333.6 mg/m^3) group, and in the teeth of several 20 ppm (83.4 mg/m^3) males (see table below).

Kidneys: A very slight degree of chronic progressive glomerulonephropathy, normally seen at this age in this strain of rat, was present in nearly all 0, 5 ppm (20.85 mg/m^3) and 20 ppm (83.4 mg/m^3) males. Male rats in the 80 ppm (333.6 mg/m^3) exposure group were more severely affected with chronic progressive glomerulonephropathy than control and lower exposure groups. In all 80 ppm (333.6 mg/m^3) females some degree of chronic progressive glomerulonephropathy was present, with fewer incidences at the lower dose levels and in controls. These early microscopic renal effects apparently increased in severity with continued exposure and resulted in significant morbidity and mortality due to renal failure during the second year.

Lungs: The lung changes were microscopically consistent with the gross observations in the high-exposure group. There were no exposure-related pulmonary changes observed in the 5 ppm (20.85 mg/m^3) and 20 ppm (83.4 mg/m^3) exposed rats. Microscopic changes in the lungs of the high exposure rats, namely multifocal aggregates of alveolar macrophages, were considered to differ from the alveolar histiocytosis seen in the controls and lower dose animals.

Teeth: There were indications of exposure-related dental fluorosis in the males.

24-Month Study (main study): The kidneys, lungs, and incisor teeth were the clear primary target organs affected after 24 months of exposure to sulfuryl fluoride, as they were after 12 months.

Kidneys: The grades of severe and very severe chronic progressive glomerulonephropathy were present in most (47/50 males and 45/50 females) of the 80 ppm exposure group. In contrast, the kidneys of only 5/50 control males and 1/50 control females were comparably affected. No significant renal effects of treatment were evident at 5 ppm (20.85 mg/m^3) or 20 ppm (83.4 mg/m^3). The sulfuryl fluoride induced renal toxicity did not result in kidney tumours.

The authors discussed the significance of the renal damage in the rats in this study. Sprague-Dawley rats exposed to 150 ppm (625.5 mg/m^3) sulfuryl fluoride in a two-generation reproduction study (Breslin et al., 1992) did not display any histopathologic evidence of kidney toxicity, even though changes in the lungs and teeth were comparable to those seen in the Fischer 344 rats in the present study. Susceptibility of Fischer 344 rats to developing nephrotoxicity following exposure to fluorinated compounds has been reported *(*Hook and Goldstein*, Toxicology of the Kidney, Second Ed., Raven Press, Ltd., New York, NY,* 1993*)*. Subchronic studies on sulfuryl fluoride exposed New Zealand White rabbits (Eisenbrandt and Nitschke, 1989), CD-l mice (Nitschke and Quast, 1993), and Beagle dogs (Nitschke *et al.,* 1992), at concentrations higher than those used in the Fischer 344 chronic rat study, failed to produce renal toxicity. Furthermore, the 18 months CD-l mouse oncogenicity study conducted simultaneously with the rat chronic study also failed to produce kidney toxicity (Quast *et al.,* 1993). In a chronic Beagle dog study, exposure to 200 ppm (834 mg/m^3) sulfuryl fluoride, the highest concentration, did not result in altered clinical chemistry parameters or gross necropsy findings suggestive of renal toxicity (Quast *et al.,* 1993). It is likely that Fischer 344 rats may be uniquely sensitive to developing renal toxicity following repetitive exposure to this fluorinated molecule. Because of the lack of renal toxicity in Sprague-Dawley rats, CD-l mice, New Zealand White rabbits and Beagle dogs following sulfuryl fluoride exposure, it might be inappropriate to use the Fischer 344 rat kidney toxicity data alone for human safety assessment.

Lungs: The lungs of rats from the 24-month study showed comparable microscopic changes to those observed at 12 months. In general, the occurrence of multifocal aggregates of alveolar macrophages was classified as moderate in most of the 80 ppm (333.6 mg/m^3) exposed rats at study termination, in contrast to the slight degree at 12 months. The exposure-related effects present in this target tissue did not result in an increased incidence of pulmonary tumours. There were no effects at 5 ppm (20.85 mg/m^3) or 20 ppm (83.4 mg/m^3).

Teeth: Dental fluorosis was present in the upper incisor teeth of all 80 ppm (333.6 mg/m^3) exposed male and female rats and was statistically increased in the middle dose group of males. These microscopic changes were comparable to those observed at 12 months. There was no evidence of effects on teeth or oral tissues other than dental fluorosis.

Similar gross or microscopic changes were not observed in the incisor teeth of CD-l mice in an 18-month oncogenicity study (Quast *et al.,* 1993). Furthermore, in a subchronic study involving both rabbits and rats, there were no gross or microscopic dental changes in rabbits, whereas rats were affected *(*Eisenbrandt and Nitschke*, Fund. Appl. Toxicol.,* 12, *540-557,* 1989). Dogs subchronically exposed to sulfuryl fluoride also failed to exhibit dental changes on gross and microscopic examination (Nitschke *et al.,* 1992). In a chronic 1-year dog study, exposures of 200 ppm did not result in dental fluorosis recognised during in-life examinations or at necropsy (Quast *et al.,* 1993). Therefore, the human toxicological significance of dental fluorosis in rat incisors is doubtful.

Lesions secondary to renal disease: Due to end-stage kidney disease in the high-exposure group, there were numerous other organs with statistically significant changes. These observations were

not considered to be primary effects of exposure; rather they were expected changes associated with renal failure and early death. They were infrequently observed in the lower exposure groups and controls. Many tissues in the 80 ppm (333.6 mg/m^3) exposed rats were mineralised secondarily to chronic renal disease, sometimes showing other microscopic changes which were also due to renal failure rather than being a direct effect of exposure.

Brain: There was no evidence of effects on the brain or other parts of the nervous systems at 5 ppm (20.85 mg/m^3) or 20 ppm (83.4 mg/m^3). At 80 ppm (333.6 mg/m^3), there was an increase in (very slight) vacuolation of the cerebral cortex in females.

Tumour Incidence:

No increases in tumour incidences were seen in groups of mice exposed to sulfuryl fluoride. In addition to statistical analyses of the individual tumours, additional procedures (Peto, 1974; McConnell et al, 1986) were followed to take account of reduced survival of animals receiving the highest concentration. These did not identify any increases in tumour incidences.

Summary of histopathological findings in rats exposed to sulfuryl fluoride for up to 2 years

Sex			**Males**				**Females**			
Exposure concentration (ppm)			**0**	**5**	**20**	**80**	**0**	**5**	**20**	**80**
			12 Months							
Number of Rats Examined			**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Kidneys	Chronic progressive glomerulonephropathy, bilateral	very slight	9	10	10	0	3	1	1	9
		slight	0	0	0	10	0	0	0	1
Lungs	Alveolar histiocytosis, multifocal		10	10	10	0	10	10	10	0
	Hyperplasia, alveolar cell, focal:		0	0	1	0	0	0	0	0
	Aggregates of alveolar macrophages, multifocal	very slight	0	0	0	2	0	0	0	0
		slight	0	0	0	8	0	0	0	10
Oral tissues	Fluorosis dental, upper incisors, bilateral	very slight	0	0	3	3	0	0	0	0
		slight	0	0	0	7	0	0	0	0
			24 Months							
Number of Rats Examined			**50**	50	50	50	50	50	50	50
Kidneys	Chronic progressive glomerulonephropathy, bilateral	very slight	8	9	7	2	42	46	48*	0*
		slight	13	16	18	0*	5	1	2	3
		moderate	24	20	22	1*	0	0	0	2
		severe	4	2	2	4	0	0	0	5*[T]
		very severe	1	2	1	43*	1	0	0	40*
	Mineralisation, tubule(s):	very slight	48	48	49	5*	49	50	50	12*
		slight	0	0	0	0	0	0	0	1
	Mineralisation, secondary to renal disease:		1	2	1	45*	1	0	0	37*
	Adenoma, tubule(s), benign, primary:		0	1	0	0	0	0	0	0
	Myxosarcoma, papilla(e), malignant, primary, no metastasis:		0	0	1	0	0	0	0	0
Lung	Alveolar histiocytosis, multifocal	very slight	41	46	43	1*	46	47	45	0*
		slight	1	1	3	0	0	0	1	1
	Mineralisation, blood vessels	focal	50	50	50	28*	42	41	34	38
		multifocal	0	0	0	22*	2	1	0	9*
	Mineralisation-secondary to renal disease, alveoli/septa:		0	2	1	42*	1	0	0	37*
	Aggregates of alveolar macrophages, multifocal:	very slight	3	1	1	0	2	0	3	0
		slight	1	0	1	15*	0	0	0	6*[T]
		moderate	1	0	0	34*	0	0	0	42*
Oral	Within normal limits:		13	24	9	0	35	37	30	0

Tissues	Inflammation acute, gingiva focal:	unilateral	1	3	3	7	1	1	2	1
		bilateral	0	0	0	0	0	1	0	1
	Inflammation - chronic active, focal:	unilateral	6	5	7	1	3	1	3	0
		bilateral	5	1	2	0	0	0	0	0
	Fluorosis -dental, upper incisors, bilateral:	very slight	0	0	10*	12*^{T}	0	0	2	4^{T}
		slight	0	0	0	38*	0	0	0	46*
	Squamous cell carcinoma / papilloma:		4	1	6	0	0	1	1	0
Brain	Cerebral cortex vacuolation	very slight	2	0	1	1	1	3	3	22*
Bone	Fibrous osteodystrophy		0	2	1	44*	1	0	0	45*

*Statistically significant difference from control mean by Yate's Chi-Aquare pairwise test, alpha = 0.05.
^{T} Linear trend by Cochran-Armitage Linear Trend Test, alpha = 0.02, two-sided.

Conclusion: In this 2-year inhalation combined chronic toxicity/oncogenicity study of sulfuryl fluoride in Fischer 344 rats, no evidence for carcinogenicity was observed in either sex at any exposure concentration up to 80 ppm (333.6 mg/m^3) (approximately equivalent to 5.6 mg/kg bw/d systemic exposure) the highest concentration tested.

The NOEC was 20 ppm (83.4 mg/m^3) (approximately equivalent to 1.4 mg/kg bw/d), based on a variety of effects, including increased mortality, low body weights, very slight vacuolation in the brain, kidney pathology with associated clinical chemical effects and effects on other tissues, and pulmonary changes suggestive of irritation at 80 ppm (333.6 mg/m^3) (approximately equivalent to 5.6 mg/kg bw/d).

3. Quast, J.F., Beckman, M.J., Nitschke, K.D. (1993c) Sulfuryl fluoride: One-Year-Inhalation Toxicity Study in Beagle Dogs. Study No: Unspecified, Report No: DECO-HET K-016399-044, Unpublished, Report date: 21 October 1993.

Test Compound:	Sulfuryl fluoride (95.1% to 98.8% purity)
Batch:	WP 910826-929, WP 920131- 940 and WP 920619-953
Test Species:	Beagle dog; age and source are not stated; 4/sex/dose
Study Duration:	Study started on 13 January 1992 & 21 October 193.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 83-1, OECD 452, 87/302/EEC: Chronic Toxicity Test, MAFF: Chronic Toxicity Test Guidelines Deviations from EC guideline: None

Study: The initial study design consisted of groups of four male and four female Beagle dogs which were to be exposed to 0, 20, 80 or 200 ppm (0, 83.4 mg/m^3, 333.6 mg/m^3 or 834 mg/m^3) (0, 0.6, 2.3, 5.8 mg/kg bw/d) sulfuryl fluoride for 6 hours/day, 5 days/week for one year. However, due to excessive morbidity and mortality by approximately 9 months, the 200 ppm (834 mg/m^3) exposed group of dogs was removed from the study and necropsied.

The study was conducted using whole-body exposures under dynamic airflow conditions. Animals were observed daily and weighed prior to the initial exposure at weekly intervals for the first 13 weeks and monthly thereafter until approximately 9 months. After 9 months, the body weights were taken biweekly to monitor the progress of the chronic toxicity. Whole blood and serum samples were obtained from each animal twice prior to initiation of the study, at 3, 6 and 9 months, and once during the last 2 weeks of exposure. Haematology consisted of HCT, Hgb, RBC, WBC/differential and platelets. Clinical chemistry consisted of AP, AST, ALT, creatine kinase, UN, creatinine, total protein, albumin, globulin, glucose, cholesterol, triglycerides, total bilirubin, Na, K, P, Cl and Ca. Urinalysis was performed at 6 months and at 12 months, and

included pH, bilirubin, glucose, proteins, ketones, occult blood, urobilinogen, colour, appearance, specific gravity and microscopic examination of sediment. An ophthalmologic examination took place prior to the start of the study and again shortly before the scheduled 1-year necropsy. One-half of the lower jaw with teeth and one femur from each dog were collected and frozen at necropsy for fluoride analysis, if necessary for interpretation of study results. However, fluoride analyses were not conducted on these samples. Animals were necropsied on the day after the last exposure and 51 different tissues were collected in formalin or Bouin's fixative. Major organs (brain, heart, lung, liver, kidneys, thyroid with parathyroid, pituitary, adrenals, ovaries, and testes) were weighed from all animals except those assigned to the 200 ppm (834 mg/m^3) group which had been terminated early due to excessive pulmonary toxicity (not weighed due to lack of controls). A complete set of tissues collected at necropsy from all animals was examined by light microscopy for evaluation of exposure-related effects. Chambers were monitored analytically at 30 minute intervals using a Miran IA IR. Chamber concentrations were within 10% of target (0,21,79 and 198 ppm).

Mortality: Due to excessive morbidity and mortality (2 males and 3 females), the 200 ppm group (834 mg/m^3) was taken off test at 9 months and necropsied. There were no other deaths.

Clinical Findings: There were no exposure-related observations in the 0, 20 ppm (83.4 mg/m^3) and 80 ppm (333.6 mg/m^3) exposed groups throughout the study. At approximately 9 months into the study, several male and female dogs at the 200 ppm (834 mg/m^3) exposure level exhibited clinical signs of toxicity. The observations included, but were not limited to, laboured breathing. shallow rapid respiration, and pale or blue mucous membranes. One male dog from the 200 ppm (834 mg/m^3) group died on day 267, and another from the same group became moribund and was necropsied on day 271. One of the remaining two male dogs from the 200 ppm (834 mg/m^3) exposure group exhibited minor respiratory changes prior to removal from study on day 282. This dog had lost 782 g of body weight during the previous month. The heaviest male dog in the 200 ppm (834 mg/m^3) exposed group was clinically normal and was also necropsied on day 282, when this group was removed from the study. Three female dogs from the 200 ppm (834 mg/m^3) exposure group were sacrificed in a moribund condition on days 278 (one female) and 281 (two females). Although the remaining female dog in this group did not show clinical signs of altered respiration, she had lost 647 g of body weight during the previous month. This lone surviving 200 ppm (834 mg/m^3) exposed female dog was also necropsied on day 282.

All of the dogs, which became ill during the study exhibited a number of clinical signs indicative of impaired respiratory function. These changes were either visually observed as laboured respiration, or noted as altered respiratory sounds upon auscultation of the thoracic cavity. Occasional discolouration of the mucous membranes was observed and was consistent with the compromised respiratory function. The body temperature of some dogs was occasionally elevated; however, this was not consistently observed in the same dog on repeated examinations, nor within the group. Upon auscultation of the thoracic cavity, the heart rate and sounds were normal. In addition, the intensity of the femoral pulse appeared to be normal. Both of these findings indicated that the altered respiratory function was not due to cardiac arrhythmia.

Although microbiological cultures were taken from the lungs of several dogs, only one showed a *Haemophilus* bacterial infection. This was likely an opportunist infecting this debilitated dog and not a primary infectious agent. Food consumption was not assessed. No treatment-related effects were reported during ophthalmic observations.

Haematology, Clinical Chemistry and Urinalysis: There were no exposure-related haematologic alterations in the 20 ppm (83.4 mg/m^3) or 80 ppm (333.6 mg/m^3) exposed dogs throughout the study, nor in the 200 ppm exposed dogs through 6 months on test. However, a decrease in erythroid parameters (RBC, Hgb, HCT) and an increase in WBCs with a neutrophilia were observed in both sexes of 200 ppm exposed dogs that became ill due to impaired respiratory function. These haematologic changes were considered secondary to the observed histopathologic findings in the lungs of these dogs.

A decreased AP activity in the 20 ppm (83.4 mg/m^3) exposed males was statistically significant. This may have been due to a control dog having an elevated value in both pre-study samples. There were no alterations in clinical chemistry, which were indicative of a primary target organ effect in male or female dogs at any exposure concentration. However, minor secondary clinical chemistry changes were observed in some of the 200 ppm (834 mg/m^3) exposed dogs, which were ill and removed from study due to impaired respiratory function. There were no biologically significant findings in the urinalysis.

Pathology: The relative heart weights of male and female dogs in the 20 ppm (83.4 mg/m^3) exposed group were statistically significantly decreased. However, the terminal mean bodyweights of the 20 ppm (83.4 mg/m^3) exposed dogs were also greater than the controls and 80 ppm groups, although this was not statistically significant. Most of the relative organ weights of the 20 ppm (83.4 mg/m^3) exposed male and female dogs were decreased as a reflection of their heavier mean bodyweights. Since there was no exposure relationship and no associated histopathologic changes, no toxicological significance is attached to the decreased relative heart weights in the 20 ppm (83.4 mg/m^3) exposed males and females.

A pale focus in the spleen was also observed in a control and 80 ppm exposed male dog. There were no observations in the 80 ppm (333.6 mg/m^3) or 200 ppm (834 mg/m^3) exposed groups of dogs that were considered due to sulfuryl fluoride exposure.

There were no significant exposure-related effects observed in tissues other than the lungs of 200 ppm (834 mg/m^3) animals, which consisted of scattered darkened areas admixed with pale areas. The dark coloured areas appeared to be consolidated and were firm upon palpation, whereas the pale areas appeared normal. Lungs from dogs, which clinically exhibited laboured respiration, were predominantly consolidated and non-functional. An occasional control or 80 ppm (333.6 mg/m^3) exposed dog had pale foci in their lungs, which are routinely seen in chronic studies. A pale focus in the spleen was also observed in a control and a 80 ppm exposed male dog. There were no observations in the these exposed groups of dogs which were considered due to sulfuryl fluoride exposure.

Histopathologically, exposure-related effects were seen in the lungs, brain, thyroid gland and canine teeth during this chronic study.

Lungs: The histopathologic changes in the lungs of 200 ppm (834 mg/m^3) exposed dogs corresponded with the severity of laboured respiration in-life and were consistent with the consolidation noted at necropsy. The pulmonary changes appeared to primarily involve the peripheral portions of the lung without recognisable alterations in the major airways. Early changes appeared to be associated with an increase in the number of alveolar macrophages within scattered subpleural alveoli. A variable mixed inflammatory cell infiltrate was usually associated with these foci. In the more advanced stages of the chronic active inflammatory process, these foci apparently increased in size and hypertrophied type II pneumocytes were observed. In addition, the epithelial cells lining the respiratory and alveolar ducts in the affected

areas were hypertrophied and hyperplastic. The areas of chronic active inflammation were separated by nearly normal areas of pulmonary parenchyma. In the most severe cases, these changes ultimately resulted in pulmonary consolidation of a significant portion of all affected lobes. Associated with the chronic inflammatory reaction was a focal thickening of the pleura and thickening of the interalveolar septa. Special stains to demonstrate fibrin within these areas were not definitive; however, in the chronically inflamed areas the increased thickening of the interalveolar septa and the pleura were due to collagen deposition. Although the peripheral portions of the lungs of 200 ppm (834 mg/m^3) exposed dogs were adversely affected; their nasal turbinates, larynx, trachea and major portions of the bronchial tree were unaffected.

In the 80 ppm (333.6 mg/m^3) exposed dogs, there were three of four males and one of four females with very slight aggregations of alveolar macrophages, which were multifocal in distribution. The minor microscopic changes suggested a very slight cellular response to irritant. In this group, a very slight degree of the chronic active inflammatory process noted in the 200 ppm (834 mg/m^3) exposed group was observed in two females. The minor microscopic lung changes in the 80 ppm (333.6 mg/m^3) exposed dogs were not associated with clinical symptoms or gross consolidation. An occasional granulomatous focus was observed in the lungs of some female dogs due to apparent aspiration of feed particles or hairshafts. There were no exposure-related microscopic changes in the lungs of 20 ppm (83.4 mg/m^3) exposed dogs.

Brain: Microscopic changes in the brain were present in the head of the caudate nucleus of two of four males and three of four females in the 200 ppm (834 mg/m^3) exposure group. The microscopic appearance consisted of a focus of malacia (liquefaction necrosis) in which vessels and some neuropil persisted within the lesion. Inflammatory cells were an insignificant feature; however, there were some glitter cells (macrophages) persisting within the malacic foci. Whether the scarcity of cells (inflammatory cells) was due to cells lost at the time of tissue processing or due to migration from the site prior to the time of necropsy was undetermined. The microscopic features of the lesions indicated that they were not of recent vintage. The malacic foci were linear, dorsoventral in orientation and located midway between the lateral ventricles and the internal capsule. There were vessel(s) and their supporting interstitium present within the center of the malacic foci. The cells and neuropil immediately adjacent to the malacic foci were normal in appearance. The character of the microscopic change was suggestive of ischemic tissue damage rather than cytotoxicity to neuronal elements. There were no other recognisable changes in the numerous sections of brain stained with H&E, Luxol Fast Blue Cresyl Violet and Sevier-Munger.Clinical manifestations of neurotoxicity were not observed during the study. The additional handling and restraint associated with repeated blood collection for haematology and clinical chemistry, and catheterization for urine collection, did not induce any behaviour suggestive of neurotoxicity. The microscopic effects in the brain were confined to dogs exposed to 200 ppm (834 mg/m^3) sulfuryl fluoride.

Thyroid: The microscopic thyroid gland effects were confined to dogs in the 200 ppm (834 mg/m^3) exposure group and consisted of very slight hypertrophy of the follicular epithelium. The epithelial cells were minimally enlarged, follicles were decreased in size, and their colloid stained less intensely. There were no degenerative or inflammatory changes associated with the very slight hypertrophy.

Teeth: A minor change was observed microscopically in the canine tooth that was evaluated for possible changes suggestive of dental fluorosis. The change consisted of concentric rings, which stained slightly darker and appeared to correspond with each day of exposure. The dentine, which had formed prior to the first day of exposure, lacked these rings. As the teeth reached their

maturity, it was more difficult to recognise the presence of the rings. Other than the presence of these growth rings in the dentine, there were no other recognisable changes in the canine tooth. All of the 200 ppm (834 mg/m^3) exposed dogs and several in the 80 ppm group were affected.

Miscellaneous: Some other tissues had microscopic changes (liver and lymphoid tissue atrophy; bone marrow myeloid hyperplasia) observed more frequently in the 200 ppm (834 mg/m^3) exposed group compared with the other groups; however, they were considered secondary to the effects described in the lungs. Other microscopic changes were considered to be incidental and normally observed in chronic dog studies. There were no observations in the 20 ppm groups, which were considered to be due to sulfuryl fluoride exposure.

Summary of histopathological findings

Sex			**Males**				**Females**			
Dose			**0**	**20**	**80**	**200**	**0**	**20**	**80**	**200**
Number of dogs examined			4				4			
Bone Marrow	No. examined/within normal limits		4/4			4/3	4/4			4/3
	Hyperplasia, myeloid	slight	0				0			1
		moderate	0			1	0			
Brain-cerebellum	No. examined/within normal limits		4/4			3/2	4/4	4/3	4/4	
	Missing (stated as missing)		0			1	0			
	Inflammation, subacute, ependyma, focal:	very slight	0			1	0			
	Perivascular mononuclear (lymphoid) cell cuffing	Very slight	0				0	1	0	
Brain-cerebrum	No. examined/within normal limits		4/4			4/2	4/4	4/3	4/4	4/1
	Malacia, caudate nucleus, bilateral, focal	very slight	0			1	0			
		slight	0			1	0			2
		moderate	0				0			1
	Perivascular mononuclear (lymphoid) cell cuffing	very slight	0				0	1	0	
Brain-thalamus/ hypothalamus	No. examined/within normal limits		4/4		4/3	4/4	4/4			
	Perivascular mononuclear (lymphoid) cell cuffing	very slight	0		1	0	0			
Liver	No. examined/within normal limits		4/0				4/0			
	Aggregate(s) of reticuloendothelial cells:		4				4			
	Atrophy secondary to innition, hepatocellular:		0			2	0			3
	Pigment – haemosiderin, Kupffer cells, multifocal	very slight	0				1		4	0
		slight	0				2	0		2
Lungs	No. examined/within normal limits		4/0				4/0			
	Inflammation-chronic active, alveoli, multifocal	very slight	0			2	0		2	1
		moderate	0			1	0			
		severe	0			1	0			3
	Inflammation-fibrinous, pleura, multifocal	moderate	0			1	0			
	Inflammation-granulomatus, focal	very slight	0				1	0		
	Inflammation-granulomatus, multifocal	very slight	0				0	1	2	0
	Inflammation-suppurative, lobar, focal	severe	0			1	0			
	Inflammtaion-subacute to chronic, interstitium, multifocal	very slight	4			0	4		2	0

	Aggregates of alveolar macrophages, multifocal;	very slight	0		3	0	0		1	0	
Lymph Node-Mesenteric	No. examined/within normal limits		4/4			4/2	4/4			4/1	
	Atrophy		0			2	0			3	
Oral Tissues	No. examined/within normal limits		4/4		4/1	4/0	4/3	4/4	4/3	4/0	
	Ulcer, hard palate, focal		0				1	0			
	Fluorosis-dental, canine tooth	very slight	0		2	0	0		1	0	
		slight	0	0	1	4	0			4	

Conclusions: In this 1-year inhalation study in Beagle dogs, the NOEC was 20 ppm (83.4 mg/m^3) (approximately 0.6 mg/kg bw/d systemic exposure), based on very slight inflammation and aggregates of macrophages in alveoli at 80 ppm (333.6 mg/m^3). The highest concentration of 200 ppm (834 mg/m^3) was not tolerated beyond approximately 9 months, when this level was terminated. The primary effects were respiratory in nature (e.g., severe inflammation) although other changes were evident, notably in the brain.

4.4.4 Reproduction Study

1. Breslin, W.J., Liberacki, A.B., Kirk, H.D., Bradley, G.J., Crissman, J.W. (1992). Sulfuryl fluoride: Two-Generation Inhalation Reproduction Study in Sprague-Dawley Rats. Study No: Unspecified, Report No: K-016399-042, 042F0, 042F1, 042G0, 042G1, Unpublished, Report date: 7 January1992.

Test Compound:	Sulfuryl fluoride (93.6 to 98.8% purity. The two impurities were air and water)
Batch:	WP901011-907, WP910321-918 and WP910826-929
Test Species:	Rat (Sprague-Dawley); age and source are not stated; 30 animals/sex/dose
Study Duration:	Study started on 4 February 1991 & completed on 7 January 1992.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	US EPA 83-4, OECD No. 416, 87/302/EEC: Two-Generation Reproduction Toxicity Test, MAFF Toxicity Test Guidelines for Reproduction Studies Deviations from EC test guideline Method B.35. Two-Generation Reproduction Toxicity test: None

Study: Groups of 30 male and 30 female rats were exposed to targeted concentrations of 0, 5, 20 or 150 ppm (0, 20.85 mg/m^3, 83.4 mg/m^3 or 625.5 mg/m^3) (0, 0.4, 1.4, 10.8 mg/kg bw/d) sulfuryl fluoride via inhalation, 6 hours/day, 5 days/week prior to mating. Thereafter, males and females were exposed to these levels for 6 hrs/day, 7 days/week during mating, gestation and lactation (except gestation Day 21 to lactation Day 4, for animal welfare reasons) and through to sacrifice.

The study was conducted using whole-body exposures and the rats were exposed sulfuryl fluoride in 14.5 m^3 chambers. Chamber atmospheres concentrations were generated using a 'J-tube' method and were analysed at 30 minutes interval using a Miran IA IR. Cylinders were weighted before and after use to determine nominal concentration. The chambers ran at target measurements. The average analytical concentrations of sulfuryl fluoride in the 5, 20, and 150 ppm exposure chambers during the F0 and F1 generations were 5.0, 20.9 and 149.1 ppm and 5.2, 20.4 and 150.1 ppm, respectively.

The exposure of F0 rats began at approximately 6 weeks of age. After 10 weeks of exposure (5 days/week, excluding holidays), F0 rats were mated, one male to one female of the respective

treatment group to produce the F1 litters. Following weaning (3 weeks of age) of the F1 litters, 30 males and 30 females from each treatment group were randomly selected and assigned to the respective treatment group to become the parents (F1) for the next generation. After approximately 12 weeks of exposure following weaning of the last F1 litter, the Fl adults were bred to produce the F2 litters. Exposure of F0 and F1 adult rats were continued until the adults were sent to necropsy. All rats were housed continuously in exposure chambers following the initial exposure to sulfuryl fluoride except during the late gestation and early lactation periods, when the female rats were housed outside of the exposure chambers. Maternal rats were not exposed to sulfuryl fluoride after day 20 of gestation to the fourth day post-partum, in order to allow for parturition and initiation of lactation. Non-pregnant females were excluded from exposure for a period to equalise the number of exposure days between non-pregnant and pregnant rats. During the lactation period, pups were not placed in the exposure chambers, but remained in the nesting cages separated from the dam for 6 hrs/day on lactation days 5-21.

Each rat was observed at least daily for changes in behaviour or demeanour. All adult rats found dead or moribund were submitted for a gross pathologic examination; pups found dead during the lactation phase were examined grossly and discarded. Evaluations of litter parameters and body weights were performed regularly. Body weights were recorded weekly during the 10-week pre-breeding treatment period. Body weights for males were recorded weekly throughout the course of the study.

A complete necropsy was conducted on all F0 and F1 adults. Histological examination of potential target organs and reproductive tissues was performed on control and high dose groups. Examination of tissues from low and middle dose groups was limited to those tissues, which demonstrated treatment-related histological changes in the high dose group. At the time of weaning, 10 pups/sex/dose level from the F1 and F2 litters were randomly selected for a complete necropsy. Terminal bodyweights were not recorded. Histological examinations were not performed.

Findings:

First Generation

Mortality: Five rats died and one rat was euthanised moribund prior to the scheduled necropsy. None of the deaths or morbidity were considered treatment-related.

Clinical findings: No treatment-related effects on clinical alterations were observed in males and females in any exposure group. No effects on the body weights of F0 males exposed to 5 ppm (20.85 mg/m^3) or 20 ppm (83.4 mg/m^3) sulfuryl fluoride were observed throughout the duration of the study. The bodyweights of F0 males exposed to 150 ppm (625.5 mg/m^3), however, were significantly decreased from the control group from day 14 throughout the remainder of the study. The changes in bodyweight were progressive over the duration of exposure and were considered to be exposure related.

No effects on the body weights of F0 males exposed to 5 ppm (20.85 mg/m^3) or 20 ppm (83.4 mg/m^3) sulfuryl fluoride were observed throughout the duration of the study. The bodyweights of F0 females exposed to 150 ppm (625.5 mg/m^3), however, were decreased as compared to controls, throughout most of the study, achieving statistical significance during premating, gestation and lactation. The changes in body weight in high-exposure females were consistent with the decreased body weight of high-exposure females and were exposure related. The

bodyweight gains in 150 ppm (625.5 mg/m^3) females were significantly increased during lactation commensurate with a compensatory response. Food consumption was not measured.

Reproductive performance: No treatment-related effects were observed on the F0 male or female fertility indices, length of gestation, pup survival indices or pup sex ratio in any exposure group (see table below). The statistically significant increases in the female conception index, female fertility index and male conception index of animals exposed to 5 ppm were considered to be related to the relatively low control values.

Summary of principal reproductive indices for F0 rats exposed to sulfuryl fluoride

Indices	**F1**			
	Concentration-ppm			
	0	**5** (20.85 mg/m^3)	**20** (83.4 mg/m^3)	**150** (625.5 mg/m^3)
Number of males	30	30	30	30
Number of females	30	30	30	30
Females mating	30	30	30	30
Males siring a litter	19	26	24	22
Females giving birth	20	29	26	26
Days to mating	3.1	3.3	3.0	3.9
Gestation period (days)	22.1	21.8	21.7	21.9

Pathology:
Organ weights: Organs were not weighed.
Gross pathology: Gross pathologic changes observed in F0 adults were limited to dental fluorosis and grey or pale foci in the lungs. Dental fluorosis was recorded as 'dark, lower incisors' and appeared as very narrow brown and white horizontal bands on the upper and lower incisors. Dental fluorosis occurred in almost all adult F0 rats of both sexes exposed to 150 ppm (625.5 mg/m^3) and but not at lower concentrations. Teeth were not examined histologically, given the lack of histological correlate for dental fluorosis in the 2 year rat study.

In the lungs, aggregates of alveolar macrophages were observed grossly as multiple, round, pale or grey foci. In the F0 generation adults, lung foci were noted in 5 males exposed to 20 ppm sulfuryl fluoride, and in all males and 18 females exposed to 150 ppm (625.5 mg/m^3) sulfuryl fluoride. Pale or grey foci in the lungs were not observed in F0 males or females in the 5 ppm exposure group (see table below).

Summary of gross pathologic findings in F0 adults exposed to sulfuryl fluoride

Sex		Males				Females			
Conc. (ppm)		**0**	**5**	**20**	**150**	**0**	**5**	**20**	**150**
Number of rats examined		30	30	30	30	30	30	30	30
Lungs	Within normal limits	30	29	24	0	30	30	29	12
	Focus – grey, multifocal:	0	0	5	30	0	0	0	18
Oral tissues	Within normal limits	30	30	30	3	29	28	29	1
	Dark, lower incisors:	0	0	0	27	0	0	0	29
	Overgrown incisors, lower incisors:	0	0	0	1	0	0	1	0
	Worn/broken, upper incisors:	0	0	0	4	1	1	1	0
	Malformation, upper incisors:	0	0	0	1	0	1	0	0

Histopathology: Histopathological changes observed in adults, attributable to sulfuryl fluoride exposure, were observed in the lungs of males and females exposed to 150 ppm (625.5 mg/m^3) or 20 ppm (83.4 mg/m^3) and in the brain of males and females exposed to 150 ppm (625.5 mg/m^3) (see table below).

Summary of histopathologic findings in F0 adults

Sex			Males				Females			
Concentration (ppm)			**0**	**5**	**20**	**150**	**0**	**5**	**20**	**150**
Number of rats examined			30	30	30	30	30	30	30	30
Brain	Within normal limits		30	30	29	18	30	30	30	16
	Vacuolation, cerebrum, bilateral	very slight	0	0	0	11	0	0	0	0
		slight	0	0	0	0	0	0	0	14
	Granular cell tumour, meninges, benign, primary		0	0	0	1	0	0	0	0
Lungs	Within normal limits		25	19	16	0	23	20	8	0
	Granuloma(s) foreign body multifocal		0	0	0	0	0	0	0	1
	Inflammation - acute	very slight	2	3	0	0	0	0	0	0
	Inflammation - chronic	very slight	2	2	1	9	2	2	1	19
		slight	0	0	0	5	0	1	0	6
	Aggregates of alveolar macrophages	very slight	3	5	10	6	7	9	19	1
		slight	0	0	1	17	0	1	0	16
		moderate	0	0	0	7	0	0	0	13

Litter data (F1 pups): There were no treatment-related effects on the number of F1 pups born alive or dead, or on the litter size at any exposure level. However, the litter size of live pups at birth and on Days 1 and 4 before culling was increased slightly at 5 ppm (20.85 mg/m^3) and 20 ppm (83.4 mg/m^3) (see table below). These increases were not statistically significant and were not considered treatment-related, as a dose-response was observed. No significant treatment-related effects on the body weights of male and female F1 pups from dams exposed to 5 ppm (20.85 mg/m^3) or 20 ppm (83.4 mg/m^3) were observed at any time during the lactation. The statistically significant decrease in F1 female pup body weights on Day 4 before culling and Day 14 after culling in the 5 ppm exposure group were considered a reflection of the increased litter size in this exposure group. The bodyweights of Fl male and female pups from dams exposed to 150 ppm (625.5 mg/m^3) were significantly decreased throughout most of the lactation period. These effects were considered secondary to maternal toxicity as evidenced by the decreased maternal growth observed throughout the premating and gestation periods.

No effects attributed to exposure were observed on clinical alterations of F0 dams or F1 pups in the 5 ppm (20.85 mg/m^3) or 20 ppm (83.4 mg/m^3) exposure groups during the gestation or lactation periods. The number of F1 pups with no milk in their stomachs was increased in the 150 ppm (625.5 mg/m^3) group. The increased incidence of no milk in the stomach was consistent with the lower bodyweights of the dams and pups from the high exposure group and was considered treatment-related. However, it had no effect on pup survival.

Summary of Litter/Pup Data for F1 rats of parents exposed to sulfuryl fluoride

Pup Data			F1 Concentration (ppm)			
			0	**5**	**20**	**150**
Mean Size of F1Litters	Born Live		13.6	15.6	15.1	13.8
	Lactation Day 1		13.3	15.1	14.8	13.5
	Day 4 pre-cull		13.1	14.8	14.7	13.3
	Day 4 post-cull		7.7	8.0	8.0	8.0
	Day 14		7.7	7.9	8.0	7.9
	Day 21		7.7	7.9	8.0	7.9
Number of Pups	Birth		271	451	393	360
	Day 1		253	439	386	351
	Day 4 pre-cull		248	429	382	346
	Day 4 post-cull		138	224	208	192
	Day 14		138	222	207	189
	Day 21 (weaning)		138	222	207	189
Mean Litter Pup Body Weights	**Male**	Day 1	7.2	7.1	7.2	7.0
		Day 4 pre-cull	10.7	9.7	10.4	9.2*
		Day 4 post-cull	10.7	9.7	10.4	9.2*
		Day 14	26.5	24.7	26.6	22.0*
		Day 21 (weaning)	42.6	40.7	43.0	35.6*
	Female	Day 1	7.1	6.6	6.7	6.6*
		Day 4 pre-cull	10.4	9.3*	9.7	8.5*
		Day 4 post-cull	10.3	9.3	9.8	8.5*
		Day 14	25.8	23.3*	25.0	21.4*
		Day 21 (weaning)	41.4	38.1	41.0	34.7*

*Statistically different from control mean by Dunnett's test, alpha = 0.05.

Organ weights of F1 pups were not recorded. No gross pathologic alterations attributed to treatment were observed in F1 weanlings from any exposure group**.** Histopathology of F1 pups was not conducted.

Second Generation

Mortality: Two rats died and two rats were euthanised moribund prior to the scheduled necropsy. None of the deaths or morbidity were considered treatment related.

Clinical findings: No treatment-related effects or clinical alterations were observed in F1 males or females in any exposure group. The bodyweights of Fl rats exposed to 150 ppm (625.5 mg/m^3), were significantly lower than controls. The statistically significant increase and decreases in the lactational bodyweight gain of dams exposed to 5 ppm (20.85 mg/m^3), 20 ppm (83.4 mg/m^3) or 150 ppm (625.5 mg/m^3) sulfuryl fluoride were not considered treatment-related as lactation weights are usually highly variable, the changes observed did not follow a dose-response and the changes were inconsistent being both significantly increased and decreased.

*Reproductive performance***:** No significant effects were observed on the Fl male or female fertility indices, length of gestation, time to mating, pup survival indices or pup sex ratio in any exposure group (see table below).

Summary of principal reproductive indices for F1 rats

Indices	**F1**			
	Concentration (ppm)			
	0	**5** (20.85 mg/m^3)	**20** (83.4 mg/m^3)	**150** (625.5 mg/m^3)
Number of males	30	30	30	30
Number of females	30	30	30	30
Females mating	29	30	27	29
Males siring a litter	20	19	20	21
Females giving birth	20	23	23	26
Females weaning litters	Data not availabe-see pup data			
Days to mating	3.9	4.5	3.9	4.8
Gestation period (days)	22.0	21.8	21.8	21.8

Pathology:
Organ weights: Organs were not weighed.
Gross pathology: Gross pathologic changes observed in F1 adults, attributable to sulfuryl fluoride exposure, were limited to dental fluorosis and grey or pale foci in the lungs and were similar to the observations made on F0 adults (see table below). Dental fluorosis occurred in most adult F1 rats of both sexes exposed to 150 ppm (625.5 mg/m^3) and appeared as very narrow brown and white horizontal bands on the upper and lower incisors. The lesion was not observed in the 5 ppm (20.85 mg/m^3) or 20 ppm (83.4 mg/m^3) exposure groups or controls (see table below).

Summary of gross pathologic findings in F1 rats exposed to sulfuryl fluoride

Sex		**Males**				**Females**			
Concentration (ppm)		**0**	**5**	**20**	**150**	**0**	**5**	**20**	**150**
Number of rats examined		30	30	30	30	30	30	30	30
Lungs	Within normal limits	27	28	24	16	29	29	23	6
	Focus - pale:	1	0	5	12	0	0	5	24
	Aspirated blood - secondary to decapitation:	1	2	0	2	0	1	2	0
Oral tissues	Within normal limits:	29	29	30	8	30	30	30	10
	Dark, tooth:	0	0	0	22	0	0	0	20

Histopathology: Histopathologic changes observed in adults, attributable to sulfuryl fluoride exposure, were observed in the lungs of males and females exposed to 150 ppm (625.5 mg/m^3) or 20 ppm (83.4 mg/m^3) and in the brain of males and females exposed to 150 ppm (625.5 mg/m^3).
Lungs: The pulmonary changes were characterised as aggregates of alveolar macrophages and were observed most commonly in subpleural or peribronchial locations as described in F0 adults. The aggregates of alveolar macrophages observed commonly in the 20 ppm (83.4 mg/m^3) and 150 ppm (625.5 mg/m^3) exposure groups were morphologically the same as the normal, spontaneous aggregates of alveolar macrophages observed in the lungs of several control rats, except that the lesion was more frequently accompanied by chronic inflammation in the high exposure group (see table below).

Brain: In the brain, very slight to slight, bilaterally symmetrical, vacuolation of the caudate putamen myelinated fibre tracts was observed in F1 males and females exposed to 150 ppm (625.5 mg/m^3) sulfuryl fluoride. The brain lesion pattern was similar to that described for F0 animals.

Summary of histopathologic findings in F1 rats exposed to sulfuryl fluoride

Sex			**Males**				**Females**			
Concentration (ppm)			**0**	**5**	**20**	**150**	**0**	**5**	**20**	**150**
Number of rats examined			**30**	30	30	30	30	30	30	30
Brain	Within normal limits:		30	30	30	28	30	29	30	23
	Hypoplasia, cerebellum, unilateral, focal:		0	0	0	0	0	1	0	0
	Vacuolation, cerebrum, bilateral	very slight	0	0	0	1	0	0	0	5
		slight	0	0	0	1	0	0	0	2
Lungs	Within normal limits:		14	15	9	1	17	19	10	0
	Inflammation - chronic	very slight	1	1	0	5	1	3	3	8
		slight	1	0	0	2	0	0	1	8
		moderate	0	0	0	0	0	0	0	2
	Aggregates of alveolar macrophages	very slight	11	8	15	4	11	9	10	4
		slight	1	4	5	16	1	2	8	12
		moderate	0	0	1	9	0	0	1	14

Litter data (F2 pups): Litter parameters and pup weights at birth were unaffected by treatment. F2 pups from dams exposed to 150 ppm (625.5 mg/m^3), had lower bodyweights throughout the lactation period, with statistically significant differences on lactation Days 14 and 21 (see table below).

Summary of Litter/Pup Data for F2 rats of parents exposed to sulfuryl fluoride

Pup Data			**F1**			
			Concentration (ppm)			
			0	**5**	**20**	**150**
Mean Size of F1 Litters	Born Live		15.2	16.0	14.1	14.7
	Lactation Day 1		15.0	15.9	14.1	14.6
	Day 4 pre-cull		14.9	15.8	13.8	14.2
	Day 4 post-cull		7.8	8.0	7.9	7.9
	Day 14		7.6	8.0	7.7	7.8
	Day 21		7.6	8.0	7.7	7.8
Number of Pups	Birth		304	368	325	381
	Day 1		299	366	325	380
	Day 4 pre-cull		297	364	317	370
	Day 4 post-cull		155	184	181	206
	Day 14		152	183	177	203
	Day 21 (weaning)		152	183	176	202
Mean Litter Pup Body Weights	**Male**	Day 1	6.8	7.0	7.2	6.7
		Day 4 pre-cull	9.7	10.2	10.3	9.2
		Day 4 post-cull	9.7	10.2	10.3	9.2
		Day 14	26.1	27.4	27.0	23.9
		Day 21 (weaning)	41.5	43.8	42.9	38.3
	Female	Day 1	6.4	6.6	6.8	6.2
		Day 4 pre-cull	9.3	9.7	9.6	8.6
		Day 4 post-cull	9.7	10.2	10.3	9.2
		Day 14	26.1	27.4	27.0	23.9*
		Day 21 (weaning)	39.8	42.4	41.7	35.6*

*Statistically different from control mean by Dunnett's test, alpha = 0.05.

The number of F2 pups with no milk in their stomachs was increased in the 150 ppm (625.5 mg/m^3) exposure group but this had no effect on overall litter size or pup survival. No gross pathologic alterations attributed to treatment were observed in F2 weanlings from any exposure group. Organ weights of F2 pups was not recorded and histopathology (F2 pups) was also not conducted.

Conclusions: Under the conditions of this study, sulfuryl fluoride had no effect on reproductive parameters when inhaled by rats in a 2-generation reproduction study at concentration up to and including 150 ppm (625.5 mg/m^3) for 6 hours/day, 5-7 days for up to 20 consecutive weeks. General effects in parental animals were limited to an increased incidence of aggregates of alveolar macrophages in F0 and F1 males and females at 20 ppm (83.4 mg/m^3). At 150 ppm(625.5 mg/m^3), toxicity comprised reduced body weights, dental fluorosis alveolar macrophages and brain vacuolation.

In this reproductive toxicity study, the NOEC for reproductive effects was 150 ppm (625.5 mg/m^3) (approximately equivalent to 10.8 mg/kg bw/d systemic exposure), the highest concentration tested. Parental toxicity was evident at 150 ppm (625.5 mg/m^3), toxicity comprised reduced bodyweights, overt dental fluorosis, alveolar macrophages and brain vacuolation. These findings are consistent with those from sub-chronic studies. The parental NOEC was 5 ppm (20.85 mg/m^3) (approximately equivalent to 0.4 mg/kg bw/d systemic exposure), based on an increased incidence of aggregates of alveolar macrophages in adult F0 and F1 males and females at 20 ppm (83.4 mg/m^3).

Reduced growth in F1 and F2 pups during the lactation period was noted at 150 ppm (625.5 mg/m^3) and was the only effect in offspring. The NOEC in offspring was 20 ppm (83.4 mg/m^3) (approximately equivalent to 1.4 mg/kg bw/d systemic exposure), based on reduced growth during lactation at 150 ppm (625.5 mg/m^3).

4.4.5 Developmental Studies

1. Hanley, T.R., Calhoun, L.L., Cobel-Gerard, S.R., Hayes, W.C., Murray, J.S., Kociba, R.J., John, J.A. (1980). Vikane: Probe Teratology Study in Fischer 344 Rats and New Zealand White Rabbits. Study No: Unspecified, Report No: HET K-16399-(14), Unpublished, Report date: 19 November 1980.

Test Compound:	Viikane (not otherwise specified)
Batch:	Not stated.
Test Species:	Rat (Bred Fischer 344) & New Zealand White Rabbits; age and source are not stated
Study Duration:	Study started on 28 April 1980 & completed on 19 November 1980.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-No. QA-not stated.
Guidelines:	None–this was a probe study for dose-setting to determine maternal toxicity during pregnancy.

Rats

Study: Rats (7-9/dose) were exposed to targeted concentrations of 0, 30, 100 or 300 ppm (0, 125.1 mg/m^3, 417 mg/m^3 or 1251 mg/m^3) of test material via inhalation, 6 hours/day on days 6 though 15 of gestation. Inhalation exposures were conducted in stainless steel and glass

chambers under dynamic airflow conditions. Chamber atmospheres concentrations were analysed at 30 minutes interval using a Miran IA IR. Chamber concentrations were within 1% of the intended concentrations.

All animals were observed daily for signs of toxicity from the test material. Body weights of rats were recorded at 3-day intervals beginning on day 6 of gestation. Animals were sacrificed by decapitation on day 16 of gestation and examined for gross pathologic changes. Maternal body weights and liver and kidney weights, as well as the number of corpora lutea, and the number and position of live, dead and resorbed foetuses were recorded at the time of necropsy.

Findings:

Clinical findings: There was no mortality and no overt clinical signs of maternal toxicity were observed at any exposure levels. A significant decrease in food consumption and an increase in water consumption were noted in rats at the 300 ppm (1251 mg/m^3) level. A statistically significantly decreased maternal body weights and body weight gain, as well as significant increases in both absolute and relative kidney weights, were seen at the 300 ppm (1251 mg/m^3) exposure level. Body weight and organ weight parameters were unaffected at the 30 ppm (125.1 mg/m^3) and 100 ppm (417 mg/m^3) exposure levels.

Pathology: Gross pathologic observations related to 300 ppm (1251 mg/m^3) exposure levels were noted in the liver, kidneys and intestines. The livers of most rats at the 300 ppm (1251 mg/m^3) exposure level exhibited an equivocal to moderate degree of diffuse paleness; the kidneys showed subcapsular foci or areas of paleness. Two rats exhibited decreased intestinal contents, supporting the decreased food consumption data. No treatment related lesions were apparent at the 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3) exposure levels.

Litter data: No evidence of embryotoxicity, which could be attributed to Vikane exposure, was seen at either 30 ppm (125.1 mg/m^3) or 300 ppm (1251 mg/m^3). An increase in percentage pre-implantation loss was observed at 100 ppm (417 mg/m^3), although this was not considered to be treatment-related, as no other abnormalities were observed.

Conclusions: Maternal toxicity (decreased body weight and food consumption and increased water consumption and kidney weights) was seen in rats at the 300 ppm (1251 mg/m^3) exposure level. There was no evidence of embryotoxicity. Exposure levels up to 100 ppm (417 mg/m^3) were well tolerated by pregnant rats. Base on these results, exposure levels of 0 ppm, 25 ppm (104.25 mg/m^3), 75 ppm (312.75 mg/m^3) and 225 ppm (938.25 mg/m^3) were set for the main regulatory teratology study.

Rabbits

Study: Inseminated rabbits (5-7/dose) were exposed to targeted concentrations of 0, 30, 100 or 300 ppm (0, 125.1 mg/m^3, 417 mg/m^3 or 1251 mg/m^3) of test material via inhalation, 6 hours/day on days 6 though 18 of gestation. Inhalation exposures were conducted in stainless steel and glass chambers under dynamic airflow conditions. Chamber atmospheres concentrations were analysed at 30 minutes interval using a Miran IA IR. Chamber concentrations were within 1% of the intended concentrations.

All animals were observed daily for signs of toxicity from the test material. Body weights of rabbits were recorded on days 6, 9, 12, 15 and 19 of gestation. Animals were sacrificed by

decapitation on day 19 of gestation and examined for gross pathologic changes. Maternal body weights and liver and kidney weights, as well as the number of corpora lutea, and the number and position of live, dead and resorbed foetuses were recorded at the time of necropsy.

Findings:

Clinical findings: There was no mortality and no overt clinical signs of maternal toxicity were observed at any exposure levels. Food and water consumption was not measured. A statistically significantly decreased maternal body weight, body weight gain and absolute and relative kidney weights were seen at the 300 ppm (1251 mg/m^3) exposure level. These changes in body weight gains and organ weights were considered an indication of maternal toxicity at the 300 ppm (1251 mg/m^3) exposure level. Body weight and organ weight parameters were unaffected at the 30 ppm (125.1 mg/m^3) and 100 ppm (417 mg/m^3) exposure levels.

Pathology: Gross pathologic observations related a very slight to slight pale accentuation of the lobular pattern of the liver was seen in four of seven animals exposed to 300 ppm (1251 mg/m^3). No treatment-related lesions were apparent at the 30 ppm (125.1 mg/m^3) or 100 ppm (417 mg/m^3) exposure levels.

Litter data: No evidence of embryotoxicity, which could be attributed to Vikane exposure was seen at either 30 ppm (125.1 mg /m3) or 300 ppm (1251 mg /m3). A statistically significant increase in the percent implantations resorbed was seen in rabbits at the 100 ppm (417 mg/m^3) exposure level. However, due to the lack of a comparable effect at 300 ppm (1251 mg/m^3), this difference could not be attributed to exposure. A single rabbit foetus from a doe exposed to 300 ppm (1251 mg/m^3) exhibited exencephaly at the time of necropsy. No other abnormalities were observed.

Conclusions: Significant decreases in maternal body weight and liver weights were seen in the 300 ppm (1251 mg/m^3) exposure level. There was no evidence of embryotoxicity to rabbits. Exposure levels up to 100 ppm (417 mg/m^3) were well tolerated by pregnant rabbits during the period of organogenesis. Based on these results, exposure levels of 0 ppm, 25 ppm (104.25 mg/m^3), 75 ppm (312.75 mg/m^3) and 225 ppm (938.25 mg/m^3) were selected for the main teratology study in rabbits.

2. Hanley, T.R., Jr., Calhoun, L.L., Kociba, R.J., Cobel-Geard, S.R., Hayes, W.C., Ouellette, J.H., Scherbarth, L. M., Sutter, B. N. & John, J.A. (1981). Vikane: Inhalation Teratology Study in Rats and Rabbits. Study No: Unspecified, Report No: HET K-16399-(15), Unpublished, Report date: 26 October 1981.

Test Compound:	Vikane fumigant (purity: 99.8% sulfuryl fluoride)
Batch:	217
Test Species:	Rat (Bred Fischer 344) & NZW rabbits; age and source are not stated
Study Duration:	Study started on 9 June 1980 & completed on 26 October 1981.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated.
Guidelines:	None stated. Deviations from EC test guidelines Method B.31. Teratogenicity Study-Rodent and Non-Rodent: This study exceeds the guidelines in a number of ways: more animals used, more tissues examined. Food consumption was not measured in rabbits.

Rats

Study: Bred Fischer 344 rats (35 or 36/group) were exposed to 0, 25, 75 or 225 ppm (0, 104.25 mg/m^3, 312.75 mg/m^3 or 938.25 mg/m^3) (0, 1.8, 5.4, 16.2 mg/kg bw/d) of Vikane via inhalation, for 6 hrs/d on days 6 through 15 of gestation. A control group of 36 rats was exposed to filtered room air for 6 hours/day on days 6 through 15 of gestation. Inhalation exposures were conducted in 4.3 cubic meter Rochester-type stainless steel and glass chambers (800 L air/min.). Chamber concentrations were generated by via precision pump into the air inlet of the chambers where it was diluted to the desired concentration and mixed with incoming air by turbulence. VlKANE fumigant concentrations in the chambers were determined analytically by using a Miran I Variable Filter Infrared analyser. The mean daily time-weighted average (TWA) for exposures were within 2% of intended chamber concentrations of sulfuryl fluoride.

Animals were observed daily throughout the experimental period for indications of toxicity from the test material and any possible adverse effects from exposure were recorded. Bodyweights of rats were recorded on days 6, 9, 12, 16 and 21; food and water consumption were recorded for rats at three-day intervals beginning on day 6 of gestation. Test animals were terminated by carbon dioxide inhalation on day 21 of gestation. In addition, maternal liver and kidney weights were recorded. The uterine horns were exteriorised through a mid-line incision in the abdominal wall. The following data were recorded: 1) number and position of fetuses *in utero*, 2) number of live and dead fetuses, 3) number and position of resorption sites, 4) the number of corpora lutea, 5) the sex, bodyweight and crown-rump length of each fetus, and 6) any gross external alteration. The uteri of apparently non-pregnant animals were stained with a 10% solution of sodium sulphide and examined for evidence of implantation sites. One-half of each litter selected using a table of random numbers was examined by dissection under a low power microscope for evidence of soft tissue alterations. The heads of rat fetuses examined by dissection were removed, placed in Bouin's fixative and examined by a serial sectioning technique. All fetuses were then eviscerated, preserved in alcohol, subsequently cleared, stained with alizarin red-S, and examined for skeletal alterations.

Findings:

Clinical findings: Among rats exposed to sulfuryl fluoride, no overt signs of toxicity or effects on general demeanour were observed at any exposure level. Maternal bodyweights measured during gestation were comparable to control values at all exposure levels, and there were no significant differences from control values with respect to maternal bodyweight gains. Food consumption of rats exposed to sulfuryl fluoride was comparable to control values. However, at the 225 ppm (938.25 mg/m^3) exposure level, water consumption was significantly increased during gestation on days 6-17, as measured in 3-day interval. Water consumption during the last 3 days of gestation (days 18-20) in this group was comparable to control values. No effects on either absolute or relative weights of liver or kidney were evident.

Litter data: No statistical differences in pre-implantation loss, mean litter size, the incidence of resorptions or foetal sex ratio were observed in any exposure group (see table below). At the 225 ppm (938.25 mg/m^3) exposure level, fetal bodyweights and crown-rump lengths were statistically significantly higher than concurrent control values but differences were considered biologically negligible (mean < 4%) and considered of no relationship to treatment.

Litter data (means) for pregnant rats exposed to sulfuryl fluoride.

Parameter	Concentration-ppm			
	0	**25** (104.25 mg/m^3)	**75** (312.75 mg/m^3)	**225** (938.25 mg/m^3)
Number bred	36	35	35	36
Non-pregnant	5	6	3	5
Number dead/sacrificed	0	0	0	0
Number of total resorptions	0	0	0	1
Number of viable litters	31	29	32	31
Number of corpora lutea/dam	12	12	12	12
Number of implantations/dam	10	10	10	10
Pre-implantation loss (%)	18	13	19	23
Fetuses/litter	9	8	8	8
Number of resorptions/litter	1.52	2.07	2.03	1.94
Implantations resorbed (%)	15	20	21	20
Litters with resorptions (%)	74	93	84	81
Fetal body weights (g)	4.32	4.28	4.45	4.48
Fetal sex ratio M:F	51:49	45:55	52:48	49:51
Fetal crown-rump length	40.7	40.7	41.1	41.3

Fetal examinations: The incidence of major malformations observed externally, internally or by skeletal examination, whether considered individually or collectively, in each exposure group, was not statistically significantly different from controls in any exposure group (see table below). The number of fetuses that exhibited major malformations was higher in the control group (4 fetuses from 2 litters) than in the exposed groups (2 fetuses in 2 litters in each exposure group. The majority of malformations were microphthalmia or anophthalmia. A number of minor alterations or instances of delayed development were observed among both control and treated groups. However, this was not considered associated with exposure. Minor skeletal variations, which were observed, included statistical increases in the incidence of bilobed thoracic centra in fetuses from the 25 ppm (104.25 mg/m^3) and 225 ppm (938.25 mg/m^3) exposure groups and an increased incidence of unfused thoracic centra in the 75 ppm (312.75 mg/m^3) exposure group, when compared to controls. Other than these, the incidence of skeletal variations observed in fetues from the 25 ppm (104.25 mg/m^3), 75 ppm (312.75 mg/m^3) and 225 ppm (938.25 mg/m^3) exposure groups, were comparable to incidence among control foetuses. Therefore, the statistical increases of these minor skeletal variants, which occur spontaneously in this test species, were not considered to be evidence of fetotoxicity.

Incidences of foetal alterations

Concentrations-ppm		**0**		**25** (104.25 mg/m^3)		**75** (312.75 mg/m^3)		**225** (938.25 mg/m^3)	
Examination		**Number of fetuses (Number of litters) examined**							
	External exam.	264 (31)		244 (29)		245 (32)		245 (30)	
	Bouins head exam	118 (28)		112 (26)		111 (29)		108 (23)	
	Visceral exam.	144 (31)		132 (29)		134 (32)		136 (30)	
	Skeletal exam	264 (31)		244 (29)		245 (32)		245 (30)	
Observations[#]		fetus	litter	fetus	litter	fetus	litter	fetus	litter
Total Major Malformations[#]		4	2	2	2	2	2	2	2
Soft Tissue Alterations[#]	Anophthalmia/ Microphthalmia	2	2	2	2	2	2	2	2
Skeletal Alterations	Sternebrae-delayed ossification	90	27	83	28	70	29	76	26
	Sternebrae-unfused	9	8	7	7	6	6	5	5
	Sternebrae-fused	1	1	0	0	2	1	0	0
	Sternebrae-extra site of ossification	0	0	0	0	1	1	0	0
	Vertebrae–delayed ossification-centra	73	25	80	28	65	28	61	25
	Vertebrae-bilobed centra	11	10	22*	16	12	9	24*	17
	Vertebrae-unfused centra	2	2	2	2	7*	6	2	2
	Ribs– spurs	1	1	0	0	3	2	1	1

[#]number of fetuses or litters. *Statistically different from control values by Wilcoxon's test, alpha = 0.05.

Conclusions: Under the conditions of this study, there was no evidence of maternal toxicity, embryolethality, or fetotoxicity at exposure levels up to 225 ppm (938.25 mg/m^3) of 'Vikane'. The incidences of major malformations, considered either individually or collectively at each exposure level, were not significantly increased in any treatment group when compared to control values. The incidence of resorptions was not significantly increased among rats in any exposure group indicating that Vikane was not embryolethal at exposure levels as high as 225 ppm (938.25 mg/m^3). The NOEC for maternal and fetotoxicity is 225 ppm (938.25 mg/m^3) (approximately equivalent to 16.2 mg/kg bw/d systemic exposure), the highest dose tested.

Rabbits

Study: Inseminated NZW Rabbits (28 or 29/group) were exposed to 0, 25, 75 or 225 ppm (0, 104.25 mg/m^3, 312.75 mg/m^3 or 938.25 mg/m^3) (0, 1.4, 4.3, 13 mg/kg bw/d) of Vikane via inhalation, for 6 hrs/day on days 6 through 18 of gestation. A control group of 28 rabbits was exposed to filtered room air for 6 hours/day on days 6 through 18 of gestation. Inhalation exposures were conducted in 4.3 cubic meter Rochester-type stainless steel and glass chambers (800 L air/min.). Chamber concentrations were generated by via precision pump into the air inlet of the chambers where it was diluted to the desired concentration and mixed with incoming air by turbulence. VlKANE fumigant concentrations in the chambers were determined analytically by using a Miran I Variable Filter Infrared analyser. The mean daily time-weighted average (TWA) for exposures was within 2% of intended chamber concentrations of sulfuryl fluoride.

Animals were observed daily throughout the experimental period for indications of toxicity from the test material and any possible adverse effects from exposure were recorded. Bodyweights of rats were recorded on days 6, 9, 12, 15 and 29 of gestation. Test animals were sacrificed by carbon dioxide inhalation on day 29 of gestation. Maternal liver and kidney weights were recorded. The uterine horns were exteriorised through a mid-line incision in the abdominal wall.

The following data were recorded: 1) number and position of fetus's *in utero*, 2) number of live and dead fetuses, 3) number and position of resorption sites, 4) the number of corpora lutea, 5) the sex, bodyweight and crown-rump length of each fetus, and 6) any gross external alteration. The uteri of apparently non-pregnant animals were stained with a 10% solution of sodium sulphide and examined for evidence of implantation sites. One-half of each litter selected using a table of random numbers was examined by dissection under a low power microscope for evidence of soft tissue alterations. The heads of rat fetuses examined by dissection were removed, placed in Bouin's fixative and examined by a serial sectioning technique. All fetuses were then eviscerated, preserved in alcohol, subsequently cleared, stained with alizarin red-S, and examined for skeletal alterations.

Findings:

Clinical findings: No controls animals died or were terminated early. Among the rabbits exposed to 25 ppm (104.25 mg/m^3) of Vikane fumigant during gestation, there were two deaths recorded. The cause of death of one animal could not be determined upon gross pathologic examination. Gross necropsy of the second rabbit at 25 ppm (104.25 mg/m^3) revealed pulmonary inflammation consistent with pneumonia, most probably *Pasteurellosis*. A single death occurred among maternal rabbits in the 75 ppm (312.75 mg/m^3) exposure group, however, the cause of death could not be determined. Three deaths occurred among maternal rabbits exposed to 225 ppm (938.25 mg/m^3) Vikane which, upon gross necropsy, were attributed to severe pulmonary inflammation consistent with pneumonia, most probably *Pasteurellosis;* pulmonary inflammation is an effect of sulfuryl fluoride and these findings at 225 ppm (938.25 mg/m^3) are possibly treatment related.

The mean body weight of pregnant rabbits exposed to 225 ppm (938.25 mg/m^3) of Vikane was significantly lower than that of controls on day 29 of gestation (see table below). The overall body weight gain during gestation (days 6 through 28) was also significantly decreased compared to controls among rabbits exposed to 225 ppm (938.25 mg/m^3). There were no differences in body weight or body weight gains among rabbits exposed to 25 ppm (104.25 mg/m^3) or 75 ppm (312.75 mg/m^3) when compared to control values.

Mean body weights of maternal rabbits

Exposure (ppm)		**0**	**25** (104.25 mg/m^3)	**75** (312.75 mg/m^3)	**225** (938.25 mg/m^3)
Number of Dams		26	22	21	21
	Gestation Day				
Maternal body weight (g)	6	4036	4161	3945	4025
	9	4036	4169	3946	4065
	12	4031	4187	3952	4036
	15	4100	4256	3997	4016
	19	4116	4285	4065	3974
	29	4276	4360	4109	3965*
Maternal body weight gain (g)	6-8	0	8	1	40
	9-11	-5	18	6	-29
	12-14	69	69	46	-21*
	15-18	16	29	67	-41
	19-28	160	75	44	-9*
	6-28	240	199	163	-60*

*Statistically significantly different from control mean by Dunnett's test, alpha = 0.05.

Organ Weights: There were no differences in either absolute or relative weights of the liver or kidneys of exposed rabbits when compared to controls.

Litter data: Control and treated animals exhibited a similar pattern of implantation loss and early delivery. No adverse effects on average litter size, fetal sex ratio, or the incidence of resorptions among rabbits exposed to Vikane were observed and values, which were observed, are within the historical control range for this species observed in this laboratory. At the 225 ppm (938.25 mg/m^3) exposure level, fetal bodyweights were significantly decreased when compared to control values, and a trend toward decreased fetal crown-rump length was also noted. These parameters were unaffected in rabbits exposed to 25 ppm (104.25 mg/m^3) and 75 ppm (312.75 mg/m^3).

Litter data (means) for pregnant rabbits exposed to sulfuryl fluoride.

Parameter	**Concentration-ppm**			
	0	**25** (104.25 mg/m^3)	**75** (312.75 mg/m^3)	**225** (938.25 mg/m^3)
Number bred	28	29	28	29
Non-pregnant	5	3	6	3
Number dead/sacrificed	0	2	1	3
Number of total resorptions	1	0	3	0
Number of viable litters	19	22	18	21
Number of corpora lutea/dam	10	10	10	10
Number of implantations/dam	9	9	8	8
Pre-implantation loss (%)	11	15	14	11
Foetuses/litter	8	8	7	8
Number of resorptions/litter	1.1	0.9	2.1	1.0
Implantations resorbed (%)	13	11	16	8
Litters with resorptions (%)	45	36	57	33
Fetal bodyweights (g)	38.22	38.18	38.44	32.95*
Fetal sex ratio M:F	50:50	52:48	42:58	44:56
Fetal crown-rump length (mm)	93.6	94.5	93.8	89.7

*Significantly different from control mean using binomial distribution test, alpha = 0.05.

Fetal examinations: The incidence and pattern of malformations and external, soft tissue and skeletal alterations were similar in control and treated groups (see table below). Low incidences of small spleen, dilated renal pelvis and pale liver in the 225 ppm (938.25 mg/m^3) group are possibly treatment related given the zero background in other groups, but are likely to be secondary to low foetal weight and maternal toxicity.

Incidences of fetal alterations

	Concentration-ppm							
	0		**25** (104.25 mg/m^3)		**75** (312.75 mg/m^3)		**225** (938.25 mg/m^3)	
Examination	**Number of foetuses (Number of litters) examined**							
External exam.	153 (19)		167 (22)		145 (18)		163 (21)	
Visceral exam.	84 (19)		89 (22)		78 (18)		90 (21)	
Skeletal exam.	153 (19)		167 (22)		138 (18)		152 (20)	
Observations[#]	foetus	litter	foetus	litter	foetus	litter	foetus	litter
Total Major Malformations[#]	2	2	4	4	3	3	2	2
External alterations[#]								
Exencephaly	1	1	0	0	0	0	1	1
Soft Tissue Alterations[#]								
Persistent *truncus arteriosis* and ventricular septal defect	0	0	0	0	0	0	1	1
Patent *ductus arteriosis*	0	0	1	1	2	2	1	1
Retro-oesophageal subclavian artery	1	1	0	0	0	0	0	0
Extra vessel(s) off major arteries	4	3	3	3	1	1	6	4
Satellite vessel(s) off major arteries	60	19	46*	18	50	17	43*	20
Hamartoma adjacent to gallbaldder	2	2	5	4	6	4	7	4
Small spleen	0	0	0	0	0	0	1	1
Dilated renal pelvis	0	0	0	0	0	0	1	1
Pale liver	0	0	0	0	0	0	3	2
Skeletal Alterations								
Skull-delayed ossification	2	2	0	0	0	0	2	2
Skull-foramen	3	3	2	2	2	1	5	3
Ribs-extra ribs	63	17	75	21	65	17	58	18
Ribs-spurs	3	3	8	7	3	2	3	3
Sternebrae-unfused	1	1	2	2	1	1	2	2
Cartilage-extra cartilage	1	1	1	1	0	0	0	0
Cartilage-missing cartilage	14	5	9	7	4	4	5	1

*Statistically different from control values by Wilcoxon's test, alpha = 0.05 [#] number of foetuses or litters

Conclusions: Among rabbits, maternal toxicity, as evidenced by a loss of body weight during gestation, was observed in the 225 ppm (938.25 mg/m^3) exposure group. Decreased fetal bodyweight, indicative of a fetotoxic effect, was also observed at 225 ppm (938.25 mg/m^3). No evidence of maternal toxicity or fetotoxicity was observed among rabbits exposed to 25 or 75 ppm (312.75 mg/m^3) of 'Vikane'. The incidence of resorptions was not significantly increased among rabbits in any exposure group indicating that 'Vikane' was not embryolethal at exposure levels as high as 225 ppm (938.25 mg/m^3)**.** There was no evidence of teratogenicity. The NOEC for maternal and fetotoxicity was 75 ppm (312.75 mg/m^3) (approximately equivalent to 4.3 mg/kg bw/d systemic exposure).

4.4.7 Neurotoxicity Studies

1. Albee, R.R., Spencer, P.J., Bradley, G.J. (1993). Sulfuryl Fluoride: Electrodiagnostic, FOB and Motor Activity Evaluation of Nervous System Effects from Short-Term Exposure. Study No: Unspecified, Report No: DECO-HET K-016399-045, Unpublished, Report date: 3 May 1993.

Test Compound:	Sulfuryl fluoride (purity: 99.8%)
Batch:	WP920619-953
Test Species:	Rat (Fischer 344-female); age and source are not stated; 12 animals/dose
Study Duration:	Study started on 8 February 1993 & completed on 3 May 1993.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA
GLP & QA:	GLP-Yes. QA-not stated
Guidelines:	US EPA 82-7 (Addendum 10, 1991) Deviations from EC test guidelines: There is no guideline in the EU for this kind of neurotoxicity study

Study: The study goals were to evaluate the effects of short-term inhalation exposure to high levels (0, 100 and 300 ppm, equivalent to 0, 10, 31 mg/kg bw/d) of sulfuryl fluoride on CNS function of Fischer 344 rats. Dose selection was based primarily on the observation that changes in evoked potentials occurred in the absence of neuropathologic changes in F344 rats exposed to 100 ppm (417 mg/m^3) sulfuryl fluoride for 6 hr/day, 5 days/wk, for 13 weeks (Mattson et al, 1986). Rats exposed to 300 ppm (1251 mg/m^3) for 13 weeks had both brain lesions and evoked potential changes. This study therefore focussed on investigating the most sensitive critical (neurological) end-point, visual, auditory and somatosensory evoked potential, when trying to establish an acute NOEC for sulfuryl fluoride. The study was conducted in female rats, as these were considered the most sensitive sex, based on flash evoked potential data, in the previous 13-week neurotoxicity study.

Female Fischer 344 rats (12/concentration) were exposed to 0, 100 or 300 ppm (0, 417 mg/m^3 or 1251 mg/m^3) sulfuryl fluoride, 6 hrs/day on 2 consecutive days (this was considered to effectively represent an acute exposure of 12 hours in a 30-hour period). The animals were evaluated pre-exposure and post-exposure by a functional observational battery (FOB), grip performance, landing foot splay, motor activity and a battery of electrodiagnostic tests. Post-exposure data were collected within 5 hours after the second exposure, except for motor activity data, which were collected 18 hours after exposure. Animals were exposed to sulfuryl fluoride gas in a 14.5 m3 chamber with a pyramidal top. Concentrations of sulfuryl fluoride were generated using the glass J-tube method. The chamber concentrations were monitored with a Miran lA IR spectrophotometer. Chamber concentrations were approximately 97% of target concentration.

Findings:

Clinical Findings: There were no exposure related effects on bodyweights.

Cage-side, Hand-held and Open-Field Observations: Minor FOB differences in the 300 ppm (1251 mg/m^3) group were observed during pre-exposure and post-exposure. At pre-exposure, 10/12 of the 300 ppm (1251 mg/m^3) group exhibited virtually no resistance to removal from the home-cage compared to 6/12 of the controls, which showed no resistance and 6/12, which showed minimal resistance. During the post-exposure FOB, all groups were comparable for 'resistance to removal', but the 300 ppm (1251 mg/m^3) group was slightly less reactive to

handling than the controls. Of the observations that possibly were distributed differently according to treatment, post-exposure reactivity to handling had the greatest difference; 5/12 controls showed no resistance to handling whereas the 300-ppm (1251 mg/m^3) group had 10/12. However, this result was not statistically significant and is consistent with the differences in pre-exposure resistance to removal from the cage.

Grip performance: There were no exposure-related differences in hind limb or forelimb grip performance.

Hindlimb Landing Foot Splay: There were no exposure-related differences in hind limb landing foot splay.

Conclusion: In this study, there were no adverse exposure-related effects in any of the parameters at 300 ppm (1251 mg/m^3) (approximately equivalent to 31 mg/kg bw/d systemic exposure), the highest concentration tested.

2. Mattson, J.L., Albee, R.R., Eisenbrandt, D.L. & Nitschke, K.D. (1986) Neurological examination of Fischer 344 rats exposed to sulfuryl fluoride (Vikane Gas Fumigant) for 13 weeks:. Study No: Unspecified, Report No: K-016399-026, Unpublished, Report date: 21 November 1986.

Test Compound:	Sulfuryl fluoride (purity: 99.8%)
Batch:	TWP 830919-408
Test Species:	Rat (Fischer 344); 5 weeks old; source is not stated; 7/sex/exposure level
Study Duration:	Study started on 19 September 1984 & completed on 21 November 1986.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA
GLP & QA:	GLP-Yes. QA-not stated
Guidelines:	US EPA 82-5 Deviations from EC test guidelines: There are no guidelines in the EU for this kind of neurotoxicity study

Study: Rats were exposed to 0, 30, 100 or 300 ppm (0, 125.1 mg/m^3, 417 mg/m^3 or 1251 mg/m^3) (0, 2.2, 7.2, 22 mg/kg bw per day) sulfuryl fluoride for 6 hr/day, 5 days/week for 13 weeks. The chambers were 4.1 m^3 stainless steel and glass. The concentration of sulfuryl fluoride in each exposure chamber was determined with a MlRAN1 A infrared spectrophotometer.

Seven male and female rats/concentration were selected randomly for surgery to implant brain electrodes. Since they were so young at the start of the study, the surgery took place 2 months into the study. Epidural electrodes were inserted into the skull and supported with dental acrylic. The somatosensory electrode was placed 1.5 mm posterior and 3.0 mm lateral left of bregma, the visual cortex electrode was placed 6.8 mm posterior and 3.0 mm lateral right of bregma, and the cerebellar electrode was located 12.0 mm posterior and 0.0 mm lateral of bregma. A reference electrode was placed 7.0 mm anterior and 1.0 mm lateral left of bregma. The following responses were measured: auditory brainstem response (ABR) to clicks and pips; cortical flicker fusion (CFF) to light flashes; visual evoked response (VER) to light flash; somatosensory evoked response (SER) to tail stimulation and caudal nerve action potentials (CNAP) in the tail. During data gathering in the electrophysiological tests, the rats were fully conscious but physically restrained. Electrophysiological investigations and a limited FOB were performed after 13 weeks of exposure; no investigations were performed at intermediate time points.

Two male and two female rats exposed to 0 ppm or 300 ppm (1251 mg/m^3) sulfuryl fluoride were placed on recovery for approximately two months following 13 weeks of exposure. Because the auditory brainstem response (ABR) was clearly affected by treatment, and the ABR was considered a highly reliable response, only the ABR was evaluated during recovery.

At necropsy, the rats were euthanised and examined for gross pathologic alterations. The necropsy included *in situ* examination of the eyes by a glass slide technique with fluorescent illumination. A complete set of tissues was collected from each animal and preserved in neutral, phosphate-buffered 10% formalin. The sciatic, tibial, caudal and optic nerves were collected. Lungs were infused with formalin to their approximate normal inspiratory volume and the nasal cavity was flushed with formalin via the pharyngeal duct.

Representative sections of ear tissues were prepared for histology. Sections of the middle ears were prepared from one female and six male control animals as well as seven males from the 100 ppm (417 mg/m^3) group. Sections of the middle ears also were prepared from three control males from the standard 13-week study; these provided control tissue from animals that did not have surgical implants. A section of cerebrum was prepared from the brain of a control male and a 300-ppm (1251 mg/m^3) male that both died as a result of implant surgery. Tissues were routinely processed and stained with haematoxylin and eosin (H & E). Two male and two female rats from the 0 and 300 ppm (1251 mg/m^3) exposure groups (8 rats) constituted a recovery group and were necropsied two months post-exposure. The brains were sent to another laboratory for histopathologic examination. Each brain was bisected on the midline. The right hemisphere (half) of the brain was again bisected longitudinally. The left hemisphere was cut into five equal cross sections yielding seven tissue specimens per brain. Each longitudinally cut specimen was embedded in a paraffin block. The five transverse specimens were embedded, in groups of two and three, into two paraffin blocks. All tissue sections were cut 10 um thick and stained with H &. E. Special stains were performed with tissue sections from the highest treatment group (300 ppm-1251 mg/m^3) and control animals. Three special stains were performed: Gallocyanine, for detection of any changes in the neuronal Nissl substance; Luxol fast blue for detection of any changes in the myelin sheaths; and Bodian, for detection of any axonal changes. In addition, another special stain, Holzer, was also performed on the long-term recovery animals to detect any scarring in damaged brain areas. Because vacuoles were seen in the caudate-putamen of 300 ppm (1251 mg/m^3) rats in the standard study, step-sections assured critical re-examination of the caudate-putamen. Only Luxol fast blue-H&E staining was performed on the sections.

Findings:

General and Neurological findings: Rats of all dose groups appeared to be in good health during and at the end of the study. The only FOB findings were that rats in the 300 ppm (1251 mg/m^3) group weighed less than controls and some had unkempt fur and excessive lacrimation. No treatment-related effects were found in the 30 ppm (125.1 mg/m^3) group. Four males died, three from anaesthetic and one from a handling accident. Hind limb grip strength was normal for all rats but evoked responses were clearly altered at 300 ppm (1251 mg/m^3) and slightly altered at 100 ppm (417 mg/m^3) (see table below). The principal effect was a decrease in cortical flicker fusion (CFF) and a slowing of all waveforms at 300 ppm (1251 mg/m^3), and a slowing of the VER and SER of female rats at 100 ppm (417 mg/m^3). An apparent effect on SER at 30 ppm (125.1 mg/m^3) in females was not statistically significant with mean values well within the control range. Visual inspection of ABR's indicated that, although not statistically significant, the ABR's of 100 ppm (417 mg/m^3) male rats were also slow (although 3 males account for nearly all the poor ABR-tone responses in this group). Rectal temperatures of 300 ppm (1251

mg/m^3) rats were slightly ($p<0.05$) lower than control rats during VER, Cry, and ABR tone testing. Temperature differences decreased to non-significant level during the 35 min of electrophysiological testing. CER-S Latency increased in the treatment groups with increasing doses. The ABR results for the recovery groups showed evidence of recovery at 1 month and were within the normal ranges of response after 2 months.

Bodyweights, electrophysiological data and grip strength in rats exposed to sulfuryl fluoride for 13 weeks.

Conc. (ppm)	**0**	**30**	**100**	**300**	**0**	**30**	**100**	**300**
Sex	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Bodyweight (g)	251.10	275.75	270.06	213.80	168.14	162.84	163.57	131.29
Grip Strength (g force)	560.00	611.67	684.29	563.33	369.29	395.71	376.43	340.00
VER Latency (msec)	-0.18	-2.05	-2.38	5.91	0.00	0.05	11.87	10.90
VER Power (μV^2)	26.40	30.98	41.09	37.42	28.49	28.90	27.87	26.71
CFF (Hz)	45.26	48.33	46.86	42.67	47.71	48.57	45.14	42.67
ABR Latency (msec)	0.00	0.00	0.01	0.04	0.00	0.00	-0.03	0.05
ABR Power (μV^2)	1.69	1.80	1.36	1.41	1.62	1.71	1.86	1.40
ABR-III/V latency (msec)	0.02	0.04	0.14	0.18	0.00	0.04	-0.03	0.16
ABR-III/V Power (μV^2)	1.20	1.09	0.88	0.88	1.15	1.16	1.27	0.90
CER-S Latency (msec)	-0.07	0.07	0.64	0.89	0.25	0.55	0.72	1.27
CER-S Power (μV^2)	11.89	13.56	11.91	12.08	15.47	14.46	15.07	16.65
CER-L Latency (msec)	-0.54	0.67	1.20	2.75	0.51	0.86	-1.11	4.05
CER-L Power (μV^2)	29.45	33.08	29.97	29.93	28.61	27.27	34.43	36.86
SER-S Latency (msec)	0.06	-0.82	0.24	0.24	0.09	0.60	-0.04	-1.12
SER-S Power (μV^2)	15.20	20.95	16.90	12.78	21.81	20.67	26.12	18.08
SER-L Latency (msec)	-0.36	-0.65	0.60	3.90	0.17	2.56	4.44	5.19
SER-L Power (μV^2)	49.70	49.07	45.32	43.16	51.27	49.67	62.68	51.76
CNAP Ratio	0.91	0.94	0.92	0.92	0.92	0.94	0.93	0.94
Temp-VER	37.46	37.33	37.53	36.72	37.37	37.79	37.73	37.03
Temp-CFF	37.52	37.33	37.80	37.00	37.83	38.04	38.24	37.39
Temp-ABRT	37.54	37.53	38.00	37.27	38.07	37.87	38.29	37.40
Temp-ABRC	37.82	37.85	37.87	37.73	38.20	38.04	38.27	37.61
Temp-C/S	38.18	38.03	38.07	37.87	38.23	38.21	38.27	37.77

ABR=auditory brainstem response; III /V – peaks 3 to 5. VER=Visual evoked response. CFF=cortical flicker fusion. CER=cerebellar evoked response, S – 4 – 25 msec; L – 25 - 70 msec. SER=somatosensory evoked response, S – 2.5 – 20 msec, L – 20 - 90 msec. CNAP = Caudal nerve action potential.

Pathology: At necropsy all rats from the 100 ppm (417 mg/m^3) and 300 ppm (1251 mg/m^3) groups had mottled incisor teeth. This mottling was presumed to be due to fluorosis. Pale foci were observed on the pleural surfaces of all 300 ppm (1251 mg/m^3) rats and one male and one female rat at 100 ppm (417 mg/m^3). These pleural foci probably resulted from chronic inflammation. Histopathologic changes were seen in the brains of 300 ppm (1251 mg/m^3) rats (see table below). Vacuoles were present in the white fibre tract of the caudate-putamen. No necrosis or neuronal destruction was noted. Rats allowed to recover from 300 ppm (1251 mg/m^3) exposure for 2 months had normal brain histology.

Summary of gross and histopathology findings in rats exposed to sulfuryl fluoride for 13 weeks

Pathology Obsservations			Males (dose ppm)				Females (dose ppm)			
			0	**30**	**100**	**300**	**0**	**30**	**100**	**300**
Number of Rats Examined			3	6	7	4	5	7	7	5
Lungs	Within normal limits		3	6	6	0	5	7	6	0
	Focus - pale, pleura	focal	0	0	0	0	0	0	1	0
		multifocal	0	0	1	4	0	0	0	5
Oral Tissues	Within normal limits		3	6	0	0	5	7	0	0
	Mottled, lower incisors:		0	0	7	4	0	0	7	5
	Mottled, upper incisors:		0	0	7	4	0	0	7	5
Brain	Within normal limits		3	6	6	0	5	7	6	0
	Vacuoles, caudate-putamen		0	0	0	4	0	0	0	5
13 weeks + 2-month recovery										
Brain	Within normal limits		2	--	--	2	2	--	--	2
	Vacuoles, caudate-putamen		0	--	--	0	0	--	--	0

Incidental Findings: Three male rats from the 100 ppm (417 mg/m^3) exposure group had poor click ABR's and poor ABR responses to both 4 kHz and 16 kHz tone pips. One rat was unresponsive to a sharp noise (observational battery) and did not register an ABR. The other two rats did respond to a sharp noise on the observational battery; however, one of these registered a poor ABR and the other had a flat ABR. Middle ear histopathology did not reveal a reason for the poor ABR's. A comparable problem did not occur in female rats at 100 ppm (417 mg /m3) or in either male or female rats at 300 ppm (1251 mg /m3). The anomalous click ABR's from these three rats were, therefore, not attributed to treatment, and were removed from data analysis. The VER of one 30 ppm (125.1 mg/m^3) female rat and one 300 ppm (1251 mg/m^3) female rat was topographically so dissimilar from controls that meaningful measures of latency and correlation could not be made. For this reason, VER data from these two rats were not included in the data analysis.

*Conclusions***:** Inhalation exposure of male and female Fischer 344 rats to sulfuryl fluoride at 300 ppm (1251 mg/m^3) for 6 hr/day, 5 day/week for 13 weeks caused diminished weight gain, dental fluorosis, a slight decrease in grooming, slowing of visual, auditory and somatosensory-evoked potentials, mild pulmonary inflammation, and mild vacuolation in the brain. Auditory brainstem responses (ABR's) and brain histopathology were evaluated two months post-exposure in 2 male and 2 female rats. Both the ABR's and brain histopathology appeared normal at this time, indicating that these treatment effects were essentially reversible. Exposure to 100 ppm (417 mg/m^3) resulted in slight dental fluorosis and minor slowing of some evoked responses. All other measurements, including brain histopathology, were normal. The NOEC was 30 ppm (125.1 mg/m^3) (approximately equivalent to 2.2 mg/kg bw/d systemic exposure), based on the alterations in evoked potentials.

3. Spencer, P.J., Bradley, G.J., and Quast, J.F. (1994). Sulfuryl fluoride: Chronic Neurotoxicity Study in Fischer 344 Rats-Final Report. Study No: Unspecified, Report No: DECO-HET K-016399-040B, Unpublished, Report date: 24 March 1994.

Test Compound:	Sulfuryl fluoride (purity: 93.6% to 99.7%)
Batch:	WP 880329-752, WP 901011- 907, WP 910321-918, WP 910826-929 and WP 920131-940
Test Species:	Rat (Fischer 344); age and source are not stated; 15/sex/exposure level
Study Duration:	Study started on 17 July 1990 & completed on 24 March 1994.
Laboratory:	The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA
GLP & QA:	GLP-Yes. QA-not stated
Guidelines:	US EPA Neurotoxicity Guideline, Fed. Reg., 50: 1985 39458-39463. Paragraphs 798.6050, 798.6200 and 798.6400 Deviations from EC test guidelines: There is no guideline in the EU for a chronic neurotoxicity study

Study: This study was conducted in concert with the 2-year rat inhalation study described earlier (Quast et al, 1993). Briefly, a satellite group of 15 rats/sex/exposure level were expected to target concentrations of 0, 5, 20 or 80 ppm (0, 20.85 mg/m^3, 83.4 mg/m^3 or 333.6 mg/m^3) sulfuryl fluoride for 6 hours/day, 5 days/week for approximately 12 months.

The FOB, hind limb grip performance and motor activity assay were conducted on 15 animals/sex/group, once during the pre-study period and then at months 3, 6, 9 and 12 during the exposure period. Forelimb grip performance and hind limb landing foot splay were evaluated at month 12. After completion of 12 months of exposure, neuropathology of central and peripheral nervous tissues were conducted on 5 rats/sex/dose group, following whole body perfusion of the animals for tissue fixation.

A complete gross examination was conducted on all animals. The necropsy consisted of an examination of the external tissues and orifices. The head was removed, the cranial cavity opened and the brain, pituitary and adjacent cervical tissues were examined. The nasal cavity was flushed with the same fixative. The skin was reflected from the carcass, the thoracic and abdominal cavities were exposed and the viscera were examined in situ. All visceral tissues were dissected from the carcass and re-examined. The brain, head, spinal column with spinal cord, fore- and hind-limbs, and tail were trimmed to remove excessive skin and muscle as necessary and immersed in fixative (phosphate-buffered solution of 1.5% glutaraldehyde - 4% formaldehyde). Muscles from the hind limbs were reflected to further expose the nerves. CNS tissues were stained with H&E. Peripheral nerves (sciatic, tibial and sural) were osmicated, embedded in plastic, cut at 2-3 microns and stained with toluidine blue for exanimation.

Findings:

FOB Results: Sulfuryl fluoride had no effect at any time on handheld and open field observations, grip performance or landing foot splay in either males or females. Mean body weights of female exposure groups were significantly different over time although no one exposure group appeared to be affected. Visual examination of the body weight data indicated that the statistical model detected a difference between the 5 ppm exposure group (mean body weights were higher compared to controls) and the 80 ppm (333.6 mg/m^3) exposure group (mean body weights were lower compared to controls). Thus, the statistically significant body weight

differences for female rats were attributed to chance, and were not treatment-related. There were no statistically significant differences between any treatment level and controls.

Motor Activity: Sulfuryl fluoride had no effect at any time on any aspect of motor activity.

Neuropathology: Results of the gross and histopathologic evaluations of perfusion fixed tissues for neuropathologic assessment of rats exposed to sulfuryl fluoride for up to 12 months were found to be unaffected by exposure.

Conclusions: The neurotoxicologic NOEC for this study was ≥ 80 ppm (333.6 mg/m^3) (about equivalent to 5.6 mg/kg bw/d systemic exposure), the highest concentration tested.

4.4.8 Genotoxicity Studies

Sulfuryl fluoride has been investigated *in vitro* for its ability to induce mutations in bacterial and mammalian cells, for clastogenicity and the induction of unscheduled DNA synthesis and *in vivo* in a micronucleus study (see table below). Highest concentrations used were justified based on the results of toxicity/cytotoxicity screening. All studies were to GLP, complied with the main principles of the OECD guidelines extant at the time of performance and included positive controls, which gave acceptable results. Positive results were seen in studies with mouse lymphoma cells and rat lymphocytes. These positive results are consistent with findings with fluoride ion, which are considered not to be associated with a direct action on DNA (see IPCS, 2002). Analytical work in the mouse lymphoma assay demonstrated almost complete hydrolysis of sulfuryl fluoride to fluoride ion and fluorosulphate.

Summary of *in vitro* and *in vivo* genotoxicity studies

Test	Test object	Concentration/Dose	Purity (%) [Batch / Lot]	Results	Reference
In vitro					
Reverse mutation	S.typhimurium TA98, 100, 1535, 1537	300, 1000, 3000, 10,000 & 30,000 ppm[1]	96.5% [874]	-ve + S9 -ve - S9	Gollapudi et al (1990a)
Reverse mutation	*E. coli* WP2uvrA	100, 300, 1000, 3000, 10,000, 30,000 & 50,000 ppm[1]	99.8% [OC16160101]	-ve + S9 -ve - S9	Mecchi (2002)
Chromosome aberrations	Rat lymphocytes	100, 500, 1000, 2500, 5,000, 10,000, 25,000 & 50,000 ppm[1]	99.8% [OC16160101]	+ve +S9 [2] +ve – S9[2]	Gollapudi et al (2000)
Unscheduled DNA synthesis	Sprague Dawley rat hepatocytes	204, 408, 612, 816, 1020 ppm[3]	96.5% [874]	-ve	Gollapudi et al (1991)
Gene mutation	Mouse lymphoma L5178Y **TK +/-**	100 – 7000 ppm[4]	99.8% [OC16160101]	+ve +S9 [5] +ve – S9[5]	Gollapudi et al (2002)
In vivo					
Bone marrow micronuclei	CD-1 mice (5/sex/group/time)	50, 175, 520 ppm for 4 h. (sacrifice at 24, 48 or 72h)	99.6% [WP880329]	-ve	Gollapudi et al (1990b)

[1]–Plates exposed by placing in bags containing sulfuryl fluoride atmospheres or an equivalent amount of compressed air for 4 hours.
[2]–NOEL 2500 ppm. Findings show some consistency with those associated with the generation fluoride ion in the culture medium
[3]–Exposure by replacing some of the headspace in the 'Leighton tube' culture vessel with sulfuryl fluoride; for 18 – 19 hours.
[4]-Exposure by flushing the headspace in the culture vessel with sulfuryl fluoride; for 4 hours.
[5]-NOEL 1000 ppm. Findings show some consistency with those associated with the generation fluoride ion in the culture medium

4.4.9 OTHER STUDIES

1. Albee, R.R., Eisenbrandt, D.L., Mattsson, J.L. & Streeter, C.M. (1983). Sulfuryl Fluoride (Vikane) Induced Incapacitation in Rats. Study No: Unspecified, Report No: K-016399-018, Unpublished, Report date: 30 September 1983.

Test Compound:	Sulfuryl fluoride (purity: 99.8%)
Batch:	217
Test Species:	Rat (Fischer 344); age and source are not stated
Study Duration:	Study started on 6 July 1983 & completed on 30 September 1983.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA
GLP & QA:	GLP-Yes. QA-not stated
Guidelines:	This is not a guideline study

Study: In order to estimate the rapidity with which sulfuryl fluoride might incapacitate an individual, groups of five rats were exposed to 4,000, 10,000, 20,000 or 40,000 ppm (16680 mg/m^3, 41700 mg/m^3, 83400 mg/m^3 or 166800 mg/m^3) Vikane in a 14 litre cylindrical chamber that contained a motor-driven activity wheel. The following parameters were evaluated: the time to incapacitation, gross examination at necropsy and histological examination of selected tissues. The rats were pre-trained to walk in a self-propelled activity wheel. Chamber concentrations were primarily nominal, with only back-up by analysis with an IR. Nominal concentrations were found to be more reliable for this particular apparatus. When an animal was unable to walk, the exposure was terminated and the timer stopped.

Findings:

There was a clear dose-related decrease in the time the animals maintained the ability to walk as the concentration of sulfuryl fluoride increased (see table below). Although the 20,000 ppm (83400 mg/m^3) group remained functional longer, they were very similar to the 40,000 ppm (166800 mg/m^3) group. Both groups were unable to walk within 12 minutes and died less than 10 minutes later. The 10,000 ppm (41700 mg/m^3) group was slightly different in that they remained functional longer and lived for approximately 60 minutes after the exposure was discontinued. The rats exposed to 4,000 ppm (16680 mg/m^3) were able to walk considerably longer than one might expect, based on the results of the higher concentrations, and lived for approximately 2.5 hours after the exposure was stopped.

The rats exposed to the three highest concentrations exhibited a marked behavioural change shortly after the test atmosphere reached target concentration. Although the animals clearly went through a behavioural change shortly after the chamber reached maximum concentration, it was considered that this change was not incapacitation, only a strategy change. All rats, except those exposed to 4,000 ppm (16680 mg/m^3), appeared to be slightly cyanotic shortly after exposure started. The bluish skin discolouration disappeared within 10 minutes after the purging of the chamber with room air (in rats exposed to 10,000 ppm-41700 mg/m^3).

There was mild diarrhoea in all rats exposed to 4,000 (16680 mg/m^3), 10,000 (41700 mg/m^3) or 20,000 ppm (83400 mg/m^3). Tonic convulsions resulted in termination of the exposure in 3/20 rats, whereas the remainder of the animals were incapacitated prior to any convulsive activity. All rats, except two, exhibited tonic convulsions at which time respiration ceased and did not return for 15-30 seconds following the convulsion. Several rats died immediately after the tonic convulsion. Rats exposed to the three highest dose levels had increased salivation and

lacrimation (red stained). When the exposed rats approached death, their respiratory pattern changed from shallow and rapid to slow and deep; also, some gasping was noted.

Time (min) to incapacitation and death in rats exposed to sulfuryl fluoride

Concentration (ppm)	No. of rats	Incapacity and cessation of exposure (min)
4000 (16680 mg/m^3)	5	41.5
10,000 (41700 mg/m^3)	5	16.3
20,000 (83400 mg/m^3)	5	10.3
40,000 (166800 mg/m^3)	5	6.4

Pathology: Gross observations included vascular congestion of several tissues and most likely reflected systemic cardiovascular failure. Pulmonary congestion increased in severity as the concentration of the test chemical was increased in the atmosphere. Generally, there was a concentration-dependent increase in the distribution and severity of alveolar and interstitial oedema and haemorrhage. The injury to the lungs probably contributes significantly to the death of the animals at the 20,000 (83400 mg/m^3) and 40,000 ppm (166800 mg/m^3) exposure concentrations, however, the pulmonary injury in the rats exposed to 4,000 ppm (16680 mg/m^3) or 10,000 ppm (41700 mg/m^3) did not appear to be a major factor in the death of the animals. Possible causes include haemodynamic changes and/or capillary endothelial injury. Direct damage to the alveolar wall is another possibility. The pulmonary lesions were not specific for the test material. Such lesions may occur with shock or be due to diffuse alveolar damage from a variety of compounds.

Conclusions: All rats were moribund or died spontaneously within three hours following the termination of the exposure, and all rats had tonic convulsions prior to death. Necropsy revealed signs compatible with cardiovascular failure and acute death. Generally, there was a concentration-dependent increase in pulmonary congestion, oedema and haemorrhage. The pathogenesis of the lesions and the cause of death of animals exposed to high concentrations of sulfuryl fluoride remain to be defined.

2. Gorzinski, S.J. & Streeter, C.M. (1985). Effect of Acute Vikane Exposure on Selected Physiological Parameters in Rats. Study No: Unspecified, Report No: HET K-016399-021, Unpublished, Report date: 6 November 1985.

Test Compound:	Vikane (not otherwise stated)
Batch:	Not stated
Test Species:	Rat (Fischer 344); age and source are not stated
Study Duration:	Study started on 10 August 1983 & completed on 6 November 1985.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA
GLP & QA:	GLP-Yes. QA-not stated
Guidelines:	This is not a guideline study

Study: Experiments were conducted on 3 male rats exposed to 4000 (16680 mg/m^3) or 20000 ppm (83400 mg/m^3) Vikane and one female rat exposed at 20,000 ppm (83400 mg/m^3) to investigate EEG, ECG, blood pressure, heart rate, body temperature (with and without water

jacket) and respiration rate. Due to the short survival at 20,000 ppm (83400 mg/m^3), some measurements could not be performed. Two female rats were exposed at 4,000 ppm (16680 mg/m^3) for determination of body temperature.

Findings:

Five rats exposed to 4,000 ppm (16680 mg/m^3) of Vikane survived for 79 ± 10 minutes with a range of 65 to 90 minutes. The mean ± S.D. survival time for the 20,000 ppm (83400 mg/m^3) concentration group (N = 4) was 14 ± 4 minutes with a range of 9 to 19 minutes. The manner of death was gradual without any predictable abrupt bodily contortions characteristic of convulsive seizures. Grossly, the ears and extremities became pale, suggesting vasoconstriction in an attempt to maintain body core temperature

The response to sulfuryl fluoride was similar between exposure levels and included a decrease in heart rate, a gradual increase in blood pressure (culminating in a rapid increase in systolic and pulse pressure just prior to death), decreased respiration, occasional spiking and high frequency loss in the EEG, and power loss in the EEG. Grossly, the rats exhibited paleness of the extremities and felt cold when removed from the exposure restraint.

All physiological parameters ceased to function at about the same time the animals expired regardless of the dose level. No parameter was affected first and subsequently precipitated the death of the animal. Artificial maintenance of body temperature did not increase survival time; therefore, the loss of body temperature did not contribute significantly to the cause of death. The authors suggested that death might be associated in some manner with the blocking of the endogeneous energy-producing process of oxidative phosphorylation in glycolysis.

3. Eisenbrandt, D.L., Williams, D.M., Albee, R.R. & Streeter, C.M. (1987). Sulfuryl fluoride (Vikane Gas Fumigant): An ultrastructural Assessment of the Lungs of Rats Exposed to High Concentrations of Sulfuryl Fluoride. Study No: Unspecified, Report No: HET K-016399-023, Unpublished, Report date: 6 October 1987.

Test Compound:	Vikane gas fumigant (purity: 98.8%)
Batch:	WP 030680 217
Test Species:	Rat (Fischer 344); age and source are not stated
Study Duration:	Study started on 23 January 1984 & completed on 6 October 1987.
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA
GLP & QA:	GLP-Yes. QA-not stated
Guidelines:	This is not a guideline study

Study: Two male rats were exposed to 4,000 (16680 mg/m^3) or 20,000 ppm (83400 mg/m^3) sulfuryl fluoride while walking on a motorised activity wheel. Three control rats also were included in the study. Selection of these exposure levels was based on previous study, which revealed extensive histological changes in the lungs of rats exposed to 20,000-40,000 ppm (83400-166800 mg/m^3) sulfuryl fluoride and minimal pulmonary changes in rats exposed to 4, 000 ppm (16680 mg/m^3). Treated rats were exposed until incapacitated. The rats were submitted for necropsy soon after exposure and the lungs were fixed by vascular perfusion. Representative sections of lung were evaluated by light and electron microscopy.

The whole-body exposure was conducted in a chamber that contained a motorised, shaft-driven activity wheel. Sulfuryl fluoride was pumped into the chamber under dynamic airflow conditions.

Findings:

Clinical Observations: Rats exposed to 4,000 ppm (16680 mg/m^3) sulfuryl fluoride were incapacitated after 42-43 minutes of exposure; one rat subsequently became moribund 83 minutes after initiation of the exposure. Rats exposed to 20,000 ppm (83400 mg/m^3) sulfuryl fluoride were incapacitated after 12-13 minutes; one of these animals was moribund at that time (13 minutes) while the other rat was moribund 31 minutes after initiation of the exposure.

Light Microscopy: Histopathologic examination of lung tissue revealed minimal changes in rats exposed to 4,000 ppm (16680 mg/m^3) sulfuryl fluoride. These rats had congestion of pulmonary vessels and alveolar/interstitial oedema with or without haemorrhage. Rats exposed to 20,000 ppm (83400 mg/m^3) had more extensive congestion, oedema and haemorrhage.

Electron Microscopy: The ultrastructure of pulmonary tissue from control rats was normal. Lungs of rats exposed to 4,000 ppm (16680 mg/m^3) had multifocal alterations in the alveoli. Segmental swelling and occasional focal protrusions (blebs) from the basement membrane were observed in Type I (squamous) epithelial cells of some alveoli. Minimal focal disruptions of Type I epithelial cells were present in a few alveoli. Some alveoli contained proteinaceous fluid (oedma) and a few red blood cells, while only occasional stands of fibrin were present in the alveoli.

The lungs of rats exposed to 20,000 ppm (83400 mg/m^3) sulfuryl fluoride had more extensive ultrastructural changes. The most severe lesions consisted of multifocal destruction of the alveolar wall characterised by disruption of epithelial (Type I) and endothelial cells and the subjacent basement membrane. Less severe lesions consisted of disruption of epithelium with preservation of endothelium and basement membrane as well as a single focus of endothelial cell disruption adjacent to an intact basement and epithelium. Destruction of the alveolar wall was associated with platelet aggregation and fibrin thrombi in adjacent capillaries. A few capillaries also contained platelet aggregates where there was no destruction of the alveolar wall.

Many alveoli in the lungs of rats exposed to 20,000 ppm (83400 mg/m^3) sulfuryl fluoride contained proteinaceous fluid (oedma) while some alveoli also had strands of fibrin and RBCs. These changes were often associated with destruction of the alveolar wall, however, some alveoli with an intact wall also contained fluid, RBCss and fibrin. Alveolar interstitial tissues contained RBCs and minimal fluid or fibrin. Perivascular and peribronchial interstitial tissues has more extensive accumulation of proteinaceous fluid and a few RBCs. Proteinaceous fluid was also present in the lumen of bronchiole.

Rats exposed to 20,000 ppm (83400 mg/m^3) sulfuryl fluoride also had changes in the wall of some alveoli that were similar to those rats exposed to 4,000 ppm (16680 mg/m^3). These effects consisted of segmental swelling of Type 1 epithelial cells with occasional focal protrusions (blebs) and separation from the basement membrane. Focal disruptions of the epithelial cells also were present in some alveoli. Cellular swelling and blebs in endothelial cells were less common. Some Type II epithelial cells also were swollen.

Conclusions: Morphological changes in the lungs of rats exposed to 4000 ppm (16680 mg/m^3) sulfuryl fluoride were minimal and probably were not a significant factor in the death of the animals. On the other hand, extensive injury to the lungs of rats exposed to 20,000 ppm (83400 mg/m^3) sulfuryl fluoride probably comprised pulmonary function and contributed to the death of the animals. Factors other than pulmonary injury probably were involved in the death of animals at both concentrations.

4. Nitschke, K.D. and Miller, R.R. (1985). Sulfuryl fluoride (Vikane Gas Fumigant): Effects of Treatment with Calcium Gluconate or Anticonvulsants on Rats. Study No: Unspecified, Report No: HET K-016399-024, Unpublished, Report date: 1 April 1985.

Test Compound:	Vikane gas fumigant (purity: 98.8%)
Batch:	WP 030680 217
Test Species:	Rat (Fischer 344); age and source are not stated
Study Duration:	Study started on 2 January 1984. Completion date not stated
Laboratory:	Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, USA.
GLP & QA:	GLP-Yes. QA-not stated
Guidelines:	This is not a guideline study

Study: The present study investigated the protective and therapeutic effectiveness of calcium gluconate (CaG), an antagonist to fluoride ion toxicity, and three anticonvulsants (phenobarbital, diazepam or diphenylhydantoin) in animals exposed to lethal concentration of sulfuryl fluoride.

Groups of rats were: 1) exposed to sulfuryl fluoride, 2) pretreated with CaG and exposed to sulfuryl fluoride, or 3) exposed to sulfuryl fluoride and post-treated with CaG. Groups of 25 rats were exposed to 0, 4000 ppm (16680 mg/m^3) or 10,000 ppm (41700 mg/m^3) sulfuryl fluoride for 55, 45 or 16 min, respectively. The exposure interval for rats exposed to 4,000 (16680 mg/m^3) or 10,000 ppm (41700 mg/m^3) was sufficient to cause incapacitation or convulsions of at least some animals.

Findings:

The time to incapacitation for inactive rats exposed to 4000 ppm (16680 mg/m^3) and 10,000 ppm (41700 mg/m^3) sulfuryl fluoride was 45 and 16 min, respectively. Rats exposed to 4000 ppm (16680 mg/m^3) or 10,000 ppm (41700 mg/m^3) sulfuryl fluoride did not survive and died within 3 and 1 hr, respectively. Typically, these rats had convulsions of approximately 10 sec duration prior to death.

Pre-treatment: Six out of ten rats pre-treated with CaG followed by exposure to 4000 ppm (16680 mg/m^3) sulfuryl fluoride survived for at least 3 days. Post-treatment resulted in a slightly lower survival, 4 out of 10, over the same time period. While survival was increased in rats receiving CaG before or after exposure to 4000 ppm (16680 mg/m^3) sulfuryl fluoride, the surviving animals were extremely debilitated and there was no apparent protection from convulsions. Animals pre-treated with CaG did not survive exposure to 10,000 ppm (41700 mg/m^3) sulfuryl fluoride.

Rats pre-treated with phenobarbital were alert and active for much of the 2 hr post-exposure observation period. Convulsions were not observed during this period in any of the phenobarbital pre-treated rats. Two rats pre-treated with diphenylhydantoin exhibited

convulsions of longer duration (~30 sec) and severity during the 2-hr post-exposure period than rats exposed to sulfuryl fluoride alone. Thus, there were no further studies with diphenylhydantoin. Rats pre-treated with diazepam exhibited convulsions of longer duration (~30 sec) and severity during the 2-hr post-exposure period than rats exposed to sulfuryl fluoride alone.

Post-treatment: Increased survival of rats pre-treated with phenobarbital and diazepam prompted further studies of post-exposure treatment with these anticonvulsants. Rats were exposed to 4000 ppm (16680 mg/m^3) sulfuryl fluoride until incapacitated (~37 min) and subsequently treated with phenobarbital and diazepam. With the post-treatment of phenobarbital, several (3/5) animals exhibited mild seizures of 1 sec duration during the 2-hr post-exposure observation period; two of five had no convulsions. One rat exposed to 4000 ppm (16680 mg/m^3) sulfuryl fluoride had a convulsion of 10 sec duration while exposed but only minor body tremors after treatment with phenobarbital. Two of these rats developed very mild convulsions of less than 1 sec duration several days after exposure to sulfuryl fluoride: a low dose of phenobarbital (20 mg/kg bw/d) was given to these animals and no further convulsions were observed during the observation period. Thus, phenobarbital has utility even after convulsions have occurred.

Exposure of rats to sulfuryl fluoride followed by treatment with diazepam resulted in convulsions typical of these seen in rats exposed to sulfuryl fluoride alone. Consequently, diazepam appears to be of limited utility in comparison to phenobarbital.

An additional group of rats was exposed to 10,000 ppm (41700 mg/m^3) sulfuryl fluoride until incapacitation and then treated with phenobarbital. Although phenobarbital did not prevent the death of animals exposed to 10,000 ppm (41700 mg/m^3) sulfuryl fluoride, the phenobarbital-treated animals did not survive longer than animals exposed similarly to sulfuryl fluoride alone.

Results of Pre- and Post-Exposure Treatment with anticonvulsants on rats exposed to sulfuryl fluoride.

Group	No.	Pre-Treatment	Sulfuryl fluoride (ppm)	Post-Treatment	Number Surviving
1	10	None	4000	none	0/10
2	10	Calcium gluconate (500 mg/kg bw, i.p.)	4000	none	6/10
3	10	None	4000	Calcium gluconate (500 mg/kg bw, i.p.)	4/10
4	5	None	10000	none	0/5
5	5	Calcium gluconate (500 mg/kg bw, i.p.)	10000	none	0/5
6	5	None	10000	Calcium gluconate (500 mg/kg bw, i.p.)	0/5
7	5	None	4000	None	0/5
8	5	Phenobarbital (35 mg/kg bw, i./p.)	4000	None	5/5
9	5	Diphenylhydantoin (80 mg/kg bw, i.p.)	4000	None	0/5
10	5	Diazepam (5 mg/kg bw, i.p.)	4000	Diazepam (2.5 mg/kg, i.p.)	4/5
11	5	None	4000	Phenobarbital (35 mg/kg, i.p. and 20 mg/kg, i.v.)	5/5
12	5	None	4000	Diazepam (5 mg/kg, i.p.)	2/5
13	5	None	10,000	Phenobarbital (35 mg/kg, i.p. and 20 mg/kg, i.v.)	0/5

Conclusions: Calcium gluconate (the recommended antidote for fluoride toxicity) and phenobarbital (given before or after exposure to sulfuryl fluoride) appeared to ameliorate the acute toxic effects (seizures) and lethality in rats exposed to sulfuryl fluoride at 4,000 ppm (16680 mg/m^3) but not at 10,000 ppm (41700 mg/m^3). Treatment with diazepam followed by exposure to sulfuryl fluoride was relatively effective. However, treatment with diazepam after exposure to sulfuryl fluoride was not effective. Diphenylhydantoin is contra-indicated, inducing more severe seizures than seen in sulfuryl fluoride only animals.

Human Reports

Medical surveillance on manufacturing plant personnel

Sulfuryl fluoride has been registered by Dow (Dow AgroScieces) for use as a structural fumigant in the USA since 1959, and marketed for that use since 1961. Prior to 1975, Allied Chemical produced sulfuryl fluoride which was packaged and sold by Dow under the name 'Vikane'. Dow began producing Vikane at its Pittsburg, California plant in 1975; this plant is the only large-scale production facility for sulfuryl fluoride in the world today. This plant has 21 employees who participated in health surveillance exams every 2 years. No significant sulfuryl fluoride-related health problems have been detected in these examinations. Review of safety records and on-site medical clinic records for 1992-2001 disclosed 10 inhalation exposures and 7 skin burns, primarily related to exposure to hydrogen fluoride used in the process.

No epidemiology studies focused on health effects of sulfuryl fluoride have been done on this group of employees.

Clinical cases and poisoning incidents

Sulfuryl fluoride is used as a structural fumigant, primarily for the control of dry wood termites in the warmer climates of the United States. It's most common application is in building fumigations, where the building is first wrapped in plastic tarpaulins, and the gas is then released into the sealed structure. Chloropicrin is used as a stenching agent (lacrimator) when sulfuryl fluoride is used in dwelling fumigations (i.e. in homes). Sulfuryl fluoride also has a label use in the U.S.A., for fumigation of vehicles such as rail cars, buses and ships.

In the USA since 1993, there have been 335 reports (included incidents from prior years that were cited in subsequent litigation) of alleged human health effects associated with sulfuryl fluoride reported to the US EPA by Dow AgroSciences. These allegations were received from PROSAR, a human health poison control centre, employees of Dow AgroSciences, customers, and other sources. There were 13 human deaths, primarily resulting from unauthorised entry into the tented fumigated structure as apparent break-ins or one case in attempt to rescue a cat. The majority (60%) of the non-fatal incidents involved symptoms of eye and respiratory irritation, sore throat and cough; in some of these cases the symptoms may have been related to residual chloropicrin in the dwellings subsequent to ventilation and clearing of sulfuryl fluoride from the structure. The next most common (9%) complaint was flu-like symptoms of nausea, diarrhoea, fever, and headache. Approximately 6% complained primarily of shortness of breath or respiratory distress. From the PROSAR records of August 1997-May 2001, 2.2% of cases required treatment in a health care facility or emergency room; for June 2001-June 2002, 3.1% of cases required such treatment. 87% of cases in PROSAR records since 1997 to the present were either asymptomatic or had only minor symptoms.

Epidemiology Studies

Two epidemiology studies of fumigators who use sulfuryl fluoride have been published:

1. **Anger, W.K., Moody, L., Burg, J., Brightwell, W.S., Taylor, B.J., Russo, J.M., Dickerson, N., Setzer, J.V., Johnson, B.L., and Hicks, K. (1986). Neurobehavioral evaluation of soil and structural fumigators using methyl bromide and sulfuryl fluoride. *Neuotoxicol.* 7:137-156**

Three groups of fumigators exposed to methyl bromide (N=32), sulfuryl fluoride (N=24) or to a combination of both (N=18) were compared to a reference group (N=29) composed of workers associated with the fumigation process, but not exposed to fumigants. The investigations included a clinical neurological examination, nerve conduction measurements, neurobehavioral tests and a general medical questionnaire. A number of differences between the sulfuryl fluoride and referent groups were identified as potential confounding factors (age, level of education, alcohol consumption, illegal drug use and racial mix). These factors are noted by the study authors and investigated to an extent but it was not possible to perform statistical corrections due to the small group sizes. The sulfuryl fluoride group had more general symptoms than the referent group, but less than the methyl bromide group, but it is unclear whether the symptoms are linked with the process of fumigation, exposure to the chemicals involved or factors unrelated to fumigation. There were no significant differences between the sulfuryl fluoride fumigators and referents in: nerve conduction velocity; grip strength; co-ordination tests; neurological, visual and cognitive examinations. Some significant effects were identified in the methyl bromide group and in some tests the sulfuryl fluoride group results fell between the referents and methyl bromide fumigators. The study authors concluded that there was a pattern of effects in the sulfuryl fluoride group that merited further investigation.

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

A cross sectional study of 123 fumigation workers using methyl bromide or sulfuryl fluoride in Florida was performed in 1991–1992. The fumigation workers were compared with a group of friends or neighbours who had never been employed as pesticide applicators. The fumigators using sulfuryl fluoride for >80% of the fumigations made up the sulfuryl fluoride group (n= 91; duration of use 0.1 – 20 years, median 2.8 years). Because of the limited use of methyl bromide, the criterion for this group was set at 50% use of methyl bromide and it is likely that many of the methyl bromide group (n= 28) would also use sulfuryl fluoride. The study investigated general medical condition / history; nerve conduction velocity; vibration sensitivity; co-ordination; balance; reactions; memory; learning; visual function; balance; smell; dexterity and gross neurological abnormalities. The numerical data presented in the paper were only for fumigators *versus* controls and did not differentiate between sulfuryl fluoride and methyl bromide groups. Some statistical comparisons were performed with duration of individual fumigant use. The fumigators and controls were relatively well matched and corrections were performed for a number of parameters. Significant effects were noted with sulfuryl fluoride use on: forearm nerve conduction tests, dexterity, pattern memory and odour recognition. The forearm and dexterity results were considered to be related to physical activity involved with part of the fumigation process. It was also considered unlikely that an effect on one nerve would be related

to chemical exposures–the sulfuryl fluoride fumigators performed better in 8 / 13 nerve conduction and vibration tests. Pattern memory (p=0.05) was the only computer administered neurobehavioral test where fumigators were significantly worse than controls so it is unclear whether this is a real or chance finding. The odour recognition finding (p=0.03) was considered to be of uncertain aetiology–irritation, olfactory receptor damage or odour cognition. In both the odour recognition and pattern memory tests the methyl bromide group (which probably contained several workers using sulfuryl fluoride) performed better than controls.

5 PRODUCT USE PATTERN

Use Situations
Profume Gas Fumigant is indicated for use in different situations:

(1) For the control of insects and related pest and rodents in dwellings (including mobile homes), buildings (commercial and residential), construction materials, furnishings (household effects), shipping containers, including those containing pallets, machinery and non-food items, and vehicles, including cars, buses, surface ships, rail cars and recreational vehicles but excluding aircraft;
(2) For the control of post-harvest insect and rodent pests in non-residential structures such as food processing plants, mills, warehouses, stationary transportation vehicles (railcars, truck etc, excluding aircraft and passenger railcars), temporary and permanent fumigation chambers, and storage structures.

Preparation for fumigation

- All persons, domestic animals, pets, and desirable growing plants are removed from the structure to be fumigated. Also, remove mattresses (except water beds) and pillows completely enveloped in waterproof covers or remove covers. Food, feed, drugs (including tobacco products) and medicinal products (including those items in refrigerators and freezers) can remain in the structure if they are in plastic, glass or metal bottles , cans, or jars with the original manufacturer's air tight seal intact. If these items are not in air-tight seal, they should be removed from the fumigation sight or can be double bagged in Nylofume bags.
- Extinguish all flames, including pilot lights or water heaters, gas refrigerators, rangers, ovens, broilers, etc. Turn off or unplug all electrical heating elements, such as those in heaters, pianos, organs, etc. Shut off automatic switch controls for appliances and lighting systems, which will be included in the space to be fumigated.
- Open operable internal doors, internal openings to attics and sub-areas, storage chests, cabinets, draws, closets, and appliances (such as washers, dishwashers, dryers, microwave or conventional ovens etc. Using electric fan(s) will help provide for forced distribution and aeration of basement and other dead air spaces to facilitate rapid dispersion of gas. Refrigerators and freezer doors may be left open if the units are turned off or disconnected and all food items have been removed. However, if the applicator chooses to leave sealed food items in closed refrigerators and freezers during the fumigation, the appliances should be opened when clearing the structure until the concentration until the concentration of the gas in them is 3 ppm or less.
- *Securing Structure Entrances*
  A locking device or barricade on all exterior doors or doorways is recommended to secure the structure against unauthorised entry during the fumigation exposure period and 'Step (2)' of "Aeration Procedure 1 or 2'. A locking device or barricade must be demonstrated effective in preventing an exterior door or doorway from being opened

using normal opening or entering processes by anyone other than the certified applicator in charge of the fumigation or persons in his/her onsite direct supervision.

Operation Details

Pre-fumigation check: Check for any potential leaks.

Rate of Use: For all fumigations, the maximum recommended use rate is 1500 gh/m³ CTP with a target maximum concentration of 128 g/m³ (approximately 30700 ppm) The draft labels advised that this rate must not be exceeded. The required amount of Profume Gas Fumigant needed for specific situation is calculated by the use of Profume Fumiguide, a PC-based computer program.

Introducing the stenching agent (chloropicrin): Chloropicrin is a stenching agent introduced into the structure during fumigation. In order to avoid direct exposure to the fumigant being released, chloropicrin must be released into the structure at least 5 to 10 minutes before fumigation. Chloropicrin causes smarting of the eyes, tears and discomfort and has a very disagreeable pungent odour at very low concentration. Chloropicrin must be used by a person certified to apply Profume Gas Fumigant or under their supervision.

Introducing the Fumigant: The draft label states that the release point for the Profume Gas Fumigant should be into a large open space(s) in the fumigation site(s). The fumigant is released through a suitable leak-proof tube with a minimum burst of pressure of 3450 KPa (500 psi). The fumigant is directed into the last of air from a fan(s) that have a capacity of at least 470 L/sec (1,000 cubic feet per minute) for each 450 g of Profume Gas Fumigant released per minute. Damage to the household materials can occur of insufficient fan capacity is used for the rate of Profume Gas Fumigant released. It is recommended that protective sheeting, such as polyethylene plastic under the shooting stand, shooting hose and shooting fan can be used to further protect floors during application. To prevent damage, fumigant should not be applied directly to any surface.

Posting (signage) of Fumigated Areas: The draft label states that the applicant must post all entrances to the fumigated areas with signs showing:

(1). The SKULL and CROSSBONES symbol.
(2). The statement, “Area under fumigation, DO NOT ENTER”.
(3). The date of fumigation.
(4) Name of fumigant used.
(5) Name, address and telephone number of the applicator.

It is also stated on the draft label that only a certified operator may authorise the removal of placards, and only when the concentration of Profume Gas Fumigant in the treated area is less than 3 ppm or less.

Leak Procedures: The area around the leak is immediately evacuated. For entry into affected areas to correct problem, the draft label recommends the use of an approved positive pressure self-contained breathing apparatus (SCBA) or combination air-supplied/SCBS respirator.

Aeration: The draft label recommends that:

- During the initial one hour aeration procedure, approved respiratory protection must be worn until the concentration of Profume Gas Fumigant is confirmed not to exceed 3 ppm with an approved detection device.

Aeration Procedure 1
(For all structures fumigated at concentration of 16 g/m^3 or less may be aerated using this procedure)

These steps must be completed in sequence:
Step (1): Aerate structure with all operable windows and doors open, aided by the use of one or more fans, for a minimum period of 1 hour. Total fan capacity, using one or more fans, shall be capable of displacing a total of 2300 L/sec (5, 000 cfm)
Step (2): Secure structure and do not allow re-entry for a minimum of 6 hours from the start of aeration (first opening of the seal). During this time, the structures must remain posted.
Step (3): After the minimum 6 hours waiting period, measure the concentration of Profume Gas Fumigant in breathing zones of each room. If the concentration of Profume Gas Fumigant is greater than 3 ppm, ventilate structure with operable doors and windows for at least 10 minutes. Structures may be re-occupied when concentration is 3 ppm or less.

Aeration Procedure 2
(For all structures fumigated at concentration greater than 16 g/m^3 may be aerated using this procedure)

These steps must be completed in sequence:
Step (1): Aerate structure with all operable windows and doors open, aided by the use of one or more fans, for a minimum period of 1 hour. Total fan capacity, using ore or more fans, shall be capable of displacing a total of 2300 L/sec (5, 000 cfm)
Step (2): Secure structure and do not allow re-entry for a minimum of 8 hours from the start of aeration (first opening of the seal). During this time, the structures must remain posted.
Step (3): After the minimum 8 hours waiting period, measure the concentration of Profume Gas Fumigant in breathing zones of each room. If the concentration of Profume Gas Fumigant is greater than 3 ppm, ventilate structure with operable doors and windows for at least 10 minutes. Structures may be re-occupied when concentration is 3 ppm or less.

Re-entry Period
The draft label states that no one shall be in the fumigated areas if the level of Profume Gas Fumigant is above 3 ppm unless wearing an approved positive pressure self-contained breathing apparatus (SCBA) or combination air-supplied/SCBS respirator. The concentration of Profume Gas Fumigant must be monitored throughout the structure in the breathing zone. The structure or enclosure must be remain posted for fumigation until cleared for re-entry.

Withholding period
The draft label has not stated any withholding period.

Restraints
The following restraints are stated on the draft label:

- Do not apply when temperature within the commodity to be fumigated is below 5^{o}C.
- Do not exceed a use rate of 1500 gh/m^3 CTP with a target maximum concentration of 128 g/m^3.

Precautions
The following precautions are stated on the draft label:

- Do not use this product without the Fumiguide Program for Profume Gas Fumigant. The Profume Fumiguide is a computer program available to calculate safe and effective levels of Profume Gas Fumigant for fumigating structures and commodities.
- Never allow untrained individuals to use Profume Gas Fumigant.
- Notify appropriate owners, employees, and/or operators at the facility by providing the Fact Sheet for Profume Gas Fumigant and advising the location of fumigation. Also, provide relevant safety and health information to local fire and rescue officials for use in the event of an emergency.
- Do not connect cylinders to introduction equipment until all fumigation warning signs have been posted and the space to be fumigated is clear of people, non-target animals and secured.

General Information
The draft label states that high pressure fumigant can be forceful and there is potential for personal injury. Care must be exercised when fumigating, especially tarped commodities, so that the fumigant is not released too rapidly and "balloons" the tarp off the restraining sand or water snakes. A fog-out can also occur if the fumigant is released too rapidly, cooling the air temperature below the dew point. The rapid discharge of Profume Gas Fumigant through introduction equipment will result in cooling parts of the equipment the cylinders. Contact with the cooled equipment can cause frostbite.

When used for fumigation of enclosed spaces, such as houses and other structures, warehouse, vaults, chambers, trucks, vans, boxcars, ships and other transport vehicles, two persons trained in the use of this product, at least one being an applicator that is licensed/certified by the state, must be present during introduction of the fumigant, re-entry prior to aeration, and during the initiation of the initial aeration procedure. Two persons may not be present if monitoring is conducted remotely (outside the area being fumigated).

Training Requirements
The draft label states that the supply of this product is restricted by SUSDP Appendix J to persons authorized under relevant State Legislation. The draft label also states that the product will only be used by fumigators accredited under Dow AgroSciences PRECISION FUMIGATION Training Program.

Gas Detection Devices
The draft label states that only an approved detection device of sufficient sensitivity (LOD ≤ 1 ppm), such as the INTERSCAN gas analyse (Model GF 1900) or MIRAN vapour analyser (SapphIRe) should be used to confirm a concentration of Profume Gas Fumigant of 3 ppm or less. The INTERSCAN gas analyser GF 1900 must be calibrated within one month prior to use as detection device. All other approved detection devices must be calibrated according yo manufacturer recommendations.

Transportation of Cylinders
The draft label advises to transport the cylinders using hand truck or fork truck to witch the cylinder can be firmly secured. It is advised not to transport the cylinders in closed vehicles, where the same common airspace is occupied by personnel. On public roads, cylinders should only be transported when secured in an upright position.

Fumigation of Multi-unit Structures
When fumigating a single unit/room within or connected to a larger structure (such as town houses, villas or apartments), all units of the entire structure must be prepared as a fumigated structure, and all applicable rules, regulations and label instructions apply, such as occupant notification, structure preparation, posting, securing, and aeration. It is to be ensured that all the exterior entrance ways and exterior doors of individual units are secured with secondary locks so that only the licensed applicator in charge can gain access. During aeration, check all units within the fumigated structure for Profume Gas Fumigant concentration with an approved clearance device. If the concentration of any non-fumigated units exceeds 3 ppm, use Aeration procedure 1 or 2 to aerate the non-fumigated units, based on the initial concentration of the fumigant.

Fumigation of Connected Structures
A connected structure is defined as any structure connected with the structure to be fumigated by construction elements (e.g., pipes, conducts, ducts etc), which may allow passage of fumigant between the structures. Any connected structure must be vacated during the fumigation process unless it is isolated from the structure to be fumigated by methods, which prevent passage of the fumigant from the structure to be fumigated into the connected structure. When it is necessary to vacate any connected structure, that structure shall be considered as a fumigant structure, and all applicable rules, regulations and label instructions apply, such as occupant notification, structure preparation, posting, securing, and aeration. Profume Gas Fumigant concentration must be measured in any connected space and structure, as detailed in Aeration and Re-entry sections.

Tarpaulin Fumigations
Open all operable windows and use a highly resistant material such as a vinyl coated nylon, or polyethylene sheeting of at least 100 micron thickness when performing tarpaulin fumigation. Seal all seams and all low edges of the cover (such as with soil, sand, or weighted “snakes”). To minimise escape of gas through the soil and to avoid injury to nearby plants, wet soil outward from foundation to the cover if not sufficiently moist to act as a barrier for the gas.

Taped Fumigation
For fumigation that can be sealed with plastic, paper, or tape, seal adequately around doors, windows, vents, and other openings.

Chamber Fumigation
For chamber fumigation, use a gas-tight chamber with adequate circulation.

Fumigation of construction materials, furnishings (household effects) and vehicles
Follow preparations as appropriate as in for tarpaulin, taped and chamber fumigations and ensure that there is good confinement of the gas for the recommended period of exposure.

Fumigation of Surface Ships in Port
Surface ships in size up to and including large ocean-going ships may also be fumigated with the product to control various pests. The draft label recommends that professional fumigators and the ship’s captain (or owner) shall follow all applicable regulations. Except for persons involved in fumigation, no people, plants, or pets may be on board during fumigation. The person responsible for fumigation must notify the master of the vessel, or his representative, of the requirements relating to the personal protection equipment and detection equipment. Emergency and procedures, cargo ventilation, periodic monitoring and inspections, and the first aid measures must all be discussed with and understood by the master or his representative.

If leakage of the fumigant is detected, the person in charge of fumigation shall take action to correct the leakage or shall inform the master of the vessel or his representative, of the leakage so that corrective action can be taken. Edible commodities should not be exposed to the product and if not removed from the vessel, they should be protected from exposure. The vessel must not be moved during the fumigation and aeration periods. If re-entry is necessary before the aeration is complete, positive pressure self contained respiratory protection must be worn.

Fumigation Manual
The applicant has provided a copy of the 'Fumigation Manual' (United States edition), which will be made available to all the users. The Technical Manual provides details of operation procedures including product information, cylinder storage and use, health and fire emergencies, preparation, sealing and securing, Profume dosage and pest biology, Profume introduction and distribution, monitoring Profume gas fumigant, aeration, clearing and re-entry, chambers and stack fumigations, fumigation of bulk commodities, and troubleshooting.

5.1 PACKAGING

Profume Gas Fumigant is packaged as a compressed liquid gas in high pressure steel cylinders (1.2 m long x 25 cm diameter). Each cylinder contains 56.7 kg product (99.8% sulfuryl fluoride plus 0.2% inert ingredients-under pressure).

6 EXPOSURE ESTIMATION

6.1 PUBLIC

As the general public would not be involved with applying Profume Gas Fumigant, there is no potential for direct exposure to the product during application. However, bystander exposure is possible. In addition, the general public will be exposed to some Profume Gas Fumigant on re-occupying treated houses/areas.

The applicant has submitted bystander exposure studies, as part of worker exposure studies (see section 6.2.1.1), to determine the potential exposure to bystanders resulting from the fumigation of mills with sulfuryl fluoride. Potential bystander exposure was determined by continuous sampling of air at various distances and directions from the mills during the fumigation and aeration procedures. A summary of bystander exposure from all the studies is presented (see table below). During fumigation, the maximum 24 hr TWA multidirectional average value was 2.09 ppm at 5 m distance and the next maximum 24 hr TWA multidirectional average value was 1.77 ppm at 5 m distance from the mill. During aeration, the maximum 24 hr TWA multidirectional average value was 0.32 ppm at 5 m distance and the next maximum 24 hr TWA multidirectional average value was 0.27 ppm at 10 m distance from the mill.

The applicant has also submitted a study (see section 6.2.1.1-study 10) to assess potential exposures to residents re-entering fumigated homes following clearance of the homes at or below 5 ppm. A total of 15 homes were fumigated in Florida and California in 1994 and concentrations were determined within the homes for up to 48 hrs following clearance of the homes at or below 5 ppm. Combination of air concentrations from all 15 structures yielded daily TWA exposures of 0.41 and 0.14 ppm for the first and second 24-hr periods following aeration, respectively, and 0.28 ppm for the entire 48 hr monitoring period.

Summary of potential multi-directional bystander exposure (external sulfuryl fluoride concentration during fumigation and aeration) in mills

Study (reference)	Trial site	Duration of fumigation and aeration	Sulfuryl fluoride used	Maximum Internal Conc. (g/m^3)	Maximum multi-directional 24-hr TWA exposure (ppm) at a nominal distance from the mills									
					5 m		10 m		25 m		50 m		75 m	
					F	A	F	A	F	A	F	A	F	A
1 (Perkins, 2002)	Nafferton, Yorkshire, UK	28 hrs fumigation. Re-entry after 4 hrs of aeration	742 kg (13 cylinders)	134 g/m^3	1.77	0.16	0.39	0.10	0.20	0.07	0.14	0.08	0.07	0.04
2 (Perkins & Jones, 2002)	Nottingham, UK	23 hrs of fumigation. Re-entry after 4 hrs of aeration	462 kg (6 cylinders)	110 g/m^3	0.09	0.07	0.08	0.05	0.07	0.04	0.05	0.03	0.01	0.01 (at 70 m)
3 (Perkins, 2002)	Hedwigsburg, Germany	31 hrs of fumigation. Re-entry after 7 hrs of aeration	456 kg (8 cylinders	71 g/m^3	0.05	0.18	0.07	0.17	0.06	0.14	0.04	0.12	0.04	0.13
4 (Perkins & Blaschke, 2002):	Hedwigsburg, Germany	20 hrs of fumigation. Re-entry after 15.5 hrs of aeration	893 kg (16 cylinders	94 g/m^3	0.97	0.05	0.48	0.05	0.26	0.04	0.14	0.03	0.09	0.04
5 (Perkins, 2002)	Corato, Italy	27 hrs of fumigation. Re-entry after 27 hrs of aeration	1767 kg (32 cylinders	85 g/m^3	1.52	0.10	0.85	0.05	0.41	0.04	0.26	0.03	0.18	0.05
7 (Barnekow et al., 2002)	Maxwell, CA (ARI)	34 hrs of fumigation. Re-entry after 4 hrs of aeration	1374 kg (24 cylinders	71 g/m^3	0.89	0.32	0.70 (at 9 m)	0.27	0.45 (at 23 m)	0.16	0.52 (at 46 m)	0.15	0.21 (at 76 m)	0.09
7 (Barnekow et al., 2002)	Ligonier, IN (SOTW)	29 hrs of fumigation. Re-entry after 6 hrs of aeration	2043 kg (36 cylinders	108 g/m^3	2.09	0.16	1.30 (at 9 m)	011	0.65 (at 23 m)	0.08	0.41 (at 46 m)	0.07	0.19 (at 76 m)	0.06
8 (Barnekow et al., 2001)	Ligonier, IN (SOTW)	29 hrs of fumigation. Re-entry after 4 hrs of aeration	2051 kg (36 cylinders	116 g/m^3	0.54	0.04	0.38	0.04	0.17	0.04	0.28	0.04	0.19 (at 76 m)	0.05 (at 76 m)
8 (Barnekow et al., 2001)	Hudsom, KS, USA (SCFM)	29 hrs of fumigation. Re-entry after 4 hrs of aeration	455 kg (8 cylinders	143 g/m^3	0.59	0.5	0.39	0.04	0.23	0.02	0.17	0.02	0.17 (at 80 m)	0.01 (at 80 m)
8 (Barnekow et al., 2001)	Freeport, TX, USA (ARI, TX)	5 hrs of fumigation. Re-entry after 4 hrs of aeration	1182 kg (21 cylinders	69 g/m^3	0.22	0.22	0.13	0.13	0.09	0.09	0.11	0.11	0.12 (at 80 m)	0.12 (at 80 m)

F = Fumigation, A = Aeration.

6.2 OCCUPATIONAL EXPOSURE CHARACTERISATION

The product is not manufactured in Australia. Qualified fumigators will be the main users of the product.

6.2.1 Exposure during use

6.2.1.1 Worker Exposure Studies

1. Perkins, J.M. (2002a): Determination of atmospheric concentrations of sulfuryl fluoride following fumigation of a mill using Profume–UK 2000. Study Plan No: 000377, Report No: GHE-P-9903, Unpublished Report date: 26 July, 2002. Dow AgroSciences.

Test Compound:	Vikane Gas Fumigant (99.8% purity)-It is stated that this will be sold as Profume for the fumigation of mills.
Batch:	OC16160101
Study Duration:	The study plan was approved on 29 August 2000 and the study was completed on 26 July 2002.
Test Facilities:	The field site was at Smiths Station Flour Mills, Nafferton, Yorkshire and the field phase was conducted at Dow AgroSciences, Letcombe Laboratory, Wantage, UK. The sulfuryl fluoride determination was conducted at Minnesota Valley Testing Laboratories, inc (MVTL), New Ulm, MN, USA.
GLP & QA:	Yes
Guidelines:	US EPA Pesticide Assessment Guidelines (Subdivision U), draft OECD Guidance Document-TG\95.88, 1995-Conduct of field studies of exposure to pesticides in use, GIFAP technical monograph-14 April 1990-Monitoring studies in the assessment of field worker exposure to pesticides, and OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides during Agricultural Application, 1997.

***Objective*:** The objective of this study was to determine the potential exposure to fumigators and bystanders resulting from the fumigation of a mill with sulfuryl fluoride. Exposure to fumigators was determined by monitoring the atmospheric concentration of sulfuryl fluoride in their breathing zone using personal air samplers. Potential bystander exposure was determined by continuous sampling of air at various distances and directions from the mill during the fumigation and aeration procedures.

Methods:

Fumigation: The fumigation was conducted between the 6 September 2000 and the 8 September 200 in a disused flour mills at Nafferton, Yorkshire, UK. by a registered fumigation company (IGROX). The mill was prepared for fumigation by sealing all possible openings between the mill and the outside atmosphere. Individual gas introduction sites were placed throughout the mill on various floors to ensure rapid distribution and equilibration of the sulfuryl fluoride gas fumigant in the mill. The calculation of the equivalent of the application rate during the process of fumigation with sulfury fluoride can be describe the model CT = dosage, where C is the concentration and t is the exposure time. The mill was treated with sulfuryl fluoride to achieve a target dosage (CT) of 1814 g-h/m^3. During the fumigation and aeration, the internal concentration of the sulfuryl fluoride within the mill was monitored by using a Fumiscope.

Aeration: The aeration procedure was based on using three internal fans to push air out of the mill. Two fans were placed in the basement and two internal chimneys constructed of flat pack

plastic tubing connected o the fans and exiting out of the second floor. A further fan was placed inside the mill on the second floor by an external door. Flat pack plastic tubing was connected to this fan, through the door and positioned approximately level with roof eves. The aeration was started at 09:00 hrs on 8 September 2000 and was completed around 13:00 hrs on 8 September 2000, at which time the mill was re-entered.

Worker activities: The activity monitored in this study was the introduction of sulfuryl fluoride gas into the structure. This task included moving the cylinders, removing the protective bonnet from the cylinders, connecting and disconnecting the shooting-lines from the cylinders and opening to introduce the fumigant.

Inhalation exposure monitoring (worker exposure): Air was sampled using Personal Air Samplers with SKC low flow and pressure control adapters attached to the air sampling tube located on the collar of the workers clothing (i.e., positioned in the worker's breathing zone). Twin sampling tubes were run during the fumigation (one sampler to monitor the exposure associated with a specific task, the second sampler to provide a 4 hr time weighed average starting from the beginning of the task). All air samples were passed through tubes packed with activated charcoal. These tubes contained two sections of charcoal (i.e., two stage, 0.8/0.2g). Separate analysis of the back section was used to determine if any sulfuryl fluoride had been retained by the front (0.8g) section. The nominal flow rates used in this study were 100 mL/min for 1 to 4 hr sampling periods. The pumps were turned on, immediately prior to the worker entering the immediate area of the structure and turned off, whenever the worker left this area for a break. Pumps were re-started upon re-entry.

Atmospheric sampling (bystanders exposure): To monitor sulfuryl concentrations around the mill, static air samplers were located (where practicable) at specified distances along the approximate cardinal points (north, South, etc) from the mill, i.e., 5m, 10m, 25m, 50m and up to 75m. Samples were taken prior to the fumigation to determine background levels and during the fumigation and aeration procedures. Air concentrations at each location were determined using personal air samplers in conjunction with activated carbon sampling tubes (as above). Specimen tubes were attached to static sampling posts 1.5 m above ground level (to reflect potential human exposure). Sample period during the introduction and holding of the sulfuryl fluoride gas in the structure were approximately 8 hrs (at 50 mL/minute or approximately 24 L of air). During the aeration phase, the flow rate was increased to around 100 mL/minute (or approximately 6 L of air) and the sampling period was 1 hr. Each charcoal tube was removed and replaced with a new tube at the end of each specific monitoring period. The atmospheric concentrations were determined by taking the mass per tube and dividing by the volume of air sampled. The amount of sulfuryl fluoride found in the tubes was converted to ppm by dividing the µg of sulfuryl fluoride detected with air sample volume (L) x 4.17.

Travel/field recovery: Travel spikes (to show degradation of sulfuryl fluoride during travel) and field spikes (to demonstrate retention of sulfuryl fluoride on the tube under experimental sampling conditions) were prepared at a US laboratory prior to the start of the study as it was not possible to fortify theses under filed conditions. The applicant considers that since these samples were transported to the UK field site and then returned to the laboratory for analysis, this represents a worse case for sulfuryl fluoride loss during transit.

Sample analysis: Upon arrival at MVTL Laboratories in New Ulm, Minnesota, the samples were placed in a freezer to await analysis. The method of analysis used was based on MVTL Analytical Method F45323, based on Dow AgroSciences Laboratory report: Sulfuryl fluoride-Development

and validation of an Air Monitoring Method[1], which utilizes extraction of the sulfuryl fluoride residue form the tube with 0.04N NaOH. The extract was then heated to convert the residue to fluoride and sulphate. A fluoride ion selective electrode was then used to quantify the fluoride residue.

Results:

Travel/field/storage recovery: Sulfuryl fluoride was found to be stable under ambient conditions for 46 days, with an average of 97% remaining of the spiked amount. Under frozen conditions up to 180 days, 101% sulfuryl fluoride remained of the spiked amount. Results for the travel spikes (101 µg sulfuryl fluoride/tube) ranged from 86 µg sulfuryl fluoride/tube to 114 µg sulfuryl fluoride/tube. Sulfuryl fluoride was not found on control tubes. Fortified recovery samples (see table bellow) demonstrated acceptable recovery of sulfuryl fluoride for the method of analysis.

Recovery of sulfuryl fluoride

Fortification level	µg sulfuryl fluoride / sample added	µg sulfuryl fluoride / sample found	Percent recovery
[a]175 µg spike (LOD)	1.75	1.85	NA
[b]3.5 µg spike (LOQ)	3.5	2.47-3.86	71-110
50 µg spike	50.16	39.92-55.58	78-111
500 µg spike	501.6	357-471.2	71-94
1000 µg spike	1003.2	767.2-938.1	76-94

[a]This level used only for qualitative purposes.

[b]Target limit of quantification (LOQ) was not achieved. LOQ validated at 4.18 µg sulfuryl fluoride/tube.

Comparison of travel and field recovery data indicate no adverse effects on the retention of sulfuryl fluoride on tubes resulted from sampling ambient air at the study site.

Internal mill concentrations of sulfuryl fluoride: A Ct of 1814 g.hr/m^3 was achieved over 42 hrs period and a typical half-life (loss) time of approximately 4-7 hrs was observed. Once the mill had reached its initial maximum concentration of approximately 134 g/m^3, the internal concentration decreased.

Fumigant (operator) exposure: The fumigators handled and released product from 13 cylinders into the mill, which corresponds to 742 kg of sulfuryl fluoride (see table below). During this period, workers were exposed to atmospheric concentrations of sulfuryl fluoride of between <0.25 and 0.52 ppm, which the applicant has calculated equates to an eight hr TWA concentration of sulfuryl fluoride of 0.04 ppm.

[1] Murphy, P.G. & Contardi, J.S. (1994) Sulfuryl fluoride: Development and validation of an Air Monitoring Method, The Dow Chemical Company, Midland, MI, Report HEH2.12-38-26 (6).

Measured workers exposures for performing tasks associated with fumigation of the mill

Time exposed (min)	Sampling volume (L)	TWA concentration of sulfuryl fluoride (ppm)	
		Task	8 hr
Operator 1			
40	4	<0.25	0.01
40	4	0.52	0.04
24	2.4	ND	ND
39	3.9	<LOQ	0.01
Operator 1			
40	4	<0.25	0.01
40	4	0.46	0.04
23	2.3	<0.5	0.01

ND indicates values below the Limit of Detection (LOD) of 0.10 ppm

Bystander exposure: During the fumigation and aeration phases, the external atmospheric concentrations were determined at distances between 5 m and 75 m from the mill (see table below). The highest external sulfuryl fluoride concentration (2.46 ppm) was recorded after the initial introduction of sulfuryl fluoride gas into the mill, but these concentrations rapidly decreased with distance from the mill. The concentration rapidly decreased on onset of the aeration phase with no detectable residues present (except <LOQ at two locations only) after four hrs.

Summary of air concentration of sulfuryl fluoride with distance from the mill

		Pre Fum.	Fumigation [(b)]					Aeration [(C)]			
Timings		**1**	**2[(a)]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Location (direction)	**Distance (m)**		Sulfuryl fluoride (ppm) (nominal 8 hr)					Sulfuryl fluoride (ppm) (nominal 1 hr)			
S11 (NW)	5		2.26	2.46	1.42	0.48	0.11	<LOQ		0.18	<LOQ
S1 (E)	10		0.09	0.14	<LOQ	ND	<LOQ	ND			
S7 (SW)	10		<LOQ	0.09	0.30	<LOQ	ND				
S12 (NW)	10		1.64	1.68	0.65	1.12	0.1	<LOQ	ND	<LOQ	
S17 (SE)	10		<LOQ	0.33	<LOQ	ND		n/s	ND		
S2 (E)	25			0.05	<LOQ			ND			
S3 (S)	25			<LOQ	0.08	ND	<LOQ				
S8 (SW)	25			0.08	0.13	<LOQ	ND				
S13 (NW)	25		1.27	1.19	0.24	0.54	0.16	n/s	<LOQ		ND
S18 (SE)	25		<LOQ	0.09	ND			ND			
S4 (S)	50	ND	<LOQ								
S5 (NW)	50	ND	0.72	0.72	0.08	0.92	0.13	0.18	ND		
S9 (SW)	50		<LOQ	0.05	<LOQ	ND		ND			
S14 (W)	50			0.08	0.14	ND	<LOQ				
S19 (SE)	50	ND	<LOQ		ND						
S15 (W)	75	ND	<LOQ	0.06	0.12	ND					

(a) Timing period *ca* 5 hrs. ND indicates values below the Limit of Detection (LOD) of 0.028 ppm. <LOD indicates values above ND and below 0.07 ppm

(b) ND indicates values below the LOD of 0.02 ppm. <LOQ indicates values above ND and below the Limit of Quantification (LOQ) of 0.07 ppm

(C) ND indicates values below the LOD of 0.07 ppm. <LOQ indicates values above ND and below the Limit of Quantification (LOQ) of 0.17 ppm

The overall sulfuryl fluoride concentrations in the atmosphere around the mill during fumigation and aeration are summarised in the table below, expressed as 24 hrs TWA for each direction and distance from the mill. In addition, an overall directional average for each direction and multi-directional average for a specific distance are presented. The 24 hr TWA directional average range

from 0.03 to 0.86 ppm during fumigation to 0.04 to 0.22 ppm during aeration. The 24 hr TWA multidirectional average for each distance from the mill ranged from 0.07 to 0.39 ppm during fumigation to 0.04 to 0.10 ppm during aeration. These values excluded the 5 m value, as these are not multidirectional. The 24 hr TWA multidirectional/multi distance average ranged from 0.20 ppm during fumigation to 0.07 ppm during aeration.

Summary of 24 hr TWA concentrations of sulfuryl fluoride in the air around a fumigated mill

	Sulfuryl fluoride – 24 hr TWA -ppm (Period 1-Fumigation, Timings 2-5) [a]							**Sulfuryl fluoride – 24 hr TWA -ppm (Period 2-aeration, Timings 5-10) [b]**						
Distance (m)	**North West**	**East**	**South East**	**South**	**South West**	**West**	**Multi-directional**	**North West**	**East**	**South East**	**South**	**South West**	**West**	**Multi-directional**
5	(1.77)						**(1.77)**	(0.16)						**(0.16)**
10	1.24	0.07	0.12		0.14		**0.39**	0.25	*0.05*	*0.04*		*0.04*		**0.10**
25	0.79	0.03	0.04	0.04	0.08		**0.20**	0.17	*0.04*	*0.04*	*0.05*	*0.04*		**0.07**
50	0.54		*0.02*		0.03	0.08	**0.14**	0.23		*0.04*	*0.04*	*0.04*	*0.05*	**0.08**
75						0.07	**0.07**						*0.04*	**0.04**
Directional Average	**0.86**	**0.05**	**0.06**	**0.03**	**0.08**	**0.08**	**0.20**	**0.22**	***0.05***	***0.04***	***0.05***	***0.04***	***0.05***	**0.07**

The 5 m value in parenthesis is excluded from the multidirectional and multi-distance average as it is based on a single direction.
(a) 24 hr TWA contains 3.7 hrs contribution from sampling period 5.
(b) 24 hr TWA contains 3.8 hrs contribution from sampling period 5 and 7.3 hrs of non monitored time. This period is assumed to have the same sulfuryl fluoride concentration as the last monitored period (i.e. Timing 10).
All results in italics are based on averaging either Not Detected and/or 50% of the LOQ. The difference in the numerical values reflects the differing LOQ and ND values associated with different sampling duration/volumes.
To determine the multidirectional TWA average, a value of 50% of the LOQ value was used as the numerical value for ND.

Summary:

This study was conducted to determine the potential exposure to fumigators and bystanders resulting from the fumigation of a mill with sulfuryl fluoride. This was achieved by monitoring the atmospheric concentration of sulfuryl fluoride in the breathing zones during fumigation and by continuous sampling of air at various distances (between 5 and 75 m) and directions from the mill during the fumigation and aeration procedures.

A Ct of 1814 g.hr/m^3 was achieved over 42 hrs period and a typical half-life (loss) time of approximately 4-7 hrs was observed. Once the mill had reached its initial maximum concentration of approximately 134 g/m^3, the internal concentration decreased.

During fumigation, the fumigators handled and released product from 13 cylinders into the mill, which corresponds to 742 kg of sulfuryl fluoride. During this period, workers were exposed to atmospheric concentrations of sulfuryl fluoride of between 0.46 and 0.52 ppm, equivalent to eight hr TWA concentration of sulfuryl fluoride of 0.04 ppm.

During fumigation, concentrations of sulfuryl fluoride were detected around the mill with a maximum 4 hr TWA multidirectional value of 0.39 ppm at 10 m from the mill and a maximum 24 hr TWA uni-directional concentration of 1.77 ppm at 5 m. During aeration, the internal concentration was observed to decrease rapidly and this was mirrored by the external atmospheric concentration of sulfuryl fluoride. The 24 hr TWA multidirectional average value encompassing the aeration phase was 0.10 ppm at 10 m from the mill with a maximum 24 hr TWA uni-directional concentration of 0.16 m.

The atmospheric concentration of sulfuryl fluoride was observed to decrease rapidly in all directions from the mill during the fumigation and aeration phases. The 24 hr TWA

multidirectional/multi distance average ranged from 0.07 ppm during aeration to 0.02 ppm during fumigation.

2. Perkins, J.M. and Jones, G. (2002): Determination of atmospheric concentrations of sulfuryl fluoride following fumigation of a mill using Profume–UK 2002. Study Plan No: AF/6268/DE, Report No: 26367019-19, Unpublished Report date: 25 July, 2002. Dow AgroSciences.

Test Compound:	Vikane Gas Fumigant (99.8% purity)-It is stated that this will be sold as Profume for the fumigation of mills.
Batch:	TSN102173/OC16160101
Study Duration:	The study plan was approved on 14 March 2002 and the study was completed on 19 July 2002.
Test Facilities:	The field site was at Smiths Station Flour Mills, Langley Mill, Nottingham and the field phase was conducted at Agrisearch UK Ltd, Melbourne, Derbyshire, UK.. The sulfuryl fluoride determination was conducted at Minnesota Valley Testing Laboratories, inc (MVTL), New Ulm, MN, USA.
GLP & QA:	Yes
Guidelines:	US EPA (OPPTS 875.2500-Inhalation exposure), draft OECD Guidance Document-TG\95.88, 1995-Conduct of field studies of exposure to pesticides in use, GIFAP technical monograph-14 April 1990-Monitoring studies in the assessment of field worker exposure to pesticides, and OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides during Agricultural Application, 1997.

***Objective*:** The objective of this study was to determine the potential exposure to fumigators and bystanders by measuring the concentration of sulfuryl fluoride in the breathing zone of the fumigation workers and the atmospheric concentrations of sulfuryl fluoride in the air around the mill. Atmospheric concentrations of sulfuryl fluoride for persons re-occupying the mill, were also monitored once aeration had been completed.

Methods:

Fumigation: The fumigation was conducted in flour mills at Langley Mill, Nottingham, UK., by a registered fumigation company (IGROX). The preparation of mills and the dosage calculation for fumigation was as described for study by Perkins, 2002 (Study No. 1). A total of 6 cylinders of sulfuryl fluoride were introduced over the period of 14:31 hrs to 16:34 hrs on 6 April 2002. The mill remained under fumigation until 13:10 hrs on 7 April 2002, when it was calculated that the *Ct* would have reached the target of 1500 g.hr/m^3. At this time, the aeration process was started and this was continued until 18:58 hrs on 7 April 2002.

Aeration: The aeration procedure was based on using two internal fans with external chimneys to push air our of the mill. The top fan was switched on at 13:17 at the start of the aeration procedure to build up negative pressure inside the mill before the bottom fan was switched on at 13:40. These fans were switched off at 15:18 when the mill was entered by fumigators wearing SCBA to turn on the mill air handling system. Subsequently, additional airflow through the building was achieved by opening doors and removing sealing material from the outside of the building.

After 4 hrs of aeration, the internal concentration of the fumigated structures was tested for clearance at ≤5 ppm. Following an additional two hrs aeration period, the concentration inside that area of the mill was re-evaluated and cleared for re-occupancy at 18:58 hrs on 7 April 2002.

Worker activities: There were three separate activities covered in this mill fumigation. The first monitored activities were associated with the introduction of the fumigant gas into the mill structure. This task included moving the cylinders, weighing the cylinders, removing the protective bonnet from the cylinders, connecting the shooting-lines manifold to cylinders, opening the cylinders before introducing the fumigant into the system via a remote (outside the exclusion zone) switch and disconnection of the cylinders from the shooting line manifold system.

The second monitored activity involved the aeration of the structure following the fumigation. The aerator activities involved starting the aeration fans, unsealing the aeration plastic ducts, removing external plastic sheeting used in sealing, and opening doors from the outside of the structure. These activities were conducted external to the mill. No entry into the mill was allowed until the mill was declared clear for re-occupation (the sulfuryl fluoride concentration inside the mill was ≤5 ppm).

The third monitored activity involved entering the mill once it had been declared clear by the fumigators and removing all the equipment associated with the introduction of the fumigant and stripping the mill of all the sealing material (plastic sheeting/tape etc) used to retain the fumigant within the mill.

Inhalation exposure monitoring (worker exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). The nominal flow rates used in this study were 100 mL/min for 1 to 4 hr sampling and 50 mL/min for sampling periods greater than 4 hrs (to a maximum of 8 hrs).

Atmospheric sampling (bystanders exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). Sampling periods during the introduction and holding of the sulfuryl fluoride gas in the structure were approximately 8 hrs (at 50 L/minute or approximately 24 L of air). During the aeration phase, two sampling tubes were used in order that both 1-hr and 4-hr TWA specimens were collected. Flow rates of around 100 mL/minute (or approximately 6 L of air) were used for 1-hr specimens and 100 mL/minute (or approximately 24 L of air) were used for 4-hr specimens.

The surrounding buildings and river around the mill structure dictated the actual distances and direction of atmospheric air sampler locations. Specimens were collected from all sampling locations from the start of fumigation (introduction of gas) until the end of aeration.

Measurement of re-entry worker exposure: Once the mill had been declared clear for re-entry, air samplers were positioned on various floors within the mill building and run for a nominal twelve-hr period. A single sample tube was used at each location. A 4 hr sample interval was used for the first 4 hr post re-occupation, followed by an 8 hr sample interval to give a 12 hr monitoring period. Flow rates of approximately 100 mL/min (or approximately 24 L/hr) were used for these specimens.

Travel/field recovery: Travel spikes (to show degradation of sulfuryl fluoride during travel) and field spikes (to demonstrate retention of sulfuryl fluoride on the tube under experimental sampling conditions) were prepared at a US laboratory prior to the start of the study as it was not possible to fortify theses under filed conditions.

Sample analysis: The method of analysis was as described by Perkins, 2002 (Study No. 1).

Results:

Travel/field recovery: Procedural recovery samples (see table bellow) demonstrated acceptable recovery of sulfuryl fluoride for the method of analysis.

Summary of recovery of sulfuryl fluoride

Fortification level	µg sulfuryl fluoride / sample added	µg sulfuryl fluoride / sample found	Percent recovery
[a]175 µg spike (LOD)	1.75	1.19	68
[b]3.5 µg spike (LOQ)	3.5	2.47-3.86	[C]72-119
50 µg spike	50.16	39.92-55.58	72-103
500 µg spike	501.6	357-471.2	57-100
1000 µg spike	1003.2	767.2-938.1	68-89

[a]This level used only for qualitative purposes.

[b]Target LOQ was not achieved. LOQ validated at 4.18 µg sulfuryl fluoride/tube.

[c]A value of 27% was recorded for this spiking concentration. This result was due to analyst error and is omitted.

Procedural recoveries associated with the individual tubes (1.75 to 1000 µg sulfuryl fluoride/tube) had an overall mean recovery of 86%. There was no evidence of breakthrough of sulfuryl fluoride from the front to the back segments of the absorbed media. Analysis of the 'transit specimen' indicated that no significant losses occurred when the field spikes were run or in the case of the travel spikes during the rest of the procedures covered by the study prior to analysis of the specimens.

The target LOQ for the method of analysis of 3.5 µg sulfuryl fluoride/tube was not achieved. The calculated study LOQ was 5.5 µg sulfuryl fluoride per sample and the calculated study LOD was 1.67 µg sulfuryl fluoride per sample. All residue values equivalent to or less than the LOD are classified as "not detected" (ND).

Internal mill concentrations of sulfuryl fluoride: A Ct of 1595 g.hr/m^3 was achieved over 23 hrs fumigation period and a half-life (loss) time of approximately 14 hrs was observed. The internal concentration varied between 8000 to 27,000 ppm. The mill was aerated over a 6 hrs period, after which the mill was declared clear for re-occupancy.

Fumigant (operator) exposure: The fumigators handled and released product from 6 cylinders into the mill, which corresponds to 462 kg of sulfuryl fluoride. During this initial four hr period, the workers were exposed to atmospheric concentrations of sulfuryl fluoride of between 0.07 and 0.01 ppm (see table below). This corresponds to an equivalent 8-hr TWA atmospheric sulfuryl fluoride concentration of between 0.01 and 0.05 ppm.

When carrying out tasks associated with the initiation of aeration, workers were exposed to an equivalent 8-hr TWA atmospheric sulfuryl fluoride concentration of between 0.01 ppm. The removal of sealing material (inside & outside) and clearing of equipment from the mill after it had been declared clear, exposed workers to an equivalent 8-hr TWA atmospheric sulfuryl fluoride concentration of between 0.18 and 0.20 ppm.

Summary of worker exposure

Operator No.	Action undertaken	Time exposed (min)	TWA concentration of sulfuryl fluoride (ppm) [a b]	
			Task	8 hr
Fumigation				
1	Cylinder weighing and cracking, introduction of gas, disconnection of cylinders	31	ND	0.01
		31	<LOQ	
1	As above, 4 hr time weighed specimens	240	0.07	0.05
		240	0.07	
2	Cylinder weighing and cracking, introduction of gas	27	<LOQ	0.01
		27	ND	
2	As above, 4 hr time weighed specimens	240	0.08	0.05
		240	0.09	
Aeration				
1	Start of aeration process, undoing ties on chimney vents, switching on fans, etc.	31	<LOQ	0.01
		31	<LOQ	
1	Removing sealing material from outside of mills, clearing building of equipment and sealing material (inside and out) once mill was declared clear	193	0.35	0.20
		193	0.43	
2	Removing sealing material from outside of mills, clearing building of equipment and sealing material (inside and out) once mill was declared clear	193	0.38	0.18
		193	0.33	

(a) For approximate duration of 30 minutes: ND= not detected above LOD of 0.56 µg/m^3 (0.13 ppm). <LOQ = Below the LOQ of 1.85 µg/m^3 (0.44 ppm).
For approximately 4-hr sampling periods (included are 3-hr sampling period during aeration): ND= not detected above LOD of 0.07 µg/m^3 (0.02 ppm). <LOQ = Below the LOQ of 0.23 µg/m^3 (0.06 ppm).
(b) ppm sulfuryl fluoride = Air concentration (mg/m^3)/4.171

Bystander exposure: During the fumigation and aeration phases, the external atmospheric concentrations were determined at distances between 5 m and 70 m from the mill (see table below). The atmospheric concentration of sulfuryl fluoride decreased rapidly in all directions from the mill during both the fumigation and aeration phases. Whilst the mill was undergoing fumigation, the majority of measurements were less than the LOQ or Non Detectable. The highest external sulfuryl fluoride concentration (1.12 ppm) was recorded at the start of the aeration procedure for a 1 hr sample taken at 10 m sampling point.

Summary of air concentration of sulfuryl fluoride with distance from the mill

		Pre Fum	Fumigation [a]			Aeration [b]						Aeration [C]		
Timings		0	1	2	3	4	5	6	7	8	9	10	11	12
Location	**Distance (m)**		Sulfuryl fluoride (ppm) (nominal 8 hr)			Sulfuryl fluoride (ppm) (nominal 1 hr)						Sulfuryl fluoride (ppm) (nominal 4 hr)		
S1	5	<LOQ	<LOQ	<LOQ	ND	<LOQ	0.21	<LOQ	ND			<LOQ	<LOQ	ND
S6	5	ND	<LOQ	ND		0.49	0.33	<LOQ	ND		<LOQ	0.2	ND	
S10	5		0.19	<LOQ		1.08	0.69	<LOQ			ND	0.82		
S11	5	ND	0.27	**0.16**	<LOQ	0.94	**0.72**	**0.33**	**0.24**	ND		0.44		
S16	5	ND	0.17	<LOQ		0.77	0.37	<LOQ				0.25		
S19	5		0.13			0.74	0.42					0.37	ND	<LOQ
S2	10		0.07	<LOQ	ND	<LOQ			ND	ND		<LOQ	ND	
S7	10		ND						<LOQ			0.11		
S12	10		0.24	0.15	**0.09**	0.75	0.40	0.26	<LOQ		ND	0.5		
S15	10		0.13	<LOQ		**1.12**	0.32	<LOQ		ND		0.34		
S17	10		0.21			n/s	0.32					0.21		
S20	10		<LOQ	ND	<LOQ	0.83	0.37	ND			<LOQ	0.32		
S3	25		ND	<LOQ	ND	<LOQ		ND		ND		<LOQ	ND	<LOQ
S8	25		0.09	0.13	<LOQ			<LOQ				<LOQ	ND	
S13	25		**0.31**	<LOQ	0.08	0.52	0.25					0.29		
S14	35		0.18	<LOQ	<LOQ	0.53	0.24					0.22		
S18	25		<LOQ	ND	<LOQ	<LOQ		ND	<LOQ			<LOQ		
S4	50		ND	ND	<LOQ	ND				ND		ND		
S9	48	ND		<LOQ	0.07	ND	<LOQ					<LOQ		ND
S5	70	<LOQ		ND								<LOQ	ND	ND

(a) Timings 0, 1, 2 were approximately 8 hrs. ND indicates values below LOD of 0.02 ppm. <LOQ indicates values below LOQ of 0.06 ppm. Timing 3 approximately 6 hrs. ND = values below LOD of 0.02 ppm. <LOQ indicates values below LOQ of 0.07 ppm.
(b) Timings 6-9 were approximately 1 hr. ND indicates values below LOD of 0.07 ppm. <LOQ indicates values above ND and below the LOQ of 0.06 ppm.
(c) Timings 10-12 were approximately 4 hrs. ND indicates values below LOD of 0.02 ppm. <LOQ indicates values above ND and below the LOQ of 0.06 ppm.
Values in bold are maximum values for timing.

The overall sulfuryl fluoride concentrations in the atmosphere around the mill during fumigation and aeration are summarised in the table below, expressed as 24 hrs TWA for each direction and distance from the mill. In addition, an overall directional average for each direction and multi-directional average for a specific distance are presented. The maximum 24-hr TWA value was calculated to be 0.19 ppm (10 m sampling point) during fumigation and 0.15 ppm (5 m sampling point) during aeration. The 24-hr TWA multi-directional sulfuryl fluoride concentrations covering the fumigation phase were <0.19 ppm for all distance from the mill. The corresponding concentrations that incorporated the aeration phase were <0.15 ppm. The 24-hr multi-directional/multi-distance TWA were 0.06 ppm during fumigation and 0.04 ppm during aeration.

Summary of 24 hr TWA concentrations of sulfuryl fluoride in the air around a fumigated mill

	Sulfuryl fluoride – 24 hr TWA -ppm (Period 1-Fumigation, Timings 1-3) [(a)]						Sulfuryl fluoride – 24 hr TWA -ppm (Period 2-aeration, Timings 10-12) [(b)]					
Distance (m)	**North**	**NNE**	**South East**	**South west**	**West**	**Multi-directional**	**North**	**NNE**	**South East**	**South west**	**West**	**Multi-directional**
5	0.09	0.02	0.03	0.18	0.14	**0.09**	0.05	0.01	0.04	0.10	0.15	**0.07**
10	0.10	0.02	0.01	0.19	0.08	**0.08**	0.04	0.01	0.03	0.09	0.07	**0.05**
25	0.02	0.02	0.09	0.15	0.09	**0.07**	0.01	0.03	0.01	0.06	0.07	**0.04**
50		0.01	0.04	0.09	0.05	**0.05**		0.01	0.01	0.05	0.06	**0.03**
70		0.01				**0.01**		0.01				**0.01**
Directional Average	**0.07**	**0.02**	**0.04**	**0.15**	**0.09**	**0.06**	**0.03**	**0.01**	**0.02**	**0.08**	**0.09**	**0.04**

(a) First 24 hr TWA period is made up of timings 1, 2, 3 and a proportional average for 2 hrs from timings 4, 5, 6, 7 and 10.
(b) Second 24 hr TWA period is made up of 4 hrs contribution from timings 10, 11, 12 and a proportional average for 12 hrs derived from the results of the final 4 hr sampling timing.

Re-entry worker Exposure: Once the mill had been declared clear by the fumigation company, samplers were positioned on the various floors of the mill building and run for a nominal twelve hr period. Atmospheric concentration ranged from 0.12 to 0.46 ppm during the first four hrs post-clearance and from <0.06 to 0.57 ppm during the subsequent eight hr sampling period (see table below). Average residue found over these two periods was 0.29 and 0.26 ppm, respectively.

Sulfuryl fluoride concentrations (ppm) measured inside the mill after re-occupation

Location	**Timings**	
	Post-aeration (0-4 hr)	**Post-aeration (4-12 hr)**
S21	0.12	<LOQ
S22	0.34	0.57
S23	0.33	0.18
S24	0.17	0.54
S25	0.39	<LOQ
S26	0.19	0.33
S27	0.46	0.14
Average	**0.29**	**0.26**

LOD = 0.02 ppm, LOQ = 0.06 ppm

Summary:

This study was conducted to determine the potential exposure to fumigators and bystanders resulting from the fumigation of a mill with sulfuryl fluoride. Atmospheric concentrations of sulfuryl fluoride for persons re-occupying the mill were also monitored, after aeration had been completed over a 6 hr period.

A Ct of 1595 g.hr/m^3 was achieved over the 23 hrs fumigation period (the internal sulfuryl fluoride concentration varied between 8000 to 27,000 ppm). The mill half-life (loss) time of approximately 14 hrs suggests that the mill was effectively sealed during this period.

During fumigation, the fumigators handled and released product from 6 cylinders into the mill, which corresponds to 462 kg of sulfuryl fluoride. During this 4 hr period, workers were exposed to atmospheric concentrations of sulfuryl fluoride of between 0.07 and 0.1 ppm, equivalent to eight hr TWA concentration of sulfuryl fluoride between 0.01 and 0.05 ppm. During aeration, some work was undertaken in removing plastic sheeting from external doors and unsealing the mill aeration vents. Whilst undertaking these task, the workers were exposed to concentrations of

<LOQ for 30 minutes. During the next 3 hrs, whilst performing further tasks associated with aeration and removal of equivalent after the mill was declared clear, workers were exposed to a maximum atmospheric concentrations of sulfuryl fluoride of 0.43 ppm, equivalent to eight hr TWA concentration of sulfuryl fluoride of 0.20 pm.

During fumigation and aeration phases, sulfuryl fluoride concentrations declined with distance from the mill and the highest external sulfuryl fluoride concentration (1.12 ppm) was recorded at the start of the aeration procedure, for a 1 hr sample taken at 10 m sampling point. During fumigation, the majority of the measurements were less than the LOQ or Non Detectable and low levels (up to 0.28 ppm) were found at 5 m distance from the mill. A maximum 24 hr TWA multidirectional value of 0.09 ppm at 5 m from the mill and a maximum 24 hr TWA uni-directional concentration of 0.19 ppm at 10 m from the mill were detected. During aeration, sulfuryl fluoride could not be measured above the LOQ in the majority of the specimens and low levels (up to 1.12 ppm) were found at 10 m distance from the mill. The maximum 24 hr TWA multidirectional average value was 0.07 ppm at 5 m from the mill and a maximum 24 hr TWA uni-directional concentration of 0.15 ppm at 5 m from the mill was detected.

The concentrations of sulfuryl fluoride inside the mill after completion of aeration were shown to decline to levels of approximately 0.26 ppm during the first 12-hr period.

3. Perkins, J.M. (2002b): Determination of atmospheric concentrations of sulfuryl fluoride following fumigation of a mill using Profume–Germany 2000. Study Plan No: 000303, Report No: GHE-P-8682, Unpublished Report date: 25 July, 2002. Dow AgroSciences.

Test Compound:	Vikane Gas Fumigant (99.8% purity)-It is stated that this will be sold as Profume for the fumigation of mills.
Batch:	NB02160101
Study Duration:	The study plan was approved on 25 April 2000 and the study was completed on 25 July 2002.
Test Facilities:	The trial site was a flour mill in Hedwigsburg, Germany, and the field phase was conducted at Dow AgroSciences, Letcombe Laboratory, Wantage, UK. The sulfuryl fluoride determination was conducted at Minnesota Valley Testing Laboratories, inc (MVTL), New Ulm, MN, USA.
GLP & QA:	Yes
Guidelines:	US EPA Pesticide Assessment Guidelines (Subdivision U), draft OECD Guidance Document-TG\95.88, 1995-Conduct of field studies of exposure to pesticides in use, GIFAP technical monograph-14 April 1990-Monitoring studies in the assessment of field worker exposure to pesticides, and OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides during Agricultural Application, 1997.

***Objective*:** The objective of this study was to determine the potential exposure to fumigators and bystanders resulting from the fumigation of a mill with sulfuryl fluoride.

Methods:

Fumigation: The mill selected for this study was at Hedwigsburg, Germany and the fumigation was undertaken by a registered fumigation company (Binker Materialschutz). The preparation of mills and the dosage calculation for fumigation was as described for study by Perkins, 2002 (Study No. 1). In addition, as this mill had a flat roof, a tarpaulin was placed over the roof and secured under the eaves. During fumigation and aeration, the internal concentration within the mill was monitored as described for Study No. 1. The internal measurements were used to

confirm the target application rate (*Ct*) has been reached. In total, 17 cylinders of sulfuryl fluoride were introduced over the period of 10:50 hrs on the 29 April 2000 to 09:40 hrs on 30 April 2000. The mill remained under fumigation until 17:30 hrs on 30 April 2000 (8 hrs), when the *Ct* was calculated to have reached the target of 2016 g.hr/m^3. On reaching this value, the aeration process was started.

Aeration: The aeration procedure was based on using two internal fans with external chimneys to push air out of the mill and the air vents on the roof of the mill were also unsealed. The mill was later entered by fumigators wearing SCBA to turn on the mill air handling system. After 6-7 hrs of aeration, the internal fumigated structures were tested for clearance at or below 5 ppm using an Interscan unit. After approximately 7 hrs of aeration, the mill was declared clear for re-occupancy.

Worker activities: The activity monitored in this study was the introduction of sulfuryl fluoride gas into the structure. This task included moving the cylinders, removing the protective bonnet from the cylinders, connecting and disconnecting the shooting-lines from the cylinders and opening to introduce the fumigant.

Inhalation exposure monitoring (worker exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). The nominal flow rates used in this study were 100 mL/min for 1 to 4 hr sampling and 50 mL/min for sampling periods greater than 4 hrs (to a maximum of 8 hrs).

Atmospheric sampling (bystanders exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). Sampling periods during the introduction and holding of the sulfuryl fluoride gas in the structure were approximately 8 hrs (at 50 L/minute or approximately 24 L of air). During the aeration phase, the sampling period was initially 2 hrs followed by one hour sampling. Flow rates of around 100 mL/minute (or approximately 6 L of air) were used for 1-hr specimens and 100 mL/minute (or approximately 12 L of air) were used for 2-hr specimens.

Travel/field recovery: Travel spikes (to show degradation of sulfuryl fluoride during travel) and field spikes (to demonstrate retention of sulfuryl fluoride on the tube under experimental sampling conditions) were prepared at a US laboratory prior to the start of the study as it was not possible to fortify these under field conditions.

Sample analysis: The method of analysis was as described for study by Perkins, 2002 (Study No. 1).

Results:

Travel/field recovery: Procedural recovery samples (see table below) demonstrated acceptable recovery of sulfuryl fluoride for the method of analysis.

Summary of recovery of sulfuryl fluoride

Fortification level	µg sulfuryl fluoride / sample added	µg sulfuryl fluoride / sample found	Percent recovery
[a]175 µg spike (LOD)	1.75	3.4	68
[b]3.5 µg spike (LOQ)	3.5	1.85-4.61	58-132
50 µg spike	50.16	27.81-60.51	55-121
500 µg spike	501.6	272.54-446.07	59-89
1000 µg spike	1003.2	626.06-725.16	62-71

[a]This level used only for qualitative purposes. Calculated LOD = 22.3

[b]Target LOQ was not achieved. LOQ calculated at 7.65 µg sulfuryl fluoride/tube.

There was no evidence of breakthrough of sulfuryl fluoride from the front to the back segments of the absorbed media. Analysis of the 'transit specimen' indicated that no significant losses occurred when the field spikes were run with the study air samplers (recovery 74%-78%) or in the case of the travel spikes (recovery 72%-87%) during the rest of the procedures covered by the study prior to analysis (i.e. shipment and storage).

The target LOQ for the method of analysis of 3.5 µg sulfuryl fluoride/tube was not achieved. The calculated study LOQ was 7.65 µg of sulfuryl fluoride per sample and the calculated study LOD was 2.3 µg sulfuryl fluoride per sample. All residue values equivalent to or less than the LOD are classified as "not detected" (ND).

Internal mill concentrations of sulfuryl fluoride: A Ct of 2016 g.hr/m^3 was achieved over 31 hrs fumigation period (internal concentration varied between 10000 to 22,000 ppm). The half-life (loss) time of approximately 12 to 16 hrs suggests that the mill was effectively sealed during fumigation. The mill was aerated over a 7 hrs period, after which the mill was declared clear for re-occupancy. During the aeration phase, the internal concentration of the mill was reduced from approximately 50, 000 mg/m^3 to 20 mg/m^3 (5 ppm).

Fumigant (operator) exposure: The fumigators handled and released product from 8 cylinders into the mill, which corresponds to 456 kg of sulfuryl fluoride. During the initial four hr period which included introduction of gas or monitoring inside the exclusion zone, the workers were exposed to atmospheric concentrations of sulfuryl fluoride of between <0.3 ppm (LOQ) to 0.44 ppm (see table below). During this period, if a single worker conducted all these tasks, the equivalent 8-hr TWA atmospheric sulfuryl fluoride concentration would be no greater than 0.12 ppm. Subsequent tasks involving the use of Fumiscope and the removal of shooting lines following the last introduction of gas prior to aeration showed concentrations of <LOQ, i.e. <0.6 ppm, equivalent to an 8 hr TWA of 0.05 ppm.

During the aeration phase, the internal concentration of the mill was reduced from around 50,000 mg/m^3 to 20 mg/m^3 (5 ppm). Tasks undertaken at the start of aeration involving the removal of plastic, gave exposures to atmospheric concentrations of 3.35 to 11.8 ppm for 103 and 13 minutes, respectively, which equates to an equivalent 8 hr TWA of 0.72 and 0.32 ppm, respectively.

Summary of worker exposure

Date (Sampling period)	Action undertaken	Time exposed (min)	TWA concentration of sulfuryl fluoride (ppm)	
			Task	8 hr
Fumigation				
29/4/00 (10:47-11:48)	Shooting gas – 3 cylinders opened	61	<0.31[(a)]	0.04 [(b)]
29/4/00 (11:48-12:50)	Monitoring inside exclusion zone -3 cylinders changed	62	0.44	0.05
29/4/00 (12:47-13:48)	Monitoring inside exclusion zone -2 cylinders changed	61	<0.31	0.04
29/4/00 (13:47-15:07	Monitoring inside exclusion zone	79	<0.31	0.05
Total period of exposure		**263**	**0.22**	**0.12**
30/4/00 (12:25-13:18)	Fumiscope measurement in van inside exclusion zone	53	<0.31	0.03
30/4/00 (13:22-13:57)	Removal of shooting lines, piping, heat exchanger –clean filter system	36	<0.61	0.05
Aeration				
30/4/00 (17:21-19:07)	General work and aeration on top of mill- removing plastic	103	3.35	0.72
30/4/00 (17:45-17:58)	Aeration on top of mill- removing plastic	13	11.8	0.32

(a) For nominal one hr sampling. <LOQ = 0.31 ppm. For nominal 30 minutes sampling. <LOQ = 0.61 ppm.
(b) 8 hr TWA = Air concentration (ppm) x sampling period/480). Calculated from the sum of the individual concentrations (for LOQ assume 50% (i.e. 015) and pro rata for duration.

Bystander exposure: During the fumigation and aeration phases, the external atmospheric concentrations were determined at distances between 5 m and 75 m from the mill (see table below). The atmospheric concentration of sulfuryl fluoride decreased rapidly in all directions from the mill during both the fumigation and aeration phases. Whilst the mill was undergoing fumigation, the majority of measurements were either Non Detectable or <LOQ (i.e. 0.01 ppm). The highest external sulfuryl fluoride concentration (4.22 ppm) was recorded after an initial 2 hr period of aeration for a 1 hr sample taken at 10 m sampling point.

Summary of air concentration of sulfuryl fluoride with distance from the mill

		Pre Fum	Fumigation [a]				Aeration [b]						
Timings		1	2	3	4	5	6	7	8	9	10	11	12
Location	Distance (m)		Sulfuryl fluoride (ppm) (nominal 8 hr)				Sulfuryl fluoride (ppm) (nominal 1 hr)						
S1	5	<LOQ	<LOQ	ND		<LOQ	<LOQ				0.33	ND	<LOQ
S6	5		<LOQ	ND		<LOQ	0.52	<LOQ	0.37	<LOQ	ND	<LOQ	
S11	5		<LOQ			0.28	<LOQ	0.39	<LOQ		ND	0.34	<LOQ
S16	5	ND	ND		<LOQ		<LOQ	1.29	<LOQ		ND	0.34	ND
S2	10		<LOQ	ND		<LOQ	<LOQ				<LOQ	ND	<LOQ
S7	10			ND		<LOQ	<LOQ			ND	ND	<LOQ	ND
S12	10		<LOQ		0.26	0.29	0.35	4.22	0.45	<LOQ	ND	0.48	<LOQ
S17	10		<LOQ	ND		<LOQ	<LOQ	0.51	<LOQ		ND	<LOQ	ND
S3	25		<LOQ		ND		ND	<LOQ		ND	<LOQ		
S8	25	ND	ND		0.1	ND	<LOQ	ND	<LOQ	ND			<LOQ
S9	25		n/s				<LOQ	0.77	<LOQ		ND	<LOQ	ND
S13	25		<LOQ		0.24	0.23	<LOQ	1.81	0.43	<LOQ	ND	0.66	<LOQ
S18	25		ND			<LOQ	<LOQ		n/s	ND		<LOQ	ND
S20	25		n/s				0.29	<LOQ		ND		<LOQ	ND
S4	50		<LOQ		ND		ND	<LOQ		ND	<LOQ	ND	<LOQ
S14	50		ND		<LOQ	0.13	<LOQ	0.98	<LOQ	ND		0.39	<LOQ
S19	50	ND	<LOQ		ND	<LOQ	<LOQ		ND			<LOQ	ND
S5	75	<LOQ	ND				ND	<LOQ		ND	<LOQ	ND	
S10	75		n/s				<LOQ	0.98		ND		<LOQ	
S15	75	ND	ND		<LOQ	0.1	<LOQ	1.02	<LOQ		ND	0.31	<LOQ

(a) Timing 1 was approximately 4 hrs. Timings 2 to 5 were approximately 8 hrs duration. ND indicates values below LOD of 0.03 ppm. <LOQ indicates values below LOQ of 0.01 ppm.
(b) Timing 6 was approximately 2 hrs. ND indicates values below LOD of 0.05 ppm. <LOQ indicates values below LOQ of 0.15 ppm. Timings 7-12 were approximately 1 hr. ND indicates values below LOD of 0.09 ppm. <LOQ indicates values below LOQ of 0.31 ppm. n/s = specimen lost

The overall sulfuryl fluoride concentrations in the atmosphere around the mill during fumigation and aeration are summarised in the table below, expressed as 24 hrs TWA for each direction and distance from the mill. In addition, an overall directional average for each direction and multi-directional average for a specific distance is presented. The maximum 24-hr uni-directional TWA values were 0.15 ppm (10 m sampling point) during fumigation and 0.37 ppm (10 m sampling point) during aeration. The maximum 24-hr multi-directional TWA values were 0.07 ppm (10 m sampling point) during fumigation and 0.18 ppm (5 m sampling point) during aeration. The 24-hr multi-directional/multi-distance TWA were 0.05 ppm during fumigation and 0.15 ppm during aeration.

Summary of 24 hr TWA concentrations of sulfuryl fluoride in the air around a fumigated mill

	Sulfuryl fluoride – 24 hr TWA -ppm (Period 1-Fumigation, Timings 2-5) [(a)]						Sulfuryl fluoride – 24 hr TWA -ppm (Period 2-aeration, Timings 5-14) [(b)]					
Distance (m)	**North**	**East**	**South**	**West**	**SE/SW**	**Multi-directional**	**North**	**East**	**South**	**West**	**SE/SW**	**Multi-directional**
5	(0.04)	(0.04)	0.09	(0.04)	n/s	**0.05**	0.15	0.16	0.30	0.14	n/s	**0.18**
10	(0.04)	(0.03)	0.15	(0.04)	n/s	**0.07**	(0.12)	(0.09)	0.37	0.10	n/s	**0.17**
25	(0.04)	(0.03)	0.13	(0.03)	n/s	**0.06**	(0.11)	(0.11)	0.27	(0.09)	0.13	**0.14**
50	(0.04)	n/s)	0.05	(0.04)	n/s	**0.04**	(0.11)	(n/s	0.17	(0.09)	n/s	**0.12**
75	(0.03)	n/s)	0.05	n/s)	n/s	**0.04**	(0.08)	n/s	0.17	n/s	0.18	**0.13**
Directional Average	**(0.04)**	**(0.04)**	**0.09**	**(0.04)**	**n/s**	**0.05**	**(0.11)**	**0.12**	**0.26**	**0.10**	**0.15**	**0.15**

(a) 24 hr TWA period contains 3.2 hrs contribution from sampling period 5.
(b) 24 hr TWA period contains 5.0 hrs contribution from sample period 5 and includes 11 hrs of non monitored time. This period of time is assumed to have the same sulfuryl fluoride concentration as the last mentioned period (i.e. Timing 14).
All results in parenthesis are based on averaging either Non Detected and/or 50% of the LOQ. The difference in the numerical values reflects the differing LOQ and ND values associated with different sampling duration/volumes.

Summary:

This study was conducted to determine the potential exposure to fumigators and bystanders resulting from the fumigation of a mill with sulfuryl fluoride.

A Ct of 2016 g.hr/m^3 was achieved over the 31 hrs fumigation period (the internal sulfuryl fluoride concentration varied between 8000 to 27,000 ppm). The mill half-life (loss) time of approximately 12 to 16 hrs suggests that the mill was effectively sealed during this period.

During fumigation, the fumigators handled and released product from 8 cylinders into the mill, which corresponds to 456 kg of sulfuryl fluoride. During this 4 hr period, workers were exposed to atmospheric concentrations of sulfuryl fluoride of between <0.3 ppm (LOQ) to 0.44 ppm. During this period, if a single worker conducted all these tasks, the equivalent 8-hr TWA atmospheric sulfuryl fluoride concentration would be no greater than 0.12 ppm. Subsequent tasks involving the use of Fumiscope and the removal of shooting lines following the last introduction of gas prior to aeration showed concentrations of <LOQ, i.e. <0.6 ppm, equivalent to an 8 hr TWA of 0.05 ppm.

Tasks undertaken at the start of aeration involving the removal of plastic, gave exposures to atmospheric concentrations of 3.35 to 11.8 ppm for 103 and 13 minutes, respectively, which equates to an equivalent 8 hr TWA of 0.72 and 0.32 ppm, respectively.

During fumigation and aeration phases, sulfuryl fluoride concentrations declined with distance from the mill. Whilst the mill was undergoing fumigation, the majority of measurements were either Non Detectable or <LOQ (i.e. 0.01 ppm). The highest external sulfuryl fluoride concentration (4.22 ppm) was recorded after an initial 2 hr period of aeration, for a 1 hr sample taken at 10 m sampling point. The maximum 24-hr uni-directional TWA values were 0.15 ppm (10 m sampling point) during fumigation and 0.37 ppm (10 m sampling point) during aeration. The maximum 24-hr multi-directional TWA values were 0.07 ppm (10 m sampling point) during fumigation and 0.18 ppm (5 m sampling point) during aeration. The 24-hr multi-directional/multi-distance TWA were 0.05 ppm during fumigation and 0.15 ppm during aeration.

4. Perkins, J.M. and Blaschke, U.D.O. (2002): Determination of atmospheric concentrations of sulfuryl fluoride and occupational exposure of fumigators during the structural fumigation of a mill using Profume–Germany 2002. Study Plan No: DOS 299/023404, Report No: GHE-P-9910, Unpublished Report date: 25 July, 2002. Dow AgroSciences.

Test Compound:	Vikane Gas Fumigant (99.8% purity)-It is stated that this will be sold as Profume for the fumigation of mills.
Batch:	PE13160101
Study Duration:	The study plan was approved on 16 April 2002 and the study was completed on 25 July 2002.
Test Facilities:	The trial site was a mill in Hedwigsburg, Germany, and the field phase was conducted at Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, UK. The sulfuryl fluoride determination was conducted at Minnesota Valley Testing Laboratories, inc (MVTL), New Ulm, MN, USA.
GLP & QA:	Yes
Guidelines:	OECD Series on Testing and Assessment No. 9 "Guidance Document on the conduct of field studies of occupational exposure to pesticides during agricultural application, Pairs 1997, OECD/GD(97)148.

***Objective*:** The objective of this study was to determine the potential exposure to fumigators and bystanders resulting from the fumigation of a mill with sulfuryl fluoride. Atmospheric concentrations of sulfuryl fluoride for persons re-occupying the mill were also monitored once aeration had been completed.

Methods:

Fumigation: The mill selected for this study was at Hedwigsburg, Germany and the fumigation was undertaken by a registered fumigation company (Binker Materialschutz). The preparation of mills and the dosage calculation for fumigation was as described for study by Perkins, 2002 (Study No. 1). During fumigation and aeration, the internal concentration within the mill was monitored as described for Study No. 1. The internal measurements were used to confirm the target application rate (*Ct*) has been reached.

In total, 16 cylinders of sulfuryl fluoride were introduced over the period of 19:00 hrs on the 3 May 2002 to 03:00 hrs on 4 May 2002 (8 hrs). The mill remained under fumigation until 15:00 hrs on 4 May 2002 (20 hrs), when the *Ct* was calculated to have reached 1484 g.hr/m^3, On reaching this value, the aeration process was started and the process continued until 06:30 hr on 5 May 2002, when it was confirmed that sulfuryl fluoride concentration in the building were ≤5 ppm.

Aeration: The aeration procedure was started at 15:10 h and was based on using three internal fans with external chimneys to push air out of the mill. These were switched off when the mill was entered at 20:08 h by fumigators wearing SCBA to turn on the mill air handling system. Additional airflow through the building was achieved by opening at least two windows in the stairway.

Worker activities: There were three separate activities covered in this mill fumigation. The first monitored activities were associated with the introduction of the fumigant gas into the mill structure. This task included moving the cylinders, weighing the cylinders, removing the protective bonnet from the cylinders, connecting and disconnecting the shooting-lines from the cylinders and opening the cylinders to introduce the fumigant.

The second monitored activity involved the aeration of the structure following the fumigation. These activities involved starting the aeration fans, unsealing the aeration plastic ducts, removing external plastic sheeting used in sealing, and opening doors/windows from the outside of the structure. These activities were conducted external to the mill.

The third monitored activity involved entering the mill once it had been declared clear by the fumigators and removing all the equipment associated with the introduction of the fumigant and stripping the mill of all the sealing material (plastic sheeting/tape etc) used to retain the fumigant within the mill.

Inhalation exposure monitoring (worker exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). The nominal flow rates used in this study were 100 mL/min for 1 to 4 hr sampling and 50 mL/min for 8 hrs sampling periods.

Atmospheric sampling (bystanders exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). Sampling periods during the introduction and holding of the sulfuryl fluoride gas in the structure were approximately 8 hrs (at 50 L/minute or approximately 24 L of air). During the aeration phase, one hour and four hour sampling was undertaken. Flow rates of around 100 mL/minute (or approximately 6 L of air) were used for 1-hr specimens and 50 mL/minute (or approximately 12 L of air) were used for 4-hr specimens.

Measurement of re-entry worker exposure: Once the mill had been declared clear for re-entry, air samplers were positioned on various floors within the mill building and run for three nominal eight hour periods. A single sample tube was used at each location. Each charcoal tube was removed and replaced with a fresh tube at the end of each specific monitored period. Samples were collected using a flow rate of 50 mL/min.

Travel/field recovery: Travel spikes (to show degradation of sulfuryl fluoride during travel) and field spikes (to demonstrate retention of sulfuryl fluoride on the tube under experimental sampling conditions) were prepared at a US laboratory prior to the start of the study as it was not possible to fortify these under field conditions.

Sample analysis: The method of analysis was as described by Perkins, 2002 (Study No. 1).

Results:

Travel/field recovery: Procedural recovery samples (see table below) demonstrated acceptable recovery of sulfuryl fluoride for the method of analysis.

Summary of recovery of sulfuryl fluoride

Fortification level	µg sulfuryl fluoride / sample added	µg sulfuryl fluoride / sample found	Percent recovery
[a]175 µg spike (LOD)	1.75	1.64	93
[b]3.5 µg spike (LOQ)	3.5	2.54-4.12	72-118
50 µg spike	50.16	39.1-52.1	78-104
500 µg spike	501.6	365-453	73-90
1000 µg spike	1003.2	744-1016	74-101

[a]This level used only for qualitative purposes.

[b]Target LOQ was not achieved. LOQ calculated at 4.89 µg sulfuryl fluoride/tube.

Analysis of the 'transit specimen' indicated that no significant losses occurred when the field spikes were run with the study air samplers (recovery 74%-100%) or in the case of the travel spikes (recovery 73%-100%) during the rest of the procedures covered by the study prior to analysis (i.e. shipment and storage). There was no evidence of breakthrough of sulfuryl fluoride from the front to the back segments of the absorbed media.

The calculated study LOQ was 4.89 µg of sulfuryl fluoride per sample and the calculated study LOD was 1.47 µg sulfuryl fluoride per sample. All residue values equivalent to or less than the LOD were classified as "not detected" (ND).

Internal mill concentrations of sulfuryl fluoride: A Ct of 1484 g.hr/m^3 was achieved over 20 hrs fumigation period. Once the mill had reached its initial maximum concentration of 94 g/ m^3, the internal concentration declined to 60 g/ m^3 during the fumigation phase. This equates to an internal concentration of 14, 000 to 20,000 ppm. The half-life (loss) time of approximately 16 hrs suggests that the mill was effectively sealed during fumigation. The mill was aerated over a 15.5 hrs period, after which the mill was declared clear for re-occupancy.

Fumigant (operator) exposure: The fumigators handled and released product from 16 cylinders into the mill, which corresponds to 893 kg of sulfuryl fluoride. Over the initial four hr period, workers undertaking the introduction of gas or monitoring inside the exclusion zone, were exposed to atmospheric concentrations of sulfuryl fluoride of between 0.35 ppm to 0.42 ppm (see table below). During the following four hrs, workers undertaking the introduction of gas or monitoring inside the exclusion zone, workers were exposed to atmospheric concentrations of sulfuryl fluoride of between 1.12 ppm to 1.73 ppm. These results gave an equivalent 8-hr TWA atmospheric sulfuryl fluoride concentration between 0.8 ppm and 1.06 ppm for this task.

During the aeration phase, the internal concentration of the mill was reduced from around 50,000 mg/m^3 to 20 mg/m^3 (5 ppm). Tasks undertaken at the start of aeration involving setting up and connecting the aeration fans and the removal of external plastic sealing from the roof, gave exposure to atmospheric concentrations of sulfuryl fluoride ranging from 1.67 ppm to 3.07 ppm over a period of up to 203 minutes. This equates to an 8 hr TWA of 0.71 ppm to 1.13 ppm. Once the mill was declared <5ppm, two workers were monitored for task associated with further aeration procedure such as setting up and operating fans on non-accessible areas of the structure, removing equipment from the mill and removing internal sealing materials. These procedures gave exposure to atmospheric concentrations of sulfuryl fluoride ranging from 0.46 to 2.41 ppm over a period of up to 240 minutes. Once the workers had completed their task and assuming that no additional exposure occurred, the 8 hr TWA would equate to 0.21 to 1.21 ppm.

Summary of worker exposure

Date (Sampling period)	Action undertaken	Time exposed (min)[a]	TWA concentration of sulfuryl fluoride (ppm)[b]	
			Task	8 hr
Fumigation				
3/5/2002 (18:54-22:52)	Operator 1 Shooting gas – 8 cylinders opened & monitoring inside exclusion zone	238	0.35	1.06
3-4/5/2002 (22:50-02:57)	Operator 1 Shooting gas – 8 cylinders opened & monitoring inside exclusion zone	247	1.73	
3/5/2002 (18:54-22:59)	Operator 2 Shooting gas – 8 cylinders opened & monitoring inside exclusion zone	245	0.42	0.80
3-4/5/2002 (22:55-03:05)	Operator 2 Shooting gas – 8 cylinders opened & monitoring inside exclusion zone	250	1.12	
Aeration[c]				
4/5/2002 (1500-19:17)	Operator 1 Setting up and connecting the aeration fans and removal of external plastic sealing from the roof. General work and aeration on top of the mill-removing plastic sheeting	176	3.07	1.13
5/5/2002 (07:40-11:40)	Operator 1 Removing equipment and sealing from mill	240	2.41	1.21
4/5/2002 1500-19:46)	Operator 2 Setting up and connecting the aeration fans and removal of external plastic sealing from the roof. General work and aeration on top of the mill-removing plastic sheeting	203	1.67	0.71
5/5/2002 (08:25-12:05)	Operator 2 Removing equipment and sealing from mill	220	0.46	0.21

(a) Earliest and last recorded time for period calculations.
(b) Air concentration (ppm) x (sampling period)+Air concentration (ppm)x(sampling period)/480).
(c) Each action undertaken during aeration occurred within a separate 8 hr period, therefore the 8 hr TWA was calculated by multiplying the concentration by the sampling period, divided by 480 (8x60 minutes).

Bystander exposure: During the fumigation and aeration phases, the external atmospheric concentrations were determined at distances between 5 m and 75 m from the mill (see table below). The atmospheric concentration of sulfuryl fluoride decreased rapidly in all directions from the mill during both the fumigation and aeration phases. Whilst the mill was undergoing fumigation, the majority of measurements were either Non Detectable or <LOQ (i.e. 0.05 ppm). The highest external sulfuryl fluoride concentration (3.82 ppm) was recorded after an initial 4 hr period of aeration for a 4 hr sample taken at 10 m sampling point.

Summary of air concentration of sulfuryl fluoride with distance from the mill (4 and 8 hr TWA during aeration)

		Pre Fum	Fumigation			Aeration [c]				
Sampling event		**1**	**2**	**3**	**4**	**14**	**15**	**16**	**17**	**18**
Timing (hrs)			**0-8**	**8-16**	**16-20**	**0-4**	**4-8**	**8-12**	**12-20**	**20-28**
Location	**Distance (m)**		**Sulfuryl fluoride (ppm) (nominal 8 and 4 hr TWA)[a]**			**Sulfuryl fluoride (ppm) (nominal 4 and 8 hr TWA)[b]**				
S1	5	ND	ND	ND	ND	ND	<LOQ	<LOQ	ND	ND
S6	5		0.50	1.90	0.70	0.61	0.08	ND	ND	ND
S11	5		0.30	2.06	1.27	3.35	0.42	ND	ND	ND
S16	5	ND	0.11	2.96	0.80	0.98	0.08	ND	ND	ND
S2	10	ND	0.62	ND	ND	<LOQ	ND	<LOQ	ND	ND
S7	10		0.06	0.09	<LOQ	ND	<LOQ	ND	ND	ND
S12	10		0.31	1.80	1.09	3.82	0.49	ND	ND	ND
S17	10	ND	ND	0.26	0.12	0.05	0.05	ND	ND	ND
S3	25		0.09	ND	ND	ND	ND	ND	ND	ND
S8	25	ND	0.06	0.13	<LOQ	ND	ND	ND	ND	ND
S13	25		0.36	0.93	0.85	1.69	0.39	ND	ND	ND
S18	25	ND	<LOQ	<LOQ	ND	<LOQ	<LOQ	ND	ND	ND
S4	50	ND	<LOQ	ND	ND	<LOQ	ND	ND	ND	ND
S9	50		0.18	0.16	<LOQ	ND	ND	ND	ND	ND
S14	50		0.05	0.46	0.32	0.74	0.17	ND	ND	ND
S19	50	ND	ND	ND	ND	<LOQ	<LOQ	ND	ND	ND
S5	75		ns	ND	ND	ND	ND	ND	ND	ND
S10	75		ND	ns	Ns	ND	<LOQ	ND	ND	ns
S15	75		ND	0.33	0.27	0.21	0.16	ND	ND	ND
S20	42		0.23	0.38	<LOQ	0.22	<LOQ	ND	ND[pf]	ND

(a) ND = non detected above LOD of 0.02 ppm; data reported as <LOQ indicates values below LOQ of 0.05 ppm. n/s = no sample taken; pf = pump failure, sampler not operating properly.

The overall sulfuryl fluoride concentrations in the atmosphere around the mill during fumigation and aeration are summarised in the table below, expressed as 24 hrs TWA for each direction and distance from the mill. In addition, an overall directional average for each direction and multi-directional average for a specific distance is presented. The maximum 24-hr uni-directional TWA values were 1.54 ppm (5 m sampling point) during fumigation and 0.10 ppm (10 m sampling point) during aeration. The maximum 24-hr multi-directional TWA values were 0.97 ppm (5 m sampling point) during fumigation and 0.05 ppm (5 & 10 m sampling points) during aeration. The 24-hr multi-directional/multi-distance TWA were 0.39 ppm during fumigation and 0.04 ppm during aeration.

Summary of 24 hr TWA concentrations of sulfuryl fluoride in the air around a fumigated mill

	Sulfuryl fluoride – 24 hr TWA -ppm (Period 1-Fumigation, Timings 2-4, 14, 15)[(a)]						**Sulfuryl fluoride – 24 hr TWA -ppm (Period 2-aeration, Timings 15-18)**					
Distance (m)	**North**	**East**	**South**	**West**	**SE[b]**	**Multi-directional**	**North**	**East**	**South**	**West**	**SE[b]**	**Multi-directional**
5	(0.02)	1.01	1.54	1.30		**0.97**	(0.06)	0.06	0.09	0.03		**0.05**
10	0.23	0.07	1.50	0.12		**0.48**	(0.05)	(0.04)	0.10	0.03		**0.05**
25	0.04	0.08	0.85	(0.09)		**0.26**	(0.02)	(0.04)	0.08	(0.04)		**0.04**
50	(0.06)	0.13	0.34	(0.03)	0.25	**0.14**	(0.02)	(0.02)	0.05	(0.04)	(0.02)	**0.03**
75	(0.05)	(0.02)	0.20			**0.09**	(0.02)	(0.04)	0.05			**0.04**
Directional Average	**0.08**	**0.26**	**0.89**	**0.39**	**0.25**	**0.39**	**(0.04)**	**0.03**	**0.07**	**0.03**	**(0.02)**	**0.04**

(a) Timing 15 is prorated between both 24 hr periods. (b) Actually located at 42 m.
All results in parenthesis are based on averaging either Non Detected and/or 50% of the LOQ. The difference in the numerical values reflects the differing LOQ and ND values associated with different sampling duration/volumes.

Re-entry worker Exposure: After the mill had been declared clear (<5 ppm sulfuryl fluoride), sulfuryl fluoride concentration were measured within the mill over a period of 24 hrs (three 8 hrs intervals) (see table below). The sulfuryl fluoride concentration in the mill varied from <LOQ to 1.28 ppm, depending on the location within the mill and the period after the mill had declared clear. The average concentration within the mill was observed to decline with the post clearance time from 0.67 ppm (8 hrs) to 0.33 ppm (16 hrs) and 0.19 ppm at 24 hrs.

Sulfuryl fluoride concentrations (ppm) measured inside the mill after aeration

Location	Timings		
	Post-aeration (0-8 hr)	**Post-aeration (8-16 hr)**	**Post-aeration (16-24 hr)**
1st floor	0.39	0.42	0.28
2nd floor	1.28	0.53	0.32
3rd floor	0.31	0.10	<LOQ
4th floor	0.57	0.20	0.06
5th floor	0.66	0.25	0.15
6th floor	0.91	0.33	0.13
5th floor	0.56	0.46	0.36
Mill average	**0.67**	**0.33**	**0.19**

Summary:

This study was conducted to determine the potential exposure to fumigators and bystanders resulting from the fumigation of a mill with sulfuryl fluoride. Atmospheric concentrations of sulfuryl fluoride for persons re-occupying the mill were also monitored, after aeration had been completed.

A Ct of 1484 g.hr/m^3 was achieved over 20 hrs fumigation period. Once the mill had reached its initial maximum concentration of 94 g/ m^3, the internal concentration declined to 60 g/ m^3 during the fumigation phase. This equates to an internal concentration of 14, 000 to 20,000 ppm. The half-life (loss) time of approximately 16 hrs suggests that the mill was effectively sealed during fumigation.

The fumigators handled and released product from 16 cylinders into the mill, which corresponds to 893 kg of sulfuryl fluoride. Over the initial four hr period, workers undertaking the introduction of gas or monitoring inside the exclusion zone, were exposed to atmospheric concentrations of sulfuryl fluoride of between 0.35 ppm to 0.42 ppm (see table below). During the following four hrs, workers undertaking the same activity were exposed to atmospheric concentrations of sulfuryl fluoride of between 1.12 ppm to 1.73 ppm. These results gave an equivalent 8-hr TWA atmospheric sulfuryl fluoride concentration between 0.8 ppm and 1.06 ppm for this task.

Tasks undertaken at the start of aeration involving setting up and connecting the aeration fans and the removal of external plastic sealing from the roof, gave exposure to atmospheric concentrations of sulfuryl fluoride ranging from 1.67 ppm to 3.07 ppm over a period of up to 203 minutes. This equates to an 8 hr TWA of 0.71 ppm to 1.13 ppm. Further aeration procedure such as setting up and operating fans on non-accessible areas of the structure, removing equipment from the mill and removing internal sealing materials, gave exposure to atmospheric concentrations of sulfuryl fluoride ranging from 0.46 to 2.41 ppm over a period of up to 240 minutes. This equates to an 8 hr TWA of 0.21 to 1.21 ppm.

During the fumigation and aeration phases, the atmospheric concentration of sulfuryl fluoride decreased rapidly in all directions from the mill during both the fumigation and aeration phases. Whilst the mill was undergoing fumigation, the majority of measurements were either Non Detectable or <LOQ (i.e. 0.05 ppm). The highest external sulfuryl fluoride concentration (3.82 ppm) was recorded after an initial 4 hr period of aeration for a 4 hr sample taken at 10 m sampling point. The maximum 24-hr uni-directional TWA values were 0.15 ppm (10 m sampling point) during fumigation and 0.37 ppm (10 m sampling point) during aeration. The maximum 24-hr multi-directional TWA values were 0.07 ppm (10 m sampling point) during fumigation and 0.18 ppm (5 m sampling point) during aeration. The 24-hr multi-directional/multi-distance TWA were 0.05 ppm during fumigation and 0.15 ppm during aeration.

After the mill had been declared clear, sulfuryl fluoride concentration were measured within the mill over a period of 24 hrs. The average concentration within the mill was observed to decline with the post clearance time from 0.67 ppm (8 hrs) to 0.33 ppm (16 hrs) and 0.19 ppm at 24 hrs.

5. Perkins, J.M. (2002c): Determination of atmospheric concentrations of sulfuryl fluoride following fumigation of a mill using Profume–Italy 2001. Study Plan No: 010073, Report No: GHE-P-9902, Unpublished Report date: 25 July, 2002. Dow AgroSciences.

Test Compound:	Vikane Gas Fumigant (99.8% purity)-It is stated that this will be sold as Profume for the fumigation of mills.
Batch:	OC16160101
Study Duration:	The study plan was approved on 12 July 2001 and the study was completed on 25 July 2002.
Test Facilities:	The trial site was a mill in Corato, Italy and field phase was conducted at Dow AgroSciences, Letcombe Laboratory, Wantage, UK. The sulfuryl fluoride determination was conducted at Minnesota Valley Testing Laboratories, inc (MVTL), New Ulm, MN, USA.
GLP & QA:	Yes
Guidelines:	US EPA Pesticide Assessment Guidelines (Subdivision U), draft OECD Guidance Document-TG\95.88, 1995-Conduct of field studies of exposure to pesticides in use, GIFAP technical monograph-14 April 1990-Monitoring studies in the assessment of field worker exposure to pesticides, and OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides during Agricultural Application, 1997.

***Objective*:** The objective of this study was to determine the potential exposure to fumigators and bystanders resulting from the fumigation of a mill with sulfuryl fluoride.

Methods:

Fumigation: The mill selected for this study was at Corato, Italy and the fumigation was undertaken by a registered fumigation company (Vitillo Liberato). The preparation of mills and the dosage calculation for fumigation was as described for study by Perkins, 2002 (Study No. 1). During fumigation and aeration, the internal concentration within the mill was monitored as described for Study No. 1. The internal measurements were used to confirm the target application rate (*Ct*) has been reached. In total, 32 cylinders of sulfuryl fluoride were introduced over the period of 07:22 hrs to 11:36 hrs on the 28 July 2001. The mill remained under fumigation until 06:15 hrs on 29 July 2001 (23 hrs), when the *Ct* was calculated to have reached the target of 1300 g.hr/m^3. The half-life over this phrase was calculated to be around 15 hrs. On reaching this value, the aeration process was started.

Aeration: The aeration procedure started on 29 July at 06:15 hrs and was based on using two internal fans with external chimneys to push air out of the mill. After around 10 hrs of aeration, internal concentrations in the majority of the mill were <5 ppm, however localised concentrations of 5 to 10 ppm were detected. The study authors report that they were unable to further reduce these localised concentrations over the next 8 hrs due to a failure with the mill air handling system. The aeration phase continued overnight finishing at approximately 09:00 hrs on 39 July 2001 (total aeration time of around 27 hrs). As this extended period of aeration was considered atypical by the applicant, measurements for workers clearing the mill of fumigation equipment and internal air measurements post re-occupation were no taken.

Worker activities: The activity monitored in this study was the introduction of sulfuryl fluoride gas into the structure and was similar to as described for study by Perkins, 2002 (Study No. 1). This included moving the cylinders, removing the protective bonnet from the cylinders, connecting and disconnecting the shooting-lines from the cylinders and opening to introduce the fumigant.

Inhalation exposure monitoring (worker exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). The nominal flow rates used in this study were 100 mL/min for 1 hr and 4 hr sampling periods and 50 mL/min for sampling periods greater than 4 hrs (to a maximum of 8 hrs).

Atmospheric sampling (bystanders exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). Sampling periods during the introduction and holding of the sulfuryl fluoride gas in the structure were approximately 8 hrs (at 50 L/minute or approximately 24 L of air). During the aeration phase, two sampling tubes were used at each static sampling so that one hr and four hr TWA samples could be collected. Flow rates of around 100 mL/minute (or approximately 6 L of air) were used for 1-hr specimens and 100 mL/minute (or approximately 12 L of air) were used for 2-hr specimens.

Travel/field recovery: Travel spikes (to show degradation of sulfuryl fluoride during travel) and field spikes (to demonstrate retention of sulfuryl fluoride on the tube under experimental sampling conditions) were prepared at a US laboratory prior to the start of the study as it was not possible to fortify these under field conditions.

Sample analysis: The method of analysis was as described by Perkins, 2002 (Study No. 1).

Results:

Travel/field recovery: Procedural recovery samples (see table below) demonstrated acceptable recovery of sulfuryl fluoride for the method of analysis.

Summary of recovery of sulfuryl fluoride

Fortification level	µg sulfuryl fluoride / sample added	µg sulfuryl fluoride / sample found	Percent recovery
[a]175 µg spike (LOD)	1.75	1.08	62
[b]3.5 µg spike (LOQ)	3.5	2.65-4.25	76-120
50 µg spike	50.16	36.8-53.3	73-106
500 µg spike	501.6	389.8-435.8	77-87
1000 µg spike	1003.2	785-941	78-94

[a]This level used only for qualitative purposes.

[b]Target LOQ was not achieved. LOQ calculated at 5.82 µg sulfuryl fluoride/tube.

Analysis of the 'transit specimen' indicated that no significant losses occurred when the field spikes were run with the study air samplers (recovery 76%-140%) or in the case of the travel spikes (recovery 55%-93%) during the rest of the procedures covered by the study prior to analysis (i.e. shipment and storage). There had been some breakthrough of sulfuryl fluoride from the front section of the tube, representing 4% and 3% respectively of the spiked amount. The applicant concluded that the breakthrough was not significant and only the front sections of the exposure samples were analysed.

The calculated study LOQ was 5.82 µg of sulfuryl fluoride per sample and the calculated study LOD was 1.47 µg sulfuryl fluoride per sample. As the calculated LOQ was above the target LOQ, the calculated LOQ was used to report the study results. All residue values equivalent to or less than the lowest validated level were classified as "not detected" (ND).

Internal mill concentrations of sulfuryl fluoride: A Ct of 1387 g.hr/m^3 was achieved over 27 hrs fumigation period. Once the mill had reached its initial maximum concentration of 85 g/ m^3, the internal concentration decreased slowly. The half-life (loss) time of approximately 15 hrs suggests that the mill was effectively sealed during fumigation. The mill was aerated over a 27 hrs period, after which the mill was declared clear for re-occupancy. The study authors' reports that the mills air handling system could not be started after the initial 10 hrs aeration period and this contributed to the total time taken to aerate the mill.

Fumigant (operator) exposure: The fumigators handled and released product from 32 cylinders into the mill, which corresponds to 1767 kg of sulfuryl fluoride. Over the initial approximately 2.7 hrs period, workers undertaking the introduction of gas or monitoring inside the exclusion zone, were exposed to atmospheric concentrations of sulfuryl fluoride of between 1.44 ppm to 1.76 ppm, equivalent to an 8-hr TWA atmospheric sulfuryl fluoride concentration between 0.54 ppm and 0.57 ppm (see table below).

Summary of worker exposure during fumigation

Date	Action undertaken	Time exposed (min)	TWA concentration of sulfuryl fluoride (ppm)	
			Task	8 hr [a]
28/07/2001	Operator 1 Shooting gas – 8 cylinders opened & monitoring inside exclusion zone	163	1.44	0.54
28/07/2001	Operator 1 Shooting gas – 8 cylinders opened & monitoring inside exclusion zone	163	1.76	
28/07/2001	Operator 2 Shooting gas – 8 cylinders opened & monitoring inside exclusion zone	157	1.76	0.57
28/07/2001	Operator 2 Shooting gas – 8 cylinders opened & monitoring inside exclusion zone	157	1.70	

(a) 8 hr TWA values given are based on mean of two sample tubes and given prorate for duration.

During the aeration phase, the internal concentration of the mill was reduced from around 35,000 mg/m^3, in the majority of the mill, to approximately 20 mg/m^3 (5 ppm) within 10 hrs. However, localised concentrations in the mill ranging between 5 ppm and 10 ppm were detected after 10 hrs. The total aeration time to reduce all internal concentrations below 5 ppm was given as 27 hrs. The study authors' reports that the mills air handling system could not be started during the first 10 hrs

aeration period and this contributed to the total time taken to aerate the mill. The study authors considered the period of aeration unrepresentative of normal commercial practice and no measurements of workers clearing the mill of fumigation equipment or internal air measurements (re-entry exposures) were taken.

Bystander exposure: During the fumigation and aeration phases, the external atmospheric concentrations were determined at distances between 5 m and 75 m from the mill (see table below). The atmospheric concentration of sulfuryl fluoride decreased rapidly in all directions from the mill during both the fumigation and aeration phases. The data indicate that the low level concentrations of sulfuryl were detected around the mill during the fumigation phase. The concentration rapidly decreased on onset of the aeration phase with no detectable residues present after 8 hrs. The highest external sulfuryl fluoride concentration (3.62 ppm) was recorded during the second 8 hrs of fumigation for an 48 hr sample taken at 5 m sampling point.

Summary of air concentration of sulfuryl fluoride with distance from the mill

		Pre Fum	Fumigation			Aeration (			
Timings		1	2	3	4	17	18	19	20
Location	Distance (m)		Sulfuryl fluoride (ppm) (nominal 8 hr TWA)[a]			Sulfuryl fluoride (ppm) (nominal 4 hr TWA)[a]			
S1	5	<LOQ	1.22	1.17	3.3	1.4	0.09	n/s	n/s
S6	5	<LOQ	0.43	1.03	0.94	0.45	0.09	n/s	n/s
S11	5	<LOQ	0.9	0.98	0.22	<LOQ	<LOQ	n/s	n/s
S16	5	<LOQ	1.89	3.62	3.61	0.46	0.13	n/s	n/s
S2	10		0.31	0.59	2.22	1.21	0.07	ND	ND
S7	10		0.17	0.91	0.77	0.81	0.07	ND	ND
S12	10		0.35	0.53	0.2	<LOQ	<LOQ	ND	ND
S17	10		1.25	1.11	1.67	0.16	0.09	ND	ND
S3	25		0.13	0.26	0.8	0.2	0.07	ND	ND
S8	25		0.07	0.4	0.13	0.21	<LOQ	ND	ND
S13	25		0.26	0.57	0.16	<LOQ	0.07	ND	ND
S18	25		0.44	1.48	0.7	0.12	0.09	ND	ND
S4	50		<LOQ	0.19	0.27	<LOQ	ND	ND	ND
S9	50		<LOQ	0.29	0.1	0.46	ND	ND	ND
S14	50		<LOQ	0.48	0.17	<LOQ	ND	ND	ND
S19	50		0.72	0.58	0.22	<LOQ	ND	ND	ND
S5	75	<LOQ	<LOQ	0.14	0.17	ND	ND	ND	ND
S10	75	<LOQ	<LOQ	0.22	0.11	0.64	ND	ND	ND
S15	75	<LOQ	<LOQ	0.24	0.09	<LOQ	ND	ND	ND
S20	75	ND	0.32	0.31	0.21	<LOQ	ND	ND	ND

(a) ND = non detected above LOD of 0.02 ppm; data reported as <LOQ indicates values below LOQ of 0.07 ppm.
n/s = no sample taken;

The overall sulfuryl fluoride concentrations in the atmosphere around the mill during fumigation and aeration are summarised in the table below, expressed as 24 hrs TWA for each direction and distance from the mill. In addition, an overall directional average for each direction and multi-directional average for a specific distance is presented. The maximum 24-hr uni-directional TWA values were 2.73 ppm (5 m sampling point) during fumigation and 0.15 ppm (5 m sampling point) during aeration. The maximum 24-hr multi-directional TWA values were 1.52 ppm (5 m sampling point) during fumigation and 0.10 ppm (5 m sampling points) during aeration. The 24-hr multi-directional/multi-distance TWA were 0.65 ppm during fumigation and 0.05 ppm during aeration.

Summary of 24 hr TWA concentrations of sulfuryl fluoride in the air around a fumigated mill

	Sulfuryl fluoride – 24 hr TWA -ppm (Period 1-Fumigation, Timings 2-4, 17)[a]					Sulfuryl fluoride – 24 hr TWA -ppm (Period 2-aeration, Timings 17-20)[b]				
Distance (m)	**North**	**East**	**South**	**West**	**Multi-directional**	**North**	**East**	**South**	**West**	**Multi-directional**
5	1.92	0.77	0.65	2.73	**1.52**	0.13	0.10	0.03	0.15	**0.10**
10	1.10	0.64	0.33	1.32	**0.85**	0.06	0.06	0.02	0.08	**0.05**
25	0.38	0.20	0.30	0.78	**0.41**	0.03	0.03	0.03	0.05	**0.04**
50	0.15	0.19	0.20	0.51	**0.26**	(0.02)	0.03	0.02	0.06	**0.03**
75	0.10	0.21	0.11	0.31	**0.18**	(0.02)	0.03	0.02	0.07	**0.05**
Directiona Average	**0.73**	**0.40**	**0.37**	**1.13**	**0.65**	**0.05**	**0.05**	**0.05**	**0.08**	**0.05**

(a) 24 hr TWA contains 2 hrs contribution from sampling period 17.
(b) 24 hr TWA contains 2 hrs contribution from sampling period 17 and includes 10 hrs of non-monitored time. This period is assumed to have the same sulfuryl fluoride concentration as the last monitored period (i.e. Timing 20). The contribution from Timing 17 to each 24 hr period was adjusted for the distribution of the concentration over the hrs 1 and 2 compared to 3 and 4. All results in parenthesis are based on averaging either Non Detected and/or 50% of the LOQ. The difference in the numerical values reflects the differing LOQ and ND values associated with different sampling duration/volumes.

Summary:

This study was conducted to determine the potential exposure to fumigators and bystanders resulting from the fumigation of a mill with sulfuryl fluoride. Atmospheric concentrations of sulfuryl fluoride for persons re-occupying the mill were also monitored, after aeration had been completed.

A Ct of 1387 g.hr/m^3 was achieved over 27 hrs fumigation period. Once the mill had reached its initial maximum concentration of 85 g/ m^3, the internal concentration decreased slowly. The half-life (loss) time of approximately 15 hrs suggests that the mill was effectively sealed during fumigation

The fumigators handled and released product from 32 cylinders into the mill, which corresponds to 1767 kg of sulfuryl fluoride. Over the initial 2.7 hrs period, workers undertaking the introduction of gas or monitoring inside the exclusion zone, were exposed to atmospheric concentrations of sulfuryl fluoride of between 1.44 ppm to 1.76 ppm, equivalent to an 8-hr TWA atmospheric sulfuryl fluoride concentration between 0.54 ppm and 0.57 ppm.

During the aeration phase, mills air handling system could not be started during the first 10 hrs aeration period and this contributed to the total time taken to aerate the mill (27 hrs). The study authors considered the period of aeration unrepresentative of normal commercial practice and no measurements of workers clearing the mill of fumigation equipment or internal air measurements (re-entry exposures) were taken.

During the fumigation and aeration phases, the external atmospheric concentrations were determined at distances between 5 m and 75 m from the mill. The atmospheric concentration of sulfuryl fluoride decreased rapidly in all directions from the mill during both the fumigation and aeration phases. The data indicate that the low level concentrations of sulfuryl were detected around the mill during the fumigation phase. The highest external sulfuryl fluoride concentration (3.62 ppm) was recorded during the second 8 hrs of fumigation for an 48 hr sample taken at 5 m sampling point. The maximum 24-hr uni-directional TWA values were 2.73 ppm (5 m sampling point) during fumigation and 0.15 ppm (5 m sampling point) during aeration. The maximum 24-hr

multi-directional TWA values were 1.52 ppm (5 m sampling point) during fumigation and 0.10 ppm (5 m sampling points) during aeration. The 24-hr multi-directional/multi-distance TWA were 0.65 ppm during fumigation and 0.05 ppm during aeration.

6. Barnekow, D.E., Byrne, D.E. and Foster, D.R. (2002a): Sulfuryl fluoride exposure potential to workers involved in the fumigation and aeration of mills using Profume– North America. Study Plan No: 010052, Report No: GH-C 5374, Unpublished Report date: 1 March 2002. Dow AgroSciences LLC.

Test Compound:	Vikane Gas Fumigant (99.8% purity)-It is stated that this will be sold as Profume for the fumigation of mills.
Batch:	TSN102173/OC16160101/TSN102633/OC16160101
Study Duration:	The study was initiated on 13 April 2001 and completed on 1 March 2002.
Test Facilities:	The study sites were located at Ligonier, IN, Hudson, KS and at Freeport, TX. The field phase was conducted at Paragon Research Services, 332 W. Fountain Way, Fresno, California and Dow AgroSciences LLC, 9339 Zionsville Rd, Indianapolis, Indiana. The sulfuryl fluoride determination was conducted at Minnesota Valley Testing Laboratories, inc (MVTL), New Ulm, MN, USA.
GLP & QA:	Yes
Guidelines:	US EPA (OPPTS 875.2500-Inhalation exposure)

***Objective*:** The objective of this study was to determine the potential exposure to sulfuryl fluoride during the fumigation and aeration of mills. Worker exposure was assessed during the introduction of the fumigant and during the aeration phase at the Ligonier and Hudson test sites and only the introduction of the fumigant at Freeport test site.

Methods:

Fumigation: The fumigation was conducted in three US commercial cereal grain mill structures at Ligonier, IN (Start of the West Milling Company-SOTW), Hudson, KS (Stafford Country Flour Milling Compnay-SCFM) and at Freeport, TX (American Rice, Inc-ARI) by professional pest control operators. The preparation of mills and the dosage calculation for fumigation was as described for study by Perkins, 2002 (Study No. 1). During fumigation and aeration, the internal concentration within the mill was monitored as described for Study No. 1. The internal measurements were used to confirm that the target application rate (*Ct*) of 1200 g.hr/m^3 has been reached.

For SOTW mill fumigation (mill volume of 14, 640 m^3), a total of 36 cylinders of sulfuryl fluoride were introduced and the *Ct* target of 1130 g.hr/m^3 was achieved over 29 hrs. For SCFM mill fumigation (mill volume of 3, 341 m^3), a total of 8 cylinders of sulfuryl fluoride were introduced and the *Ct* target of 1515 g.hr/m^3 was achieved over 29 hrs. For ARI mill fumigation (mill volume of 23, 645 m^3), a total of 21 cylinders of the planned 41 cylinders were introduced when the monitoring line revealed that sulfuryl fluoride had breached a seal separating the grain silos to be fumigated from the rest of the plant. From the exterior of the silos, workers wearing SCBA attempted to seal the leak but were unsuccessful. The fumigation was halted and aeration commenced after approximately 4.5 hrs into the fumigation. The calculated *Ct* was 263 g.hr/m^3.

Aeration: The aeration process was initiated by unsealing the exhaust stacks and remotely activating the exhaust fans. After approximately 10 minutes, an opening in the sealed structure was created, opposite to the exhaust fans to provide a fresh air intake into the negatively pressurised building. Over the course of the aeration process, additional doorways and windows were unsealed and opened. The mill air-handling system was also unsealed and activated to

facilitate the aeration procedure. After approximately 4 to 10 hrs after the start of aeration, the fumigated structures were tested for clearance at or below 5 ppm according to the proposed aeration procedure. Once the structure had been tested for clearance at or below 5 ppm, re-occupancy by the mill employees was allowed.

Worker activities: There were two worker activities monitored in this study. The first monitored activities were associated with the introduction of the fumigant gas into the mill structure. This task included moving the cylinders, removing the protective bonnet from the cylinders, connecting and disconnecting the shooting-lines from the cylinders and opening the cylinders to introduce the fumigant. The second monitored activity involved the aeration of the structure following the fumigation. The aerator activities involved starting the aeration fans, unsealing the aeration plastic ducts, removing external plastic sheeting used in sealing, and opening doors from the outside of the structure. These activities were conducted external to the mill. Both these activities were monitored at the SOTW and SCFM test sites. At the ARI, TX test site, monitoring was only done during fumigation.

Inhalation exposure monitoring (worker exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). The nominal flow rates used in this study were 100 mL/min. Sample periods were approximately 4 hrs (equivalent to approx. 24 L of air).

Atmospheric sampling (bystanders exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). Sampling periods during the introduction and holding of the sulfuryl fluoride gas in the structure and for the post clearance activities were approximately 8 hrs (at 50 L/minute or approximately 24 L of air). During the aeration phase, 1-hr and 4-hr TWA specimens were collected. Flow rates of around 100 mL/minute (or approximately 6 L of air) were used for 1-hr specimens and 100 mL/minute (or approximately 24 L of air) were used for 4-hr specimens. Atmospheric air sampler locations were selected around each mill structure. The sites geography dictated the actual distances and direction. Sampling commenced at the start of fumigation and continued until the post-clearance tasks had been completed.

Travel/field recovery: Travel spikes (to show degradation of sulfuryl fluoride during travel) and field spikes (to demonstrate retention of sulfuryl fluoride on the tube under experimental sampling conditions) were prepared at a US laboratory prior to the start of the study as it was not possible to fortify these under field conditions.

Sample analysis: The method of analysis was as described by Perkins, 2002 (Study No. 1).

Results:

Travel/field recovery:
Recoveries for the travel and field spikes are shown in the following table. For the recovery data for monitoring up to 4 hrs, high recoveries were seen at the 14.63 µg sulfuryl fluoride/sample spiking level (186% to 214%) for the ARI, TX mill. The authors have not provided any reasons for these results. All other travel recoveries were in the range 56% to 136%. With field spikes, as was found with the travel spikes, high recovery results were obtained at the 14.63 µg sulfuryl fluoride/sample spiking level. However, these spikes occurred at the SCFM mill, where these recoveries ranged from 183% to 210%. Recoveries for the 14.63 µg spikes at the other two mills ranged from 41% to 132%. For the recovery data for 4 hr and 8 hr monitoring periods, low recoveries for the SCFM mill were found at the 14.63 µg sulfuryl fluoride/sample spiking level

(42-43%). The authors have not provided any reasons for these results. All other travel recoveries were in the range 63% to 136%.

Summary of recovery data for trave and field spikes for different mills

Travel/field spikes	Recovery data for different mills (%)		
	SOTW	**SCFM**	**ARI, TX**
Data for monitoring periods up to 4 hrs			
Travel spikes	56-105	76-123	90-214
Field spikes	41-82	92-210	85-144
Data for 4 hr and 8 hr monitoring periods			
Travel spikes	73-111	42-136	62-127
Field spikes	54-84	65-101	68-118

Procedural recovery samples demonstrated acceptable recovery of sulfuryl fluoride for the method of analysis. The calculated LOD for the three mills was 1.31 µg sulfuryl fluoride/tube, which is below the target LOD. The target LOQ for the analytical method was not met. The LOQ for the analytical method was calculated to be 4.37 µg of sulfuryl fluoride per sample. Therefore, the target study LOD of 1.75 µg of sulfuryl fluoride per sample and the calculated LOQ of 4.37 µg sulfuryl fluoride per sample are used to report these study results.

Internal mill concentrations of sulfuryl fluoride: The final Ct of 1130, 1515 and 263 g.hr/m^3 at the SOTW, SCFM and ARI, TX mills was achieved when the fumigation was ceased. Half-life (loss) times observed during the fumigation of SCFM and ARI, TX mills were similar at 10.4 h and 12.6 h, respectively. The SOTW mill had a shorter half-loss time at 5.6 h. The aeration of the mills to an internal sulfuryl fluoride concentration equal to or less than 5 ppm took around 4 hr, 9 h and 4 h for the SOTW, SCFM and ARI, TX mills, respectively. The average equilibrium concentration for the SOTW, SCFM and ARI, TX mills was 116 g/m^3, 143 g/m^3 and 69 g/m^3, respectively.

Fumigant (operator) exposure: The total amount of sulfuryl fluoride introduced into the test mills was 2051 kg (36 cylinders), 455 kg (8 cylinders) and 1182 kg (21 cylinders) into the SOTW, SCFM and ARI, TX mills, respectively.

During fumigation, workers were exposed to atmospheric concentrations of sulfuryl fluoride ranged from 3.88 ppm to 4.35 ppm at SOTW mill, 9.2 ppm to 17.2 ppm at SCFM mill and 3.18 and 4.11 ppm at ARI, TX mill. These are equivalent to an 8-hr TWA atmospheric sulfuryl fluoride concentration between 1.94 ppm and 2.18 ppm at SOTW mill, 2.5 and 4.20 at SCFM mill and 0.84 and 1.28 ppm at ARI, TX mill. The geometric mean 8 hr TWA sulfuryl fluoride exposure for fumigators and aerators was 1.90 ppm and 0.37 ppm, respectively. The geometric mean 8 hr TWA sulfuryl fluoride exposure for all workers was 0.99 ppm. Two workers at the SCFM test site were involved in non-commercial practice of disconnection/reconnection of fumigant shooting lines. Exclusion of the two replicates from the these workers, reduced the geometric mean 8 hr TWA sulfuryl fluoride exposure for fumigators to 1.46 ppm, with the overall worker geometric mean 8 hr TWA sulfuryl fluoride exposure reducing to 0.74 ppm.

Summary of workers exposure during fumigation and aeration

Mill/replicate	Sampling period (min)	Air concentration (mg/m^3)	TWA concentration of sulfuryl fluoride (ppm)	
			Task	8 hr*
SOTW				
Fumigator	240	18.15	4.35	2.18
Fumigator	240	16.19	3.88	1.94
Aerator	158	2.84	0.68	0.22
Aerator	283	1.09	0.26	0.15
SCFM				
Fumigator	130	38.43	9.2**	2.5**
Fumigator	117	71.82	17.2**	4.20**
Aerator	416	11.75	2.82	1.26
Aerator	362	5.27	1.26	0.45
ARI, TX				
Fumigator	150	17.13	4.11	1.28
Fumigator	127	13.26	3.18	0.84

*Air concentration **(**mg/m^3) x (sampling period/480)/4.17 mg/m^3 (where 4.17 mg/m^3 = 1 ppm for sulfuryl fluoride

**Workers involved in non-commercial practice of disconnecting/reconnecting the same cylinder.

Summary:

Three commercial cereal grain mill structures were fumigated to determine the potential exposure to sulfuryl fluoride during the fumigation and aeration of mills. Worker exposure was assessed during the introduction of the fumigant and during the aeration phase at the SOTW and SCFM test sites and only the introduction of the fumigant at the ARI, TX test site.

The final Ct of 1130, 1515 and 263 $g.hr/m^3$ at the SOTW, SCFM and ARI, TX mills was achieved. Half-life (loss) times observed during the fumigation of SCFM and ARI, TX mills were 10.4 h and 12.6 h, respectively. The SOTW mill had a shorter half-loss time at 5.6 h. The aeration of the mills to an internal sulfuryl fluoride concentration equal to or less than 5 ppm took around 4 hr, 9 h and 4 h for the SOTW, SCFM and ARI, TX mills, respectively. The average equilibrium concentration for the SOTW, SCFM and ARI, TX mills was 116 g/m^3, 143 g/m^3 and 69 g/m^3, respectively.

The total amount of sulfuryl fluoride introduced into the test mills was 2051 kg (36 cylinders), 455 kg (8 cylinders) and 1182 kg (21 cylinders) into the SOTW, SCFM and ARI, TX mills, respectively. During fumigation, workers were exposed to an 8-hr TWA atmospheric sulfuryl fluoride concentration between 1.94 ppm and 2.18 ppm at SOTW mill, 2.5 and 4.20 at SCFM mill and 0.84 and 1.28 ppm at ARI, TX mill. The geometric mean 8 hr TWA sulfuryl fluoride exposure for fumigators and aerators was 1.90 ppm and 0.37 ppm, respectively. The geometric mean 8 hr TWA sulfuryl fluoride exposure for all workers was 0.99 ppm. Two workers at the SCFM test site were involved in non-commercial practice of disconnection/reconnection of fumigant shooting lines. Exclusion of the two replicates from the these workers, reduced the geometric mean 8 hr TWA sulfuryl fluoride exposure for fumigators to 1.46 ppm, with the overall worker geometric mean 8 hr TWA sulfuryl fluoride exposure reducing to 0.74 ppm.

7. Barnekow, D.E., Byrne, D.E. and Foster, D.R. (2002b): Determination of atmospheric concentrations of sulfuryl fluoride following fumigation of mills using Profume– North America 2000. Study Plan No: 000329, Report No: GH-C 5311, Unpublished Report date: 11 February 2002. Dow AgroSciences LLC.

Test Compound:	Vikane Gas Fumigant (99.8% purity)-It is stated that this will be sold as Profume for the fumigation of mills.
Batch:	TSN102173/OC16160101
Study Duration:	The study was initiated on 17 May 2000 and completed on 11 February 2002.
Test Facilities:	The study sites were located at Maxwell, CA and Ligonier, IN. The field phase was conducted at Paragon Research Services, 332 W. Fountain Way, Fresno, California and Dow AgroSciences LLC, 9339 Zionsville Rd, Indianapolis, Indiana. The sulfuryl fluoride determination was conducted at Minnesota Valley Testing Laboratories, inc (MVTL), New Ulm, MN, USA.
GLP & QA:	Yes
Guidelines:	US EPA (OPPTS 875.2500-Inhalation exposure)

***Objective*:** The objective of this study was to characterise the dissipation of sulfuryl fluoride from fumigated mills and determine the potential exposure to workers and bystanders. The study consisted of three phases: 1) fumigation, 2) aeration and 3) post-clearance.

Methods:

Fumigation: The fumigation was conducted in two US commercial cereal grain mill structures at Maxwell, CA (American Rice, Inc-ARI) and at Ligonier, IN (Start of the West Milling Company-SOTW) by professional pest control operators. The preparation of mills and the dosage calculation for fumigation was as described for study by Perkins, 2002 (Study No. 1). During fumigation and aeration, the internal concentration within the mill was monitored as described for Study No. 1. The internal measurements were used to confirm the target application rate (*Ct*) has been reached.

For SOTW mill fumigation, the contents of 31 cylinders of sulfuryl fluoride were introduced over the period of 09:15 hrs to 12:20 hrs on 24 June 2000. After evaluation of half-loss, an additional 5 cylinders were added to reach the targeted *Ct* within the target exposure period (36 hrs). The mill remained under fumigation until 14:10 hrs on 25 June (29 hrs), when the *Ct* was calculated to have reached 1653 g.hr/m^3. On reaching this value, the aeration process was started. Aeration of the mill to an internal sulfuryl fluoride concentration of < 5ppm took 6 hrs.

For ARI mill fumigation, introduction of the sulfuryl fluoride started at 19:11 on 26 May 2002 and was completed at 20:33 on 26 May 2000. The contents of 17 cylinders of sulfuryl fluoride were introduced into the mill. After evaluation of half-loss, an additional 7 cylinders were added to reach the targeted *Ct* within the target exposure period. The mill remained under fumigation until 05:19 hrs on 28 June 2000 (34 hrs), when the *Ct* was calculated to have reached 1345 g.hr/m^3. On reaching this value, the aeration process was started. Aeration of the mill to an internal sulfuryl fluoride concentration of < 5ppm was achieved in approximately 4 hrs.

Aeration: The aeration of the two mills was achieved in the manner described for study by Barnekow et al., 2002 (Study No. 6).

Worker activities: Two worker activities, as described for study by Barnekow et al., 2002 (Study No. 6), were monitored during the mill fumigation at the SOTW site. These were the introduction

of the sulfuryl fluoride fumigant into the structure and aeration of the structure following fumigation. No measurements of these activities were taken at the ARI site.

Inhalation exposure monitoring (worker exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). The nominal flow rates used in this study were 100 mL/min. Sample periods were approximately 4 hrs (equivalent to approx. 24 L of air).

Atmospheric sampling (bystanders exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). Sampling periods during the introduction and holding of the sulfuryl fluoride gas in the structure and for the post clearance activities were approximately 8 hrs (at 50 L/minute or approximately 24 L of air). During the aeration phase, 1-hr TWA specimen was collected. Flow rates of around 100 mL/minute (or approximately 6 L of air) were used for 1-hr specimens and 50 mL/minute (or approximately 24 L of air) were used for 8-hr specimens. Atmospheric air sampler locations were selected around each mill structure. The sites geography dictated the actual distances and direction. Sampling commenced at the start of fumigation and continued until the post-clearance tasks had been completed.

Travel/field recovery: Travel spikes (to show degradation of sulfuryl fluoride during travel) and field spikes (to demonstrate retention of sulfuryl fluoride on the tube under experimental sampling conditions) were prepared at a US laboratory prior to the start of the study as it was not possible to fortify these under field conditions.

Sample analysis: The method of analysis was as described for study by Perkins, 2002 (Study No. 1).

Results:

Travel/field recovery: Average recoveries for the ARI and SOTW travel spikes were 47%, 78%, 66% and 102%, 91%, 73% for the 15 µg, 100 µg and 1000 µg fortification levels. Recoveries of sulfuryl fluoride from all of the travel spikes averaged 76±20%. Field sample analytical results were not adjusted for travel spike recoveries. Average recoveries for the ARI and SOTW field spikes were 14%, 62%, 66% and 91%, 75%, 65% for the 15 µg, 100 µg and 1000 µg fortification levels. Recoveries of sulfuryl fluoride from all of the field spikes averaged 63±22%. Field sample analytical results were not adjusted for field spike recoveries.

Procedural recovery samples demonstrated acceptable recovery of sulfuryl fluoride for the method of analysis. The target LOD and LOQ were 1.75 µg of sulfuryl fluoride/tube and 3.50 µg of sulfuryl fluoride/tube, respectively. The calculated LOD and LOQ for the ARI mill were 1.69 µg of sulfuryl fluoride/tube and 5.63 µg of sulfuryl fluoride/tube, respectively. The calculated LOD and LOQ for the SOTW mill were 1.48 µg of sulfuryl fluoride/tube and 4.93 µg of sulfuryl fluoride/tube, respectively. Since the calculated LOD was less than the target LOD and the calculated LOQ was greater than the target LOQ, the target LOD and the calculated LOQ were used to report study results.

Internal mill concentrations of sulfuryl fluoride: The final Ct of 1345 g.hr/m^3 and 1653 g.hr/m^3 was achieved over 34 hrs and 29 hrs fumigation periods for the ARI and SOTW mills, respectively. The average equilibrium concentrations for the ARI and SOTW mills were 71 g/m^3 and 108 g/m^3, respectively. The half-life (loss) times observed during fumigation at ARI and SOTW mills were 9.0 hr and 6.5 hrs, respectively. Each mill was successfully aerated to an acceptable internal sulfuryl fluoride concentration in less than 6 hrs following fumigation.

Fumigant (operator) exposure: Fumigators handled and released product from 24 to 36 cylinders into the mills, which corresponds to 1374 kg to 2043 kg of sulfuryl fluoride, at ARI and SOTW mills, respectively. At SOW mill, the specific 8-hr TWA sulfuryl fluoride exposure ranged from 1.6 to 2.34 ppm for fumigators and 0.57 to 2.39 ppm for aeration workers. The geometric mean 8 hr TWA sulfuryl fluoride exposure for all workers was 1.51 ppm.

Summary of workers exposure during fumigation and aeration at SOTW mill

Replicate	Sampling period (min)	Air concentration (mg/m^3)	TWA concentration of sulfuryl fluoride (ppm)	
			Task	8 hr*
Fumigator	212	15.2	3.64	1.6
Fumigator	210	22.3	5.34	2.34
Aerator	347	31.8	7.62	2.39
Aerator	217	5.3	1.27	0.57

*Air concentration **(**mg/m^3) x (sampling period/480)/4.17 mg/m^3 (where 4.17 mg/m^3 = 1 ppm for sulfuryl fluoride

Bystander exposure: During the fumigation and aeration phases, the external atmospheric concentrations were determined at distances between 5 m and >76 m from the mills. The atmospheric concentration of sulfuryl fluoride decreased rapidly in all directions from the mills during both the fumigation and aeration phases.

ARI mill results: During the fumigation, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 0.89, 0.70, 0.45, 0.52, 0.21 and 0.07 ppm, for the approximate distances of 5, 9, 23, 46, 76, >76 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.47 ppm. During aeration, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 0.32, 0.27, 0.16, 0.15, 0.09 and 0.06 ppm, for the approximate distances of 5, 9, 23, 46, 76, >76 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the aeration phase were 0.17 ppm.

The evaluation notes that the recoveries for the field spikes at this site were low (all but one sample were between 20% and 56%). Results for the field samples have not been adjusted by the applicant for the low level of field recovery observed at this site.

SOTW mill results: During the fumigation, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 2.09, 1.30, 0.65, 0.41, 0.19 and 0.06 ppm, for the approximate distances of 5, 9, 23, 46, 76, >76 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.78 ppm. During aeration, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 0.16, 0.11, 0.08, 0.07, 0.06 and 0.04 ppm, for the approximate distances of 5, 9, 23, 46, 76, >76 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the aeration phase were 0.09 ppm.

Summary of 24 hr TWA multi-directional sulfuryl fluoride concentrations in the air around fumigated mills

Distance (m)	ARI Mill (Sulfuryl fluoride – 24 hr TWA –ppm)		SOTW Mill (Sulfuryl fluoride – 24 hr TWA –ppm)	
	Fumigation	Aeration	Fumigation	Aeration
5	0.89	0.32	2.09	0.16
9	0.70	0.27	1.30	0.11
23	0.45	0.16	0.65	0.08
46	0.52	0.15	0.41	0.07
76	0.21	0.09	0.19	0.06
>76	0.07	0.06	0.06	0.04
Average	**0.47**	**0.17**	**0.78**	**0.09**

Summary:

The objective of this study was to characterise the dissipation of sulfuryl fluoride from fumigated mills and determine the potential exposure to workers and bystanders.

The final Ct of 1345 g.hr/m^3 and 1653 g.hr/m^3 was achieved over 34 hrs and 29 hrs fumigation periods for the ARI and SOTW mills, respectively. The average equilibrium concentrations for the ARI and SOTW mills were 71 g/m^3 and 108 g/m^3, respectively. The half-life (loss) times observed during fumigation at ARI and SOTW mills were 9.0 hr and 6.5 hrs, respectively. Each mill was successfully aerated to an acceptable internal sulfuryl fluoride concentration in less than 6 hrs following fumigation.

Fumigators handled and released product from 24 to 36 cylinders into the mills, which corresponds to 1374 kg to 2043 kg of sulfuryl fluoride, at ARI and SOTW mills, respectively. At SOWT mill, the specific 8-hr TWA sulfuryl fluoride exposure ranged from 1.6 to 2.34 ppm for fumigators and 0.57 to 2.39 ppm for aeration workers. The geometric mean 8 hr TWA sulfuryl fluoride exposure for all workers was 1.51 ppm.

During the fumigation and aeration phases, the external atmospheric concentrations were determined at distances between 5 m and >76 m from the mills. The atmospheric concentration of sulfuryl fluoride decreased rapidly in all directions from the mills during both the fumigation and aeration phases. At ARI mill during the fumigation, the multi-directional 24 hr TWA sulfuryl fluoride concentrations during were 0.89, 0.70, 0.45, 0.52, 0.21 and 0.07 ppm, for the approximate distances of 5, 9, 23, 46, 76, >76 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase at this mill were 0.47 ppm. During aeration at ARI mill, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 0.32, 0.27, 0.16, 0.15, 0.09 and 0.06 ppm, for the approximate distances of 5, 9, 23, 46, 76, >76 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the aeration phase at this mill were 0.17 ppm.

At SOTW mill during the fumigation, the multi-directional 24 hr TWA sulfuryl fluoride concentrations during were 2.09, 1.30, 0.65, 0.41, 0.19 and 0.06 ppm, for the approximate distances of 5, 9, 23, 46, 76, >76 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase at this mill were 0.78 ppm. During aeration at SOTW mill, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 0.16, 0.11, 0.08, 0.07, 0.06 and 0.04 ppm, for the approximate distances of 5, 9, 23, 46, 76, >76 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the aeration phase at this mill were 0.09 ppm.

8. Barnekow, D.E., Byrne, D.E., Foster, D.R. and Robb, C.K. (2001): Determination of atmospheric concentrations of sulfuryl fluoride following fumigation of mills using Profume–North America 2001. Study Plan No: 010039, Report No: GH-C 5352, Unpublished Report date: 20 December 2001. Dow AgroSciences LLC.

Test Compound:	Vikane Gas Fumigant (99.8% purity)-It is stated that this will be sold as Profume for the fumigation of mills.
Batch:	TSN102173/OC16160101/TSN102633/PE13160101
Study Duration:	The study was initiated on 13 April 2001 and completed on 20 December 2001.
Test Facilities:	The study sites were located at Ligonier, IN, Hudson, KS and at Freeport, TX. The field phase was conducted at Paragon Research Services, 332 W. Fountain Way, Fresno, California and Dow AgroSciences LLC, 9339 Zionsville Rd, Indianapolis, Indiana. The sulfuryl fluoride determination was conducted at Minnesota Valley Testing Laboratories, inc (MVTL), New Ulm, MN, USA.
GLP & QA:	Yes
Guidelines:	US EPA (OPPTS 875.2500-Inhalation exposure)

***Objective*:** The objective of this study was to characterise the dissipation of sulfuryl fluoride from fumigated mills and determine the potential exposure to workers re-entering the mill after clearance and bystanders. The potential exposure to bystanders was determined by the measurement of atmospheric concentration of sulfuryl fluoride at various directions and distances away from the treated structures during the fumigation and aeration stages. The potential exposure to workers re-entering the mill after clearance was assessed during post-clearance phase with static air monitoring station placed in 5 locations in the mill.

Methods:

Fumigation: The fumigation was conducted in three US commercial cereal grain mill structures at Ligonier, IN (Start of the West Milling Company-SOTW), Hudson, KS (Stafford Country Flour Milling Compnay-SCFM) and at Freeport, TX (American Rice, Inc-ARI) by professional pest control operators. The preparation of mills and the dosage calculation for fumigation was as described for study by Perkins, 2002 (Study No. 1). During fumigation and aeration, the internal concentration within the mill was monitored as described for Study No. 1.

For SOTW mill fumigation (mill volume of 14, 640 m^3), a total of 36 cylinders of sulfuryl fluoride were introduced and the *Ct* target of 1130 g.hr/m^3 was achieved over 29 hrs and the aeration process was started at this time. For SCFM mill fumigation (mill volume of 3, 341 m^3), a total of 8 cylinders of sulfuryl fluoride were introduced and the *Ct* target of 1515 g.hr/m^3 was achieved over 29 hrs. At this time, the aeration process was started. For ARI mill fumigation (mill volume of 23, 645 m^3), a total of 21 cylinders of the planned 41 cylinders were introduced when the monitoring line revealed that sulfuryl fluoride had breached a seal separating the grain silos to be fumigated from the rest of the plant. From the exterior of the silos, workers wearing SCBA attempted to seal the leak but were unsuccessful. The fumigation was halted and aeration commenced after approximately 4.5 hrs into the fumigation. The calculated *Ct* was 263 g.hr/m^3.

Aeration: The aeration process was initiated by unsealing the exhaust stacks and remotely activating the exhaust fans. After approximately 10 minutes, an opening in the sealed structure was created, opposite to the exhaust fans to provide a fresh air intake into the negatively pressurised building. Over the course of the aeration process, additional doorways and windows were unsealed and opened. The mill air-handling system was also unsealed and activated to facilitate the aeration procedure. After approximately 4 to 10 hrs after the start of aeration, the

fumigated structures were tested for clearance at or below 5 ppm according to the proposed aeration procedure. Once the structure had been tested for clearance at or below 5 ppm, re-occupancy by the mill employees was allowed.

Air monitoring for re-entry workers: A Fumiscope was used to monitor sulfuryl fluoride concentrations inside the structure during the fumigation and aeration periods. The Interscan was used to determine instantaneous sulfuryl fluoride concentrations inside the mill from the time shortly after the internal mill concentrations reached the limit of detection of the Fumiscope until concentrations decreased below the limit of detection of the Interscan, at which point use of the Interscan was discontinued. In addition, charcoal sorbent tubes connected by flexible tubing to small battery operated SKC sampling pumps were used to continuously collect various TWA samples. TWA air monitoring commenced just before the introduction of the fumigant into the structure and continued until approximately 12 hrs post-clearance. Air sampling times were kept as close as possible to 1 hr (at 100 mL/min or approximately 6 L of air) and 4 or 8 hr ((at 100 mL/min or 50 mL/min, respectively, or approximately 6 L of air).

Air monitoring for bystanders: A series of air sampling sites were placed around the mill and external air sampling was scheduled with the thee phases of the structural fumigation procedure in mind: fumigation, aeration, and post-clearance. Fumigation sampling periods were collected on approximately 8 hr intervals during the introduction and holding of the sulfuryl fluoride gas in the structure. The aeration period was collected in both 1-hr and 4-hr intervals beginning with the start of the aeration procedure and end upon clearance of the mill. Post-clearance interval was collected for 8 hr starting after the sulfuryl fluoride concentrations in the mill were 5 ppm or less. In addition to the external air monitoring post-clearance, five monitoring stations were set-up inside the mill. Internal post-clearance air monitoring samples were collected in 4-hour intervals for three sequential periods for a total of 12 hrs of continuous monitoring.

Travel/field recovery: Travel spikes (to show degradation of sulfuryl fluoride during travel) and field spikes (to demonstrate retention of sulfuryl fluoride on the tube under experimental sampling conditions) were prepared at a US laboratory prior to the start of the study as it was not possible to fortify these under field conditions.

Sample analysis: The method of analysis was as described by Perkins, 2002 (Study No. 1).

Results:

Travel/field recovery: Average recoveries for the travel fortified controls for SOTW, SCFM and ARI, TX were 80%, 79%, 100% and 41%, 96%, 121% and 74%, 64%, 120% for the 15 µg, 100 µg and 1000 µg fortification levels, respectively. Recoveries of sulfuryl fluoride from all of the travel spikes averaged 86±26%. Field sample analytical results were not adjusted for travel spike recoveries. Average recoveries for the field exposed fortified controls for SOTW, SCFM and ARI, TX were 58%, 78%, 68% and 84%, 79%, 73% and 72%, 60%, 110% for the 15 µg, 100 µg and 1000 µg fortification levels, respectively. Recoveries of sulfuryl fluoride from all of the filed spikes averaged 77±214%. Field sample analytical results were not adjusted for field exposed spike recoveries.

Procedural recovery samples demonstrated acceptable recovery of sulfuryl fluoride for the method of analysis. The target LOD of 1.75 µg of sulfuryl fluoride/tube was used to report the study results for all three mills. The calculated LOQ of 3.57 µg of sulfuryl fluoride/tube for SOTW, 5.04

µg of sulfuryl fluoride/tube for SCFM and 2.21 µg of sulfuryl fluoride/tube for ARI, TX, were used to report the study results.

Internal mill concentrations of sulfuryl fluoride: Equilibrium concentrations (maximum sulfuryl fluoride concentration measured before decline) from the 4 Fumiscope monitoring locations ranged from 102-128 g/m^3, 105-159 g/m^3 and 52-80 g/m^3 for the initial fumigant introduction to the SOTW, SCFM and ARI, TX mills, respectively. The average equilibrium concentrations for the SOTW, SCFM, and ARI, TX mills was 116 g/m^3, 143 g/m^3 and 69 g/m^3, respectively. The final Ct products were 1130, 1515 and 263 g.hr/m^3 at the SOTW, SCFM and ARI, TX mills. The half-loss times of 5.6 hr, 10.4 hr and 12.6 hr were observed at SOTW, SCFM and ARI, TX mills, respectively. The average terminal (sulfuryl fluoride concentration just before initiation of aeration) sulfuryl fluoride concentration for the SOTW, SCFM, and ARI, TX mills was 2.8 g/m^3, 54 g/m^3 and 53 g/m^3, respectively. The aeration of the mills to an internal sulfuryl fluoride concentration equal to or less than 5 ppm took approximately 4 hr, 9 h and 4 hr for the SOTW, SCFM and ARI, TX mills, respectively.

Bystander exposure: During fumigation and aeration, the external atmospheric concentrations were determined at sampling distances of 5 m, 10 m, 25 m, 50 m, 80 m, and >80 m from the mill. The atmospheric concentration of sulfuryl fluoride diminished with increasing distance.

SOTW: During the fumigation, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 0.54, 0.38, 0.17, 0.28, 0.19 and 0.31 ppm, for the approximate distances of 5, 10, 25, 50, 76, >76 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.31 ppm. During aeration, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 0.04, 0.04, 0.04, 0.04, 0.05 and 0.05 ppm, for the approximate distances of 5, 10, 25, 50, 76, >76 m, respectively, from the mill. The multi-directional 24-h TWA sulfuryl fluoride concentrations during the aeration were equal to or less than 0.05 ppm for all distances from the mill.

SCFM: During the fumigation, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 0.59, 0.39, 0.23, 0.17, 0.17 and 0.12 ppm, for the approximate distances of 5, 10, 25, 50, 80, >80 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.28 ppm. During aeration, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 0.5, 0.04, 0.02, 0.02, 0.02 and 0.01 ppm, for the approximate distances of 5, 10, 25, 50, 80, >80 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.03 ppm.

ARI, TX: The multi-directional 24 hr TWA sulfuryl fluoride concentrations measured both during fumigation and aeration phases were 0.22, 0.13, 0.09, 0.11 and 0.12 ppm, for the approximate distances of 5, 10, 25, 50, 80, >80 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.13 ppm.

Summary of 24 hr TWA multi-directional sulfuryl fluoride concentrations in the air around fumigated mills

Distance (m)	SOTW Mill (Sulfuryl fluoride – 24 hr TWA-ppm)		SCFM Mill (Sulfuryl fluoride – 24 hr TWA-ppm)		ARI, TX Mill (Sulfuryl fluoride – 24 hr TWA –ppm)
	Fumigation	Aeration	Fumigation	Aeration	Fumiagtion
5	0.54	0.04	0.59	0.05	0.22
9	0.38	0.04	0.39	0.04	0.13 (at 10 m)
23	0.17	0.04	0.23	0.02	0.09 (at 25 m)
46	0.28	0.05	0.17	0.02	0.11 (at 50 m)
76	0.19	0.05	0.17	0.02	0.12 (at 80 m)
>76	0.31	0.05	0.12	0.01	--
Average	**0.31**	**0.04**	**0.28**	**0.03**	**0.13**

Internal post-clearance air monitoring: Analysis of the air monitoring samples collected post-clearance in the mills revealed that the highest 8-hr TWA value was approximately 5 ppm during the first 8 hr of monitoring in the SCFM mill on one floor. On average, the concentration of sulfuryl fluoride in the mills continued to decline over the monitoring period. The mill-wide 8-h TWA value was 0.31 ppm and 3.24 ppm for the SOTW and SCFM mills, respectively. Air samples collected during the subsequent 4-hr period showed a decline in sulfuryl fluoride concentration in the mills. The mill-wide 4-h TWA value was 0.29 ppm and 2.05 ppm for the SOTW and SCFM mills, respectively. An overall average 8-hr TWA sulfuryl fluoride concentration for both mills during the first 8-hr post-clearance was 1.77 ppm.

TWA concentrations of sulfuryl fluoride detected in the atmospheric air inside the mills

Mill	Sample location	Concentration of sulfuryl fluoride (ppm)	
		8-hr TWA	4-hr TWA
SOTW	1E	0.06	0.17
	2E	0.26	0.19
	3E	0.21	0.15
	4E	0.17	0.14
	5E	0.84	0.80
SCFM	1E	2.21	2.86
	2E	3.48	2.11
	3E	2.36*	1.91
	4E	4.85	2.75
	5E	3.32	0.58

*Missing sample analysis due to the loss of sample in the field. 8-hr TWA was calculated with the second 4-h period sample of the first 8-h of sampling.

Summary:

Three commercial cereal grain mills were fumigated to characterise the dissipation of sulfuryl fluoride from fumigated mills and determine the potential exposure to workers re-entering the mill after clearance and bystanders.

The final Ct products were 1130, 1515 and 263 g.hr/m^3 at the SOTW, SCFM and ARI, TX mills. The half-loss times of 5.6 hr, 10.4 hr and 12.6 hr were observed at SOTW, SCFM and ARI, TX mills, respectively. A total of 36 and 8 cylinders of sulfuryl fluoride were introduced and the *Ct* targets of 1130 and 1515 g.hr/m^3 was achieved over 29 and 29 hrs For SOTW and SCFM mills, respectively. For ARI, TX, 21 cylinders of the planned 41 cylinders were introduced when fumigation was halted due to an unstoppable leakage and aeration commenced after

approximately 4.5 hrs into the fumigation. The calculated *Ct* was 263 g.hr/m^3. The half-loss times of 5.6 hr, 10.4 hr and 12.6 hr were observed at SOTW, SCFM and ARI, TX mills, respectively. The aeration of the mills to an internal sulfuryl fluoride concentration equal to or less than 5 ppm took approximately 4 hr, 9 h and 4 hr for the SOTW, SCFM and ARI, TX mills, respectively.

During fumigation and aeration, the external atmospheric concentrations were determined at sampling distances of 5 m, 10 m, 25 m, 50 m, 80 m, and >80 m from the mill. The atmospheric concentration of sulfuryl fluoride diminished with increasing distance. At SOTW mill, the overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.31 ppm. The multi-directional 24-h TWA sulfuryl fluoride concentrations during the aeration were equal to or less than 0.05 ppm for all distances from the mill. At SCFM, the overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.28 ppm. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.03 ppm. At ARI, TX, the overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase was 0.13 ppm.

Analysis of the air monitoring samples collected post-clearance in the mills revealed that the highest 8-hr TWA value was approximately 5 ppm during the first 8 hr of monitoring in the SCFM mill on one floor. On average, the concentration of sulfuryl fluoride in the mills continued to decline over the monitoring period. The mill-wide 8-h TWA value was 0.31 ppm and 3.24 ppm for the SOTW and SCFM mills, respectively. The mill-wide 4-h TWA value was 0.29 ppm and 2.05 ppm for the SOTW and SCFM mills, respectively. An overall average 8-hr TWA sulfuryl fluoride concentration for both mills during the first 8-hr post-clearance was 1.77 ppm.

9. Barnekow, D.E., Byrne, S.L. and Foster, D.R. (2002): Determination of exposure potential to workers and atmospheric concentrations of sulfuryl fluoride during and following fumigation of mills using Profume–North America 2002. Study Plan No: 020039, Report No: GH-C 5465, Unpublished Report date: 26 June 2002. Dow AgroSciences LLC.

Test Compound:	Vikane Gas Fumigant (99.8% purity)-It is stated that this will be sold as Profume for the fumigation of mills.
Batch:	TSN102633/PE13160101
Study Duration:	The study was initiated on 23 April 2002 and completed on 26 June 2002.
Test Facilities:	The study site was located at Ligonier, IN. The field phase was conducted at Paragon Research Services, 332 W. Fountain Way, Fresno, California and Dow AgroSciences LLC, 9339 Zionsville Rd, Indianapolis, Indiana. The sulfuryl fluoride determination was conducted at Minnesota Valley Testing Laboratories, inc (MVTL), New Ulm, MN, USA.
GLP & QA:	Yes
Guidelines:	US EPA (OPPTS 875.2500-Inhalation exposure)

***Objective*:** The objective of this study was to characterise the dissipation of sulfuryl fluoride from fumigated mills and determine the potential exposure to workers and bystanders. The study consisted of three phases: 1) fumigation, 2) aeration and 3) post-clearance.

Methods:

Fumigation: The fumigation was conducted in a US commercial cereal grain mill structures at Ligonier, IN (Start of the West Milling Company-SOTW) by professional pest control operators.

The preparation of the mill and the dosage calculation for fumigation was as described for study by Perkins, 2002 (Study No. 1). During fumigation and aeration, the internal concentration within the mill was monitored as described for Study No. 1.

A total of 36 cylinders of sulfuryl fluoride were introduced into the mill, started at 19:04 on 10 May 2002 and completed at 00:15 on 11 May 2002. The mill remained under fumigation until 10:18 hrs on 11 May 2002 (15 hrs), the calculated *Ct* of 1629 g.hr/m^3 was achieved and the aeration process started at this time. An internal sulfuryl fluoride concentration of ≤ 1ppm was achieved in approximately 12 hrs.

Aeration: The aeration of the mill was achieved in the manner described for study by Barnekow et al., 2002 (Study No. 6). The study authors reports that, during the unsealing process, a flexible exhaust duct which was inadvertently pulled away from the main exhauts duct, could not be re-connected. As a result, aeration of the mill was condcuted with the exhaust release point at ground level and not from an elevated position as was intended.

Worker activities: Two worker activities, as described for study by Barnekow et al., 2002 (Study No. 6), were monitored during the mill fumigation at the SOTW site. One group of workers (fumigators) conducted the introduction of the sulfuryl fluoride fumigant into the structure, remotely activating the introduction of the fumigant into the mill. The second activity involved the aeration of the structure following the fumigation.

Inhalation exposure monitoring (worker exposure): Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). The nominal flow rates used in this study were 100 mL/min. Sample periods were approximately 4 hrs (equivalent to approx. 24 L of air).

Atmospheric sampling (bystanders exposure): Atmospheric air sampler locations were selected around each mill structure. The sites geography dictated the actual distances and direction. Sampling commenced at the start of fumigation and continued until the post-clearance tasks had been completed. Air was sampled in the manner as described for study by Perkins, 2002 (Study No. 1). Sampling periods during the introduction and holding of the sulfuryl fluoride gas in the structure and for the post clearance activities were approximately 8 hrs (at 50 L/minute or approximately 24 L of air). Specimens were also to be collected for the aeration phase of the mill fumigation. However, in view of the problems encountered on aerating the mill, the study authors reports that no results were obtained.

Measurement of re-entry worker exposure: Once the mill had been declared clear for re-entry (internal sulfuryl fluoride concentrations <5ppm), air samplers were positioned at various locations (5 locations) within the mill and run for three consecutive eight hour periods. Air was sampled using air sampling pumps with flow rates of either 50 or 100 mL/min. Air sampling intervals were kept as close as possible to 8 hr (at 50 ml/min or ~24 L of air).

Travel/field recovery: Travel spikes (to show degradation of sulfuryl fluoride during travel) and field spikes (to demonstrate retention of sulfuryl fluoride on the tube under experimental sampling conditions) were prepared at a US laboratory prior to the start of the study as it was not possible to fortify these under field conditions.

Sample analysis: The method of analysis was as described by Perkins, 2002 (Study No. 1).

Results:

Travel/field recovery: Average recoveries for the travel fortified controls were 57%, 62% and 91% for the 15 µg, 100 µg and 1000 µg fortification levels. Recoveries of sulfuryl fluoride from all of the travel spikes averaged 70±19%. Field sample analytical results were not adjusted for travel spike recoveries. Average recoveries for the field exposed fortified controls were 70%, 62%, and 84% for the 15 µg, 100 µg and 1000 µg fortification levels. Recoveries of sulfuryl fluoride from the entire field exposed fortified controls averaged 73±8%. Field sample analytical results were not adjusted for field spike recoveries.

Procedural recovery samples demonstrated acceptable recovery of sulfuryl fluoride for the method of analysis. The calculated LOD and LOQ for this study were 1.19 µg of sulfuryl fluoride and 3.98 µg of sulfuryl fluoride, respectively. The calculated LOD was less than the target LOD and the calculated LOQ was greater than the target LOQ. Therefore, the target LOD and the calculated LOQ for the mill of 1.75 µg of sulfuryl fluoride/tube and 3.98 µg of sulfuryl fluoride/tube, respectively, were used to report the study results.

Internal mill concentrations of sulfuryl fluoride: A Ct of 1626 g.hr/m^3 was achieved over 15 hrs fumigation periods. Equilibrium concentrations from the 6 Fumiscope monitoring locations ranged from 131 to 166 g/m^3, with an average equilibrium concentrations of 152 g/m^3. The average terminal sulfuryl fluoride concentrations at the end of the fumigation phase were 64 g/m^3. The half-life (loss) time observed during fumigation was 8.9 hrs. The mill was aerated in less than 12 hrs period, after which the mill was declared clear for re-occupancy.

Fumigant (operator) exposure: The fumigators handled and released product from either 15 or 20 cylinders into the mill, for a total production of 2003.05 kg of sulfuryl fluoride by two fumigators. The specific 8-hr TWA sulfuryl fluoride exposure ranged from 0.88 to 3.49 ppm for fumigators and 0.041 to 0.83 ppm for aeration workers (see table below). The geometric mean, 8 hr TWA sulfuryl fluoride exposure for fumigators and aeration workers was 0.97 and 0.18 ppm, respectively. The geometric mean, 8 hr TWA sulfuryl fluoride exposure for all workers was 0.42 ppm.

Summary of workers exposure during fumigation and aeration

Replicate	Sampling period (min)	Air concentration (mg/m^3)	8-hr TWA concentration of sulfuryl fluoride (ppm)
Fumigator	330	12.53	0.88
Fumigator	353	56.53	3.49
Aerator	188	8.792	0.83
Aerator	228	0.364	0.041

8 hr TWA sulfuryl fluoride (ppm) = Air concentration (mg/m^3) x (sampling period/480)/4.17 mg/m^3
(where 4.17 mg/m^3 = 1 ppm for sulfuryl fluoride

Bystander exposure: During the fumigation, the external atmospheric concentrations were determined at distances between 5 m and >75 m from the mill. The atmospheric concentration of sulfuryl fluoride diminished with increasing distance. During the fumigation, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 1.37, 0.52, 0.11, 0.15, 0.16 and 0.16 ppm, for the approximate distances of 5, 10, 25, 50, 77, >75 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation

phase were 0.41 ppm. No monitoring results were obtained from the aeration phase of the study due to a problem with aeration.

Internal post-clearance air monitoring: Analysis of the air monitoring samples collected post-clearance in the mill revealed that the highest 8-hr TWA value was approximately 0.66 ppm during the first 8 hr of monitoring (see table below). The mill-wide first 8 hr TWA value was 0.25 ppm. Air samples collected during two subsequent 8-h period show a general decline in sulfuryl fluoride concentration in the mill. The mill-wide 24-h TWA sulfuryl fluoride measured during that period was 0.16 ppm.

TWA concentrations of sulfuryl fluoride detected in the atmospheric air inside the mill

Sample location	Concentration of sulfuryl fluoride (ppm)	
	8-hr TWA	24-hr TWA*
1E	0.00	0.05
2E	0.66	0.30
3E	0.06	0.07
4E	0.14	0.11
5E	0.39	0.26

*24 hr TWA was calculated with the three consecutive 8 hr of sampling.

Summary:

The objective of this study was to characterise the dissipation of sulfuryl fluoride from fumigated mills and determine the potential exposure to workers and bystanders.

A Ct of 1626 g.hr/m^3 was achieved over 15 hrs fumigation periods. Equilibrium concentrations from the 6 monitoring locations within the mill ranged from 131 to 166 g/m^3, with average equilibrium concentrations of 152 g/m^3. The average terminal sulfuryl fluoride concentrations at the end of the fumigation phase were 64 g/m^3. The half-life (loss) time observed during fumigation was 8.9 hrs. The mill was aerated in less than 12 hrs period, after which the mill was declared clear for re-occupancy.

The fumigators handled and released product from either 15 or 20 cylinders into the mill, for a total production of 2003.05 kg of sulfuryl fluoride by two fumigators. The specific 8-hr TWA sulfuryl fluoride exposure ranged from 0.88 to 3.49 ppm for fumigators and 0.041 to 0.83 ppm for aeration workers. The geometric mean, 8 hr TWA sulfuryl fluoride exposure for fumigators and aeration workers was 0.97 and 0.18 ppm, respectively. The geometric mean, 8 hr TWA sulfuryl fluoride exposure for all workers was 0.42 ppm.

During the fumigation, the external atmospheric concentrations sulfuryl fluoride were determined at distances between 5 m and >75 m from the mill, the concentration diminished with increasing distance. During the fumigation, the multi-directional 24 hr TWA sulfuryl fluoride concentrations were 1.37, 0.52, 0.11, 0.15, 0.16 and 0.16 ppm, for the approximate distances of 5, 10, 25, 50, 77, >75 m, respectively, from the mill. The overall multi-directional-multi-distance 24 hr TWA sulfuryl fluoride concentrations during the fumigation phase were 0.41 ppm. No monitoring results were obtained from the aeration phase of the study due to a problem with aeration.

Analysis of the air monitoring samples collected post-clearance in the mill revealed that the highest 8-hr TWA value was approximately 0.66 ppm during the first 8 hr of monitoring. The

mill-wide first 8 hr TWA value was 0.25 ppm. Air samples collected during two subsequent 8-h period show a general decline in sulfuryl fluoride concentration in the mill. The mill-wide 24-h TWA sulfuryl fluoride measured during that period was 0.16 ppm.

10. Shurdut, B.A. (1995): Amended report for evaluation of concentrations of sulfuryl fluoride inside houses following fumigation with Vikane Gas Fumigant. Study Plan No: ECL-94013, Report No: ECL-94013 R, Unpublished Report date: 23 March 2002. DowElanco Ltd.

Test Compound:	Vikane Gas Fumigant (99 % purity)-
Batch:	IA18160101
Study Duration:	The study was initiated on 3 August 1994 and amended report was completed on 8 January 1994.
Test Facilities:	Global Human Exposure Assessment, DowElanco, 9330 Zionsville Rd, Indianapolis, IN, USA.
GLP & QA:	Yes
Guideline:	133-4.

***Objective*:** The objective of this study was to: (1) evaluate airborne concentrations of sulfuryl fluoride within houses following fumigation with Vikane Gas Fumigant and (2) assess potential exposures and subsequent health risks to residents re-entering structures following the required current aeration period.

Methods:

Fumigation: The study was conducted in 15 houses in Florida and California. All fumigations were performed by professional pest control operators as per label instructions. Once the structure was tarped and sealed by the fumigation tent crew, the sulfuryl fluoride was gravimetrically measured into the structure from the cylinder, which was located in the bed of the fumigation truck. Equilibrium concentrations of sulfuryl fluoride were determined with a Fumiscope.

Aeration: Aeration was initiated by opening the first tarpaulin seal. The structures were then aerated with all operable windows and doors opened, aided by the use of one or more fans, for a minimum of one hr. Following initial aeration, the houses were secured for the remainder of the 6 hr aeration period. This generally consisted of closing all doors and windows (which was motivated by the need to procure the security of the house when unoccupied) in single story structures and the opening of windows on the second floor of two story structures. The fumigation circulation fan remained on during this period and ceiling fans, if present, were also activated. Once the structure had been tested for clearance at or below 5 pm, the degree of ventilation used during the following 48 hrs monitoring period was independently determined by the investigator. Re-occupancy by the resident and other ancillary traffic through the monitored house was limited until all monitoring was complete.

Air monitoring: Air monitoring commenced soon after the first tarpaulin was opened. The Fumiscope and/or Miran was used to obtain terminal concentrations of sulfuryl fluoride within the structures immediately prior to tarpaulin removal. Once the first tarpaulin had been opened (T0), Miran gas analyser was used to determine instantaneous sulfuryl fluoride concentrations to approximately 24 hrs post-aeration (T0+30), at which point use of the MIRAN was discontinued. These measurements were taken either inside the structures by the co-investigators carrying the MIRAN and donning SCBA or outside the structures with a Miran unit connected to

tubing located in several of the rooms. This monitoring period represented time T0, which became reference point for all subsequent measurements taken at a given time.

In addition, charcoal sorbent tubes connected by flexible tubing to small battery operated sampling pumps were used to continuously collect 8 hr TWA samples. A total of 6 samples at each of three locations within the house were collected continuously from the time structure had been cleared at or below 5 ppm (designated as T0+6) to approximately 48 hrs or two days following clearance. Consequently, sorbent tube samples were only collected during that time period during which it was foreseeable that the resident could have re-occupied the phone. The tube was connected to a small battery operated flow pump through which air was drawn at a nominal flow rate of 50 mL/min. Air samples were collected for approximately 480 minutes.

Sample analysis: The method of analysis was as described for Perkins, 2002 (Study No. 1).

Results:

Laboratory/field recovery: Average recovery for the laboratory spikes was 91.1±2.48%, which agrees well with the method recovery of 90.6±7.21%. The mean field spike recoveries were approximately 64% and 71% for the Florida and California samples, respectively. Each 8-hr TWA air sample was then divided by either 0.64 or 0.71 to correct the sample results for any biases or losses associated with the either the collection or analysis of the samples.

Estimation of TWA Exposures: The sulfuryl fluoride concentration data measured with the pump and sorbent tubes were used to estimate potential residential exposures. Both 24 and 48 hr TWA exposures were determined (see table below). The TWA exposures used in this calculation were mean daily values (n=15) derived from air concentrations measured at each home. The first three 8-hr air samples collected following clearance were averaged together to estimate the 'Day 1 Re-entry' exposures and the second three samples for 'Day 2 Re-entry' exposures. All 8-hr samples were averaged together to determine a 'Day 1 and Day 2' TWA exposure weighed over a consecutive two day period. The estimated TWA exposures during the 24 hr period following clearance of the houses to 5 ppm or less were 0.40 ppm and 0.41 ppm for Florida and California, respectively. In addition, estimated TWA exposures further decreased during the next 24 hr period to levels of 0.11 ppm and 0.17 ppm in the same regions. Combination of air concentrations from all 15 structures yielded daily TWA exposures of 0.41 and 0.14 ppm for the first and second 24-hr periods following aeration, respectively, and 0.28 ppm for the entire 48 hr monitoring period.

Estimation of absorbed doses and Margins of Exposure (MOE): Absorbed daily doses attributed to inhalation of sulfuryl fluoride were calculated using the 24 and 48 hr TWA for all the houses evaluated (N=15) (see table below). Certain assumptions, in accordance with the US EPA RED document (1993), such as breathing rates for the adult male and female and division of work intensity between rest and light work per 24 hr period, were made. In addition, a potential absorbed dose was calculated on a one year old child weighing approximately 10 kilograms. The Task Group on Reference Man (Snyder et al., 1974) indicates that the breathing rate of a one year old child at rest is approximately 1.5 L/minute. The same reference estimates a breathing rate of 4.2 L/minute during light activity periods.

Summary of exposure assessment

Description of exposure period	Sulfuryl fluoride TWA conc. (ppm)	Estimated absorbed dose (mg/kg/day)			MOE*
		Male	Female	1 yr child (male)	
0-24 hrs Post Clearance (Day 1 Re-entry)	0.41	0.50	0.35	0.59	Male: 600 Female 857 Child: 508
24-48 hrs Post Clearance (Day 2 Re-entry)	0.14	0.17	0.11	0.20	Male: 1765 Female: 2727 Child: 1500
0-48 hrs Post Clearance (Day 1 & Day 2)	0.25	0.34	0.23	0.40	Male: 882 Female: 1304 Child: 750

*Based on a NOEL of 300 ppm in rats in a 2-day exposure study. Following species extrapolation from humans to rats, this NOEL corresponds to 290 mg/kg/day for human males and 326 mg/kg bw/day for human females.

The MOE were 580, 931 and 491 for the adult male, adult female and 1 yr old male child populations assessed during the initial 24 hr period following potential re-entry into the homes. During the subsequent 24 hr period, sulfuryl fluoride concentrations continued to decrease and margins of exposure increased to 1706, 2963 and 1450 for the same populations, respectively. These results suggests that potential doses to residents occupying structures for 24 hrs per day immediately following fumigations are low during the first day and further decreasing during subsequent days.

Summary:

A study was performed to evaluate the concentration of sulfuryl fluoride within homes following fumigation with VIKANE gas fumigant. A total of 15 homes were fumigated in Florida and California during March and April 1994. Both instantaneous and continuous TWA concentrations were determined within the homes for up to 48 hrs following clearance of the structure at or below 5 ppm (v/v).

The results demonstrated rapid dissipation of the sulfuryl fluoride from the structures during the 2 day period following clearance of the structure at or below 5 ppm (time at which resident may re-enter house). Sulfuryl fluoride concentrations ranged from 0.01 ppm to 0.58 ppm (mean=0.18 ppm) and from 0.02 ppm to 0.48 ppm (means= 0.11 ppm) at the end of 24 and 48 hrs, respectively, as measured with the pump and sorbent tube methods. In addition, reproducible graphs of the data support the fact that sulfuryl fluoride continually dissipates from a range of treated structures and, as a result, exposures to occupants are low and transient in nature.

MOE were calculated using daily TWA exposures estimated from the pump and tube air monitoring data and the acute NOEL of 300 ppm, as determined in an acute rat toxicology study. The corresponding MOE extrapolated to an adult male, female and 1 year old child population were 580, 931 and 491, respectively, for the first 24 hr period following potential residential re-entry. These results suggest that the health risks, attributed to exposures most likely incurred following re-entry into structures treated with VIKANE gas fumigant and cleared at or below the current 5 ppm level, were extremely low.

6.2.1.2 Summary of Worker Exposure Studies

A summary of fumigator and aerator exposure measured during exposure studies is presented below. Most studies have been conducted in accordance with test guidelines and all the parameters

used in these studies are comparable to the draft label for Profume Gas Fumigant and are considered adequate for this assessment.

During these studies, the fumigators handled and released product from cylinders for a maximum total production of 2051 kg of sulfuryl fluoride (Barnekow et al, 2002-Study 6 at SOTW mill). A Ct of 2016 g.hr/m^3 was achieved over 31 hrs fumigation periods. The maximum equilibrium concentrations of 143 g/m^3 were achieved ((Barnekow et al, 2002-Study 6 at SCFM mill). During fumigation, workers were exposed to a maximum 8-hr TWA atmospheric sulfuryl fluoride concentration of 2.50 ppm (Barnekow et al, 2002-Study 6 at SCFM mill). During aeration, workers were exposed to a maximum 8-hr TWA atmospheric sulfuryl fluoride concentration of 2.39 ppm (Barnekow et al, 2002-Study 7 at SOTW mill).

Summary of Fumigator and Aerator Exposures

Study (reference)	Trial site	Duration of fumigation and aeration	Sulfuryl fluoride used	Ct (g.hr/ m^3)	Maximum Internal Conc. (g/m^3)	Half-life (hrs)	Tasks Monitored	Fumigator Sulfuryl fluoride (ppm)		Aerator Sulfuryl fluoride (ppm)	
								Tasks	8-hr TWA	Tasks	8-hr TWA
1 (Perkins, 2002)	Flour Mill, Nafferton, Yorkshire, UK	28 hrs fumigation. Re-entry after 4 hrs of aeration	742 kg (13 cylinders)	1814	134 g/m^3	4-7	Fumigation: Moving cylinders, connecting / disconnecting shooting lines, opening the cylinders to introduce the fumigant	<-.25 to 0.52	0.01-0.04	Not measured	Not measured
2 (Perkins & Jones, 2002)	Langley flour mill, Nottingham, UK	23 hrs of fumigation. Re-entry after 4 hrs of aeration	462 kg (6 cylinders)	1595	110 g/m^3	14	Fumigation (as above) Aeration: Starting fans, unsealing aeration ducts, removing external sheeting used for sealing, opening doors from outside the structure.	0.07-0.1	0.01-0.05	0.33-0.43	0.01-0.18
3 (Perkins, 2002)	Hedwigsburg, Germany	31 hrs of fumigation. Re-entry after 7 hrs of aeration	456 kg (8 cylinders	2016	71 g/m^3	12-16	Fumigation (as above) Aeration (as above)	<0.31-0.44	0.03-0.12	3.35-11.8	0.32-0.72
4 (Perkins & Blaschke, 2002):	Hedwigsburg, Germany	20 hrs of fumigation. Re-entry after 15.5 hrs of aeration	893 kg (16 cylinders	1484	94 g/m^3	16	Fumigation (as above) Aeration (as above)	0.35-1.73	0.8-1.06	0.46-3.07	0.21-1.13
5 (Perkins, 2002)	Corato, Italy	27 hrs of fumigation. Re-entry after 27 hrs of aeration	1767 kg (32 cylinders	1387	85 g/m^3	15	Fumigation (as above)	1.44-1.76	0.54-0.57	Not measured	Not measured
6 (Barnekow et al, 2002)	Ligonier, IN, USA (SOTW)	27 hrs of fumigation. Re-entry after 4 hrs of aeration	2051 kg (32 cylinders	1130	116 g/m^3	5.6	Fumigation (as above) Aeration (as above)	3.88-4.35	1.94-2.18	0.26-0.68	0.15-0.22
6 (Barnekow et al, 2002)	Hudsom, KS, USA (SCFM)	29 hrs of fumigation. Re-entry after 9.5 hrs of aeration	454 kg (32 cylinders	1515	143 g/m^3	10.4	Fumigation (as above) Aeration (as above)	9.2-17.2	2.5-4.2*	1.26-2.82	0.45-1.26
6 (Barnekow et al, 2002)	Freeport, TX, USA (ARI, TX)	4.5 hrs of fumigation. Re-entry after 4 hrs of aeration	1182 kg (21 cylinders	263	69 g/m^3	12.6	Fumigation (as above)	3.18-4.11	0.84-1.28	Not measured	Not measured

7 (Barnekow et al., 2002)	Ligonier, IN (SOTW)	29 hrs of fumigation. Re-entry after 6 hrs of aeration	2043 kg (36 cylinders	1653	108 g/m^3	6.5	Fumigation (as above) Aeration (as above)	3.64-5.34	1.6-2.34	1.27-7.62	0.57-2.39

*The value of 4.2 was detected in workers involved in non-commercial practice of disconnecting/reconnecting the same cylinder

6.2.1.2 Worker Exposure Information

In occupational situations, exposure to sulfuryl fluoride gas is expected to occur mainly via inhalation. An analysis of activities during fumigation revealed that workers might be exposed to sulfuryl fluoride during the following processes/procedures:

Fumigation: Exposure to sulfuryl fluoride gas may occur during fumigation if there is any leakage.

Aeration: Exposure to sulfuryl fluoride gas may occur during aeration if the exhaust fans are not properly set and the gas is allowed to leave at the ground level. Exposure to sulfuryl fluoride gas can also during monitoring activities.

6.2.1.3 Worker Exposure Estimates

There are no exposure models available to estimate worker exposure during the use of Profume Gas Fumigant.

6.2.2 Exposure during re-entry

Post-application exposure may include re-entry by workers to the treated structures to clear the treated structures for re-occupation, and to remove the equipments associated with fumigation.

The applicant has submitted re-entry exposure studies, as part of worker exposure studies (see section 6.2.1.1), to determine the potential exposure to re-entry workers resulting from the fumigation of mills with sulfuryl fluoride. The potential exposure to workers re-entering the mills after clearance was determined during post-clearance phase with static air monitoring station placed in different locations within the mills.

Analysis of the air monitoring samples collected post-clearance in the mill revealed that the highest 8-hr TWA value was 4.85 ppm during the first 8 hr of monitoring (see table below) and 2.75 ppm during the second 8 hr of monitoring. In general, air samples collected during two subsequent 8-h period showed a general decline in sulfuryl fluoride concentration in the mill.

Summary of potential re-entry worker exposures (internal sulfuryl fluoride concentrations post-aeration)

Study (reference)	Trial site	Sulfuryl fluoride used	Maximum sulfuryl fluoride (ppm) inside the mill for period monitored after re-occupation			Comments
			Period 1	Period 2	Period 3	
2 (Perkins & Jones, 2002)	Nottingham, UK	462 kg (6 cylinders)	0.46	0.57	-	Period 1 is 0-4 hrs. Period 2 is 4-12 hrs. Re-occupation after internal concentration confirmed to be <5ppm.
4 (Perkins & Blaschke, 2002):	Hedwigsburg, Germany	893 kg (16 cylinders	1.28	0.53	0.36	Periods are all 8 hrs. Re-occupation after internal concentration confirmed to be <5ppm
8 (Barnekow et al., 2001)	Ligonier, IN (SOTW)	2051 kg (36 cylinders	0.84	0.80	-	Periods are 8 hrs for Period 1 and 4 hrs for Period 2. Re-occupation after internal concentration confirmed to be <5ppm
8 (Barnekow et al., 2001)	Hudsom, KS, USA (SCFM)	455 kg (8 cylinders	4.85	2.75	-	Periods are 8 hrs for Period 1 and 4 hrs for Period 2. Re-occupation after internal concentration confirmed to be <5ppm
9 (Barnekow et al., 2002)	Ligonier, IN (SOTW)	2005 kg (15 or 20 cylinders combined)	0.66	0.26	0.14	Periods are all 8 hrs. Re-occupation after internal concentration confirmed to be <1ppm

7. RISK ASSESSMENT AND MANAGEMENT

7.1 PUBLIC

As the inhalational exposure is expected to be transient for bystanders and re-entry a NOEC of 300 ppm, obtained in a short-term inhalational neurotoxicity study in rats, is considered to be suitable for estimating the risk. Since the NOEC is derived from a study in laboratory animals a margin of exposure (MOE) of 100 or above is considered to be acceptable. The MOE takes into account interspecies extrapolation and intraspecies variability. Based on a NOEC of 300 ppm and an acceptable MOE of 100, an upper exposure level of equal to or less than 3 ppm was calculated for bystanders and re-entry purposes.

As the general public would not be involved with applying Profume Gas Fumigant, there is no risk for direct exposure to the product during application. As all entrances to the fumigated areas will be posted with signs about the fumigation, the risk for accidental re-entry is expected to be small. The risk is also minimal on re-occupying treated areas, as proper ventilation will be performed after fumigation has stopped and the level of the gas checked in the treated areas to make sure that it is < 3ppm.

The applicant has submitted bystander exposure studies to determine the potential exposure to bystanders resulting from the fumigation of mills with sulfuryl fluoride. The data has high degree of varibility among studies and as a general rule, more exposure occurred during fumigation than aeration. During fumigation and aeration, the maximum 24 hr TWA multidirectional average values were 2.09 ppm and 0.32 ppm at 5 m distance from the mills, respectively. These values are below the acceptable exposure level of 3 ppm for bystanders. Furthermore, all the maximum values observed were below 3 ppm. Therefore, bystanders are not expected to be at risk during the use of Profume Gas Fumigant.

The applicant has also submitted a study to assess potential exposure to residents re-entering fumigated homes following clearance of the homes at or below 5 ppm. Combination of air concentrations from all 15 structures yielded daily TWA exposures of 0.41 and 0.14 ppm for the first and second 24-hr periods following aeration, respectively, and 0.28 ppm for the entire 48 hr monitoring period. These values are below the acceptable exposure level of 3 ppm for residents re-entering treated homes. Therefore, residents are not expected to be at risk during the use of Profume Gas Fumigant.

However, as the general public would not be involved with applying Profume Gas Fumigant, or with checking the level of the gas in the treated areas to make sure that it is < 3ppm, the following re-entry statement is recommended on the draft level:

"Do not enter treated structures unless instructed to do so by an authorised person".

7.2 OCCUPATIONAL USE

7.2.1 Acute Risk

Although ProFume Gas Fumigant is of low inhalation toxicity, the actual concentration of gas within the treated structures would be high, up to 128 g/m^3(around 30,000 ppm), which is well above the rat LC_{50} concentration (991-1122 ppm). During fumigation, in addition to introducing gas into structures, workers will also be conducted monitoring activities around the structures and this may include fixing any leakage. Therefore, the possibility of workers being exposed to high concentrations of Profume Gas Fumigant cannot be ruled out during fumigation. This is also the case during aeration. Furthermore, sulfuryl fluoride is a colourless and odourless gas and there may be some situations where workers are inhaling the gas without being aware of it. Therefore, based on acute inhalation risk, the use of a supplied air respirator (this includes air-hose respirator or air-line respirator or self contained breathing apparatus) is recommended when using the product. Since this requires compliance, the consequence of non-compliance will have serious effects on the health of users. Therefore, in order to provide a warning to users, it is recommended that a suitable stenching agent (e.g. chloropicrin) must be present in the structure during fumigation.

7.2.2 Risk from Repeat Exposure

The OHS risk analysis indicated that occupational risks from exposure to sulfuryl fluoride during application would be almost exclusively from acute repeated inhalation exposure to sulfuryl fluoride. Therefore, a NOEC of 20 ppm, observed in a 2-year rat study, is appropriate for risk assessment of fumigators and aerators.

The applicant has submitted exposure studies, where the potential exposure to fumigators and aerators was determined to sulfuryl fluoride. All the parameters used in these studies are comparable to the draft label for Profume Gas Fumigant and are considered adequate for this assessment. The data had high degree of variability and the maximum 8-hr TWA exposure values ranged from 0.04 to 4.2 ppm and from 0.18 to 2.39 ppm during fumigation and aeration, respectively (see table below). The maximum exposure values were 17.2 ppm and 11.8 ppm during fumigation and aeration, respectively.

Based on the exposure data obtained from these studies, MOE values have been calculated (see table below), using NOEC of 20 ppm. Since the NOEC is derived from animal toxicity testing, MOE of 100 or above are usually considered to be acceptable. The MOE takes into account both interspecies extrapolation and intraspecies variability.

MOE for Fumigator and Aerator

Study (reference)	Maximum 8-hr TWA exposure (maximum concentration) (ppm)		MOE*	
	Fumigator	Aerator	Fumigator	Aerator
1 (Perkins, 2002)	0.04 (0.52)	Not measured	500	Not measured
2 (Perkins & Jones, 2002)	0.05 (0.07)	0.18 (0.43)	400	111
3 (Perkins, 2002)	0.12 (0.44)	0.72 (11.8)	167	28
4 (Perkins & Blaschke, 2002)	1.06 (1.73)	1.13 (3.07)	19	18
5 (Perkins, 2002)	0.57 (1.76)	Not measured	35	Not measured
6 (Barnekow et al, 2002)	2.18 (4.35)	0.22 (0.68)	9	91
6 (Barnekow et al, 2002)	4.2** (17.2)**	1.26 (2.82)	5	16
6 (Barnekow et al, 2002)	1.28 (4.11)	Not measured	16	Not measured
7 (Barnekow et al., 2002)	2.34 (5.34)	2.39 (7.62)	9	8

* MOE = NOEL (20 ppm) / maximum 8-hr TWA exposure (ppm).
**The value of 4.2 was detected in workers involved in non-commercial practice of disconnecting/reconnecting the same cylinder.

During fumigation, the MOE ranged from 5 to 500 and 6 of 9 operations had a MOE that was considered to be unacceptable. During aeration, the MOE ranged from 8 to 111 and 5 of 6 operations were considered to be unacceptable. These results showed that workers are likely to be at risk of inhalation toxicity during fumigation and aeration. Furthermore, as stated above, sulfuryl fluoride is a colourless and odourless gas and there may be some situations where workers are inhaling the gas without being aware of it. Therefore, the use of a supplied air respirator (this includes air-hose respirator or air-line respirator or self contained breathing apparatus) is recommended when using the product.

7.2.3 Re-entry Risk

Post-application exposure may include re-entry by workers to the treated structures to clear the treated structures for re-occupation and to remove the equipment associated with fumigation. The applicant has submitted exposure studies to determine the potential exposure to workers re-entering treated mills after clearance (aeration completed). Analysis of the air monitoring samples collected post-clearance in the mills revealed that the highest 8-hr TWA value was 4.85 ppm during the first 8 hr of monitoring and 2.75 ppm during the second 8 hr of monitoring in one mill (one out of five). All other values (4 hr and 8 hr TWA) were less than 1.30 ppm.

Workers are not expected to be at risk following the use of Profume Gas Fumigant provided that the sulfuryl fluoride concentration in air is no more than 3 ppm at the time of re-entry.

The following re-entry statement is recommended on the draft label for Profume Gas Fumigant:

"Do not allow entry into the treated structures until the concentration of Profume Gas Fumigant is confirmed to be less than 3 ppm, measured with an approved detection device. If prior entry is required, wear supplied air respirator (this includes air-hose respirator or air-line respirator or self contained breathing apparatus)".

8. RECOMMENDED HAZARD CLASSIFICATION STATEMENTS

8.1 ACTIVE CONSTITUENT

Sulfuryl fluoride (CAS No.: 2699-79-8) is listed on the NOHSC Hazardous Substances Information System (HSIS) Database (NOHSC, 2005) with the following risk phrases:

R23/25	Toxic by inhalation and if swallowed
R36/37/38	Irritating to eyes, respiratory system and skin

The following cut-off concentrations apply for sulfuryl fluoride:

Conc. ≥ 5%	R23/25; R36/37/38
0.5% ≥ Conc. < 5%	R20/22

However, based on the submitted toxicology information, OCS has amended the classification of sulfuryl fluoride as follows:

Classification of sulfuryl fluoride under the HSIS

Risk phrases	Toxicology information
R20 Harmful by inhalation	Rat inhalation LC_{50} from 4.13 to 4.68 mg/L in 4h exposures.
R25 Toxic if swallowed	Rat oral LD_{50} 100 mg/kg bw.
Nil for eye irritation	Lacrimation and rapid blinking observed prior to death in animals exposed to ≥ 6 mg/l in an acute inhalation study.
Nil for respiratory irritation	No data available.
Nil for skin irritation	No skin irritation when exposed to vapours of sulfuryl fluoride in a whole body exposure (head out).
R48/20 Harmful: danger of serious damage to health by prolonged exposure through inhalation	NOEC of 0.08 mg/L and LOEC of 0.33 mg/L for reduced survival, renal failure, and minimal vacuolation of the cerebrum in a 24-month inhalation study of toxicity and carcinogenicity in the rat.

8.2 PRODUCT

Based on the concentrations of sulfuryl fluoride in the product (99.8%), Profume Gas Fumigant is classified as a hazardous substance in accordance with NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following risk phrases:

R20	Harmful by inhalation
R25	Toxic if swallowed
R48/20	Harmful: danger of serious damage to health by prolonged exposure through inhalation

It is the responsibility of the applicant to ensure that the classification and MSDS amendments recommended are implemented.

The Globally Harmonised System of classifications based product classification is provided in Appendix IV. Classification under the GHS (OECD, 2002) will come into force when the GHS is adopted by the Australian Government and promulgated into Commonwealth legislation.

9. REFERENCES

9.1 SUBMITTED DATA

The following studies were submitted in the current submission and the data contained in these studies were relied on.

Toxicokinetics and Metabolism

1. Mendrala, A.L., Markham, D.A., Clark, A.J., Krieger, S.M., Houtman, C.E. & Rick, D.L. (2002) Sulfuryl Fluoride: Pharmacokinetics and metabolism in Fischer 344 rats. Report No: DECO HET K-016399-059. The Dow Chemical Company, Midland, Michigan, USA.

Acute Studies

1. Anon (1959a) The Acute Oral Toxicity of Vikane, Administration of Single Doses to Male Rats, Female Rats and Guinea Pigs. Unpublished Report. The Dow Chemical Company, Midland, Michigan, USA.

2. Anon (1959b) The Acute Vapor Toxicity of Vikane As determined on Male and Female Rats, Single Exposures of Groups of Rats to High Concentrations of Vikane in Air. The Dow Chemical Company, Midland, Michigan, USA.

3. Bradley, G.J, Landry, T.D, .Battjes, J. E. & Quast, J.F. (1990) Sulfuryl Fluoride: Four-Hour Dermal Vapor Exposure in Fischer 344 Rats. Report No: K-016399-036, 036A, 036B. The Dow Chemical Company, Midland, Michigan, USA.

4. Miller, R.R. Calhoun, L.L., Keyes, D.G. & Kociba, R.J. (1980) Sulfuryl Fluoride (Vikane Fumigant) An LC_{50} Determination. Report No: K-016399-013. The Dow Chemical Company, Midland, Michigan, USA.

5. Nitschke, K.D. & Lomax, L.G. (1989) Sulfuryl Fluoride: Acute LC_{50} Study with B6C3F1 Mice. Report No: K-9016399-028, 028A, 028B. The Dow Chemical Company, Midland, Michigan, USA.

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Short-Term Studies

1. Anon (1959c) Short Term Dietary Feeding Study of Commercial Laboratory Diet Fumigated with Vikane. Report No. K-16399-005. The Dow Chemical Company, Midland, Michigan, USA.

2. Eisenbrandt, D.L., Nitschke, K.D., Streeter, C.M. & Wolfe, E.L (1985) Sulfuryl Fluoride (Vikane Gas Fumigant): 2-Week Inhalation Toxicity Probe with Rats and Rabbits. Report No. K-16399-022. The Dow Chemical Company, Midland, Michigan, USA.

3. Nitschke, K.D. & Quast, J.F. (1991) Sulfuryl Fluoride: Two-Week Inhalation toxicity Study in Beagle Dogs. Report No: K-016399-038. The Dow Chemical Company, Midland, Michigan, USA.

4. Nitschke, K.D. & Quast, J.F. (2002) Sulfuryl Fluoride: Two-Week Inhalation Toxicity Study in CD-1 Mice. Report No: DECE HET K-016399-029. The Dow Chemical Company, Midland, Michigan, USA.

Subchronic Studies

1. Nitschke, K.D. & Quast, J.F. (1993) Sulfuryl Fluoride: Thirteen Week Inhalation Toxicity Study in CD-1 Report No: K-016399-032. The Dow Chemical Company, Midland, Michigan, USA.

2. Nitschke, K.D. Dittenber, D.A. & Eisenbrandt, D.L. (1987a) Sulfuryl Fluoride (Vikane Gas Fumigant) 13-Week Inhalation Toxicity Study With Rats. Report No: K-016399-025R. The Dow Chemical Company, Midland, Michigan, USA.

3. Nitschke, K.D., Zimmer, M.A. & Eisenbrandt. (1987b) Sulfuryl Fluoride (Vikane Gas Fumigant) 13-Week Inhalation Toxicity Study With Rabbits. Report No: K-016399-025B. The Dow Chemical Company, Midland, Michigan, USA.

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Chronic Studies

1. Quast, J.F., Bradley, G.J. & Nitschke, K.D. (1993a) Sulfuryl Fluoride: 18 Month Inhalation Oncogenicity Study in CD-1 Mice. Report No: DECO-HET-K-016399-039. The Dow Chemical Company, Midland, Michigan, USA.

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Reproduction Studies

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