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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: The HED Chapter of the Reregistration Eligibility Document (RED) for Sulfuryl Fluoride, Case # 0176 (Pesticide Chemical Code 078003).

FROM: Nguyen B. Thoa, Ph.D. *NT 8/5/93*
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TO: Lois Rossi, Chief
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THRU: Andrew Rathman, Acting Chief *AR 8/5/93*
Chemical Coordination Branch
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and

Penelope Fenner-Crisp, Ph.D, Director
Health Effects Division (H7509C) *8/6/93*

Please find attached the HED Human Health Assessment for the Sulfuryl Fluoride Reregistration Eligibility Document. This chapter includes the Hazard Assessment from M. Copley of Toxicology Branch I (Attachment I), the Occupational/Residential Exposure Assessment and air monitoring data evaluations from P. Perreault and D. Jaquith of OREB (Attachment II), and the Product Chemistry Assessment from R. B. Perfetti of Chemistry Branch II (Attachment III).

Sulfuryl fluoride is a structural fumigant registered for use in closed, sealed buildings (dwellings, garages, barns, storage buildings, etc.) for control of numerous pests, including drywood termites, powder post beetles, old house

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borers, bedbugs, and clothes moths. Sulfuryl fluoride is not registered for the fumigation of stored grains or cereals. It is a gas at room temperature (25° C). All three registered end-use products are supplied as a liquefied gas in pressurized steel cylinders which contain 99% sulfuryl fluoride and 1% impurities which are present as part of the manufacturing process. Sulfuryl fluoride is classified as a restricted use pesticide based on inhalation toxicity and may only be used by trained individuals wearing a self-contained breathing apparatus (NIOSH approved). Resident/worker reentry is currently allowed at indoor air levels of 5 ppm or less.

For regulatory purposes, HED has a concern for neurotoxicity from inhalation exposure to sulfuryl fluoride.

There is a concern for neurotoxic effects both from acute exposure (residents and workers) and intermittent exposure (workers during their working life span) upon reentry of treated homes. The MOEs for acute exposure are less than 100 for residents and workers reentering homes with air levels of 4.5 ppm and above. Acceptable MOEs (≥ 100) are obtained if air levels are reduced to 2 ppm. Very young children (≤ 1 yr old) may be more susceptible than adults to sulfuryl fluoride neurotoxicity because the developing brain may be more vulnerable than the mature brain to chemical injury. Lowering the air level to 0.25 ppm (LOD for Miran detector) should make reentry conditions acceptable for even young children. According to the available indoor air monitoring data, this level may be realized within 24 hours of aeration. With more vigorous aeration procedures, a level of 0.25 ppm may possibly be realized within a few hours.

The MOEs for long term exposure to sulfuryl fluoride will be addressed when the required 90-day inhalation toxicity study is submitted and evaluated. Until then HED recommends the use of currently required self-contained breathing apparatus at all reentry air levels.

The registrant has proposed to remove the following portion of the protective clothing statement from sulfuryl fluoride labels:

"Sulfuryl fluoride is heavier than air and may be trapped inside (clothing) and cause skin injury. Wear full body clothing and shoes or disposable protective clothing. Immediately after application, remove clothing, shoes, and socks."

Based on the method of application, i.e. introduction of sulfuryl fluoride into the target area via a hose, negligible exposure to the applicator would be anticipated.

Therefore, HED agrees that the above statement may be removed from sulfuryl fluoride labels.

In addition, the proposed label includes the statement "Wear goggles or full face shield for eye protection during introduction of the fumigant." HED believes that eye and nose protection are necessary against accidental liquid splash, and therefore, supports inclusion of this statement on the label.

The following data are required to support reregistration eligibility:

a. Product Chemistry Data

- (61-1) Product Chemistry and Disclosure of Ingredients: A certification of limits on EPA form 8750-4.
- (61-2) Description of Beginning Materials and Manufacturing Process: Specific data are described in Confidential Appendix A of Attachment III.
- (62-1) Preliminary Analysis: Specific data are described in Confidential Appendix B of Attachment III.
- (62-2) Certification of Limits: These limits must be submitted on EPA Form 8750-4.
- (62-3) Analytical Methods to Verify Certified Limits: Specific data are described in Confidential Appendix C of Attachment III.

HED considers these data confirmatory.

b. Toxicological Data

- (82-5) 90-day inhalation neurotoxicity study in rats. This requirement was triggered by neurotoxic findings in several 90-day inhalation toxicity studies in rats, rabbits, and dogs, and also because of a concern for possible long term neurotoxicity in workers who are intermittently exposed to the chemical during their working life span. These data are considered confirmatory and are needed for the continued registration of sulfuryl fluoride.

c. Air Monitoring Data for Residential/Occupational Exposure

- (133-4) Additional air monitoring dissipation data down to a level of 0.25 ppm, using more sophisticated analytical methods capable of detecting residues of sulfuryl fluoride in the ppb range. These data are required to confirm the

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Agency's assumption of rapid dissipation of airborne residues and because the potential for subchronic/chronic neurotoxic effects at higher levels cannot be presently ruled out. The requirement however, is reserved until the required 90-day inhalation neurotoxicity study has been submitted and evaluated.

- Method validation data for the Miran and Interscan gas analyzers (also listed under GL § 133-4) and/or any other method used. These data are considered confirmatory.

cc: Karl Baetcke
Marion Copley
Linnea Hansen
Larry Dorsey
R. B. Perfetti
Andrew Rathman
Dave Jaquith

SCIENCE ASSESSMENTS OF SULFURYL FLUORIDE

Sulfuryl fluoride (SO_2F_2 ; trade name Vikane; Pesticide Chemical Code 078003; Case No. 0176) is a structural fumigant registered for uses in closed, sealed buildings for control of numerous pests. It is currently classified as a restricted use pesticide, based on acute inhalation toxicity. OSHA has established an 8-hr TWA limit of 5 ppm for sulfuryl fluoride, based on adverse health effects (FR vol. 57; § 114; 06/12/92). Sulfuryl fluoride has no food/feed uses.

A. PRODUCT CHEMISTRY ASSESSMENT

The physical and chemical characteristics of sulfuryl fluoride are described below (MRID #s 00104291, 00104292, and 00106655):

TCAL	Sulfuryl fluoride
Color	None
Physical State	Gas at 25°C
Odor	None
Melting Point	-136.7° C at 760 mm Hg
Boiling Point	-55.2° C at 760 mm Hg
Specific Gravity	1.32 at 25°C
Vapor Density	3.52 (air = 1)
Solubility	0.075 mg/100 cc water at 25°C 1.74 g/100 cc Wesson oil at 20°C, 1.74 g/100 cc acetone at 22°C, 2.12 g/100 cc chloroform at 22°C
Vapor Pressure	13.44 mm Hg at 25°C
Dissoc. Constant	N/A
Oct./Water Part. Coeff.	N/A
pH	N/A
Stability	Stable to heat. Slowly hydrolyzed in water but rapid in basic solution.
Oxidizing or Reducing Action	A mild oxidant
Flammability	Reduction potential is -.68V
Explodability	Not flammable
Storage Stability	Not explodable
Corrosion	for up to 6 yrs in steel cylinders
	Non-corrosive under normal storage conditions

In response to the 1985 Registration Standard, the Registrant submitted additional product chemistry data ((MRID # 470123-03)). A review of these data indicated that some additional Product Chemistry data are still required including:

- (61-1) Product Chemistry and Disclosure of Ingredients: A certification of limits on EPA form 8750-4.
- (61-2) Description of Beginning Materials and

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Manufacturing Process: Specific data are described in Confidential Appendix A of Attachment III.

- (62-1) Preliminary Analysis: Specific data are described in Confidential Appendix B of Attachment III.
- (62-2) Certification of Limits: These limits must be submitted on EPA Form 8750-4.
- (62-3) Analytical Methods to Verify Certified Limits: Specific data described in Confidential Appendix C of Attachment III.

HED considers these data confirmatory.

B. HUMAN HEALTH ASSESSMENT

1. Toxicology Assessment

Adequate animal toxicological data on sulfuryl fluoride are available and will support reregistration eligibility as a non-food/non-feed use pesticide. Some confirmatory data, however, are required (see under B.1.h). The available data are reported below.

a. Acute Toxicity

The acute toxicity data are summarized in the table below:

TEST	RESULTS	TOX. CAT.
Oral LD ₅₀ /rats (MRID # 00072289)	100 mg/kg	II
Oral LD ₅₀ /guinea pigs (MRID # 40839901)	100 mg/kg	II
1 hr LC ₅₀ in rats (MRID # 41099001)	4507 ppm (17.5 mg/L)	III
4 hr LC ₅₀ in mice (MRID # 41769101)	M = 660 ppm (2.56 mg/L) F = 642 ppm (2.49 mg/L)	IV
4 hr Dermal Vapor LC ₅₀ in rats (MRID # 41712001)	9599 ppm (37.27 mg/L)	IV
Primary Dermal Irritation	N/A	I*
Primary Eye Irritation	N/A	I*
Acute Neurotoxicity Study in rats	**	
Acute Delayed Neurotoxicity in Men	N/A***	

N/A Not applicable

* Sulfuryl fluoride causes freezing of skin and eye tissue on contact.

** Requirement satisfied by study MRID # 427720-01; see B.1.b.

*** Sulfuryl Fluoride is not an organophosphate/cholinesterase inhibitor.

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b. 2-Day Inhalation Neurotoxicity Study

In a 2-day inhalation neurotoxicity study, rats were administered sulfuryl fluoride (6 hrs/day, for 2 consecutive days) at levels of 0, 100, or 300 ppm (M - 0, 97 or 290 mg/kg/day; F - 0, 109 or 326 mg/kg/day). A NOEL was established at greater than or equal to the high dose (300 ppm). Parameters examined included electrophysiological, functional and motor activity. Other neurotoxicity parameters usually examined in this type of study were not required since they were not detected at these dose levels in 90-day or chronic rat studies. HED considers that the requirement for an acute neurotoxicity study in rats is satisfied by this study (MRID # 427720-01).

c. Subchronic Toxicity

In a general subchronic toxicity study, administration of sulfuryl fluoride to rats by inhalation for 6 hours/day for 90 days at doses of 30, 100, or 300 ppm (M - 29, 97, or 290 mg/kg/day; F - 33, 109, or 326 mg/kg/day), resulted in a NOEL of 30 ppm and an LEL of 100 ppm based on fluorosis of the teeth. Signs of toxicity at 300 ppm included decreased body weight, lesions of the nasal passage (inflammation), lung (alveolar histiocytosis), and brain (microscopic vacuolation of the caudate-putamen nucleus and white fiber tracts of the internal capsule) (M,F); and very slight hyperplasia of the collecting ducts of the kidney (F) (MRID # 4080909-02).

An inhalation neurotoxicity 90-day study in rats at the same dose levels also resulted in a NOEL of 30 ppm. The LEL of 100 ppm also had evidence of toxicity including fluorosis of the teeth, pale foci in the pleura, and aggregates of macrophages in the lung. There were also electrophysiologic signs of neurotoxicity at this dose including slowing of the visual evoked response and somatosensory response (F), and auditory brain stem response (M). At 300 ppm there was vacuolation of the caudate putamen which is consistent with the general 90-day rat study (MRID #s 408399-02, 408909-03).

Administration of sulfuryl fluoride by inhalation for 6 hours/day for 90 days to rabbits at doses of 30, 100, or 300 ppm (11, 38, or 114 mg/kg/day) resulted in similar signs of toxicity although brain lesions occurred at lower levels. The NOEL was 30 ppm. The LEL was 100 ppm based on decreased body weights, decreased liver weight and mottling of the teeth (M,F), and microscopic vacuolation of the white matter of the brain (F). In addition, at 300 ppm (M,F) there was alveolar histiocytosis, histologic changes in the nasal epithelium, and microscopic malacia to vacuolation of the internal and external capsules, putamen, and globus pallidus of the brain (MRID # 4080909-01).

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Administration of sulfuryl fluoride in a 90-day inhalation dog study (6 hours/day) at doses of 0, 30, 100 or 200 ppm resulted in a NOEL of 100 ppm (2.5 mg/kg/day) and an LEL of 200 ppm (5.0 mg/kg/day) based on decreased mean body weight and body weight gain. There were also slight histologic lesions in the caudate nucleus of the basal ganglia midbrain (M,F) at 200 ppm. In addition, one male with the above lesion also had transient clinical neurologic signs including lateral recumbency, tremors, incoordination, salivation, and tetany followed by inactivity (MRID 422566-01).

d. Developmental Toxicity

There was no developmental or overt maternal toxicity associated with administration of sulfuryl fluoride by inhalation to pregnant rats for six hours/day on gestation days 6-15 at doses of 0, 25, 75, or 225 ppm (27, 81, or 244 mg/kg/day) (MRID # 00090015). Maternal toxicity of decreased body weight gain was observed at 300 ppm in the range-finding study.

When administered by inhalation to pregnant rabbits at doses of 0, 25, 75 or 225 ppm (0, 10, 28, or 85 mg/kg/day) for six hours/day on gestation days 6-18, the NOEL for both maternal and developmental toxicity was 75 ppm. The LEL was 225 ppm for both maternal toxicity (reduced body weight gain) and developmental toxicity (reduced fetal body weights and crown rump length) (MRID # 00090015).

e. 2-Generation Reproduction Toxicity

A two-generation reproduction toxicity study in rats administered sulfuryl fluoride by inhalation at doses of 0, 5, 20, or 150 ppm (M - 0, 4, 17, or 130 mg/kg/day; F - 0, 5, 20, or 152 mg/kg/day) for 6 hours/day, 5 days/week, resulted in a parental NOEL of 5 ppm and LEL of 20 ppm based on an increased incidence of aggregates of alveolar macrophages in the lungs. At 150 ppm, there was an increased incidence of vacuolation of the myelinated caudate-putamen fiber tracts in the brain. The reproductive NOEL was 20 ppm and the LEL of 150 ppm was based on reduced pup weights in both the F1 and F2 generations (MRID # 421798-01).

f. Mutagenicity

Sulfuryl fluoride was negative for bacterial gene mutations when tested at up to cytotoxic levels with and without metabolic activation (MRID # 41603001).

Sulfuryl fluoride did not cause chromosomal aberrations when tested in the mouse micronucleus assay, at doses up to 520 ppm (80% of the acute LC50) (MRID # 41448601).

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Sulfuryl fluoride was negative in the UDS assay in rat primary hepatocytes when tested at levels of 204 to 1020 ppm (MRID # 42179802).

g. Other Toxicology Information

Human poisonings and fatalities have been reported after sulfuryl fluoride exposure. Residents entering sulfuryl fluoride fumigated houses 2 to 5 hours after aeration experienced chest pains, dyspnea, nausea, and vomiting. There have been two reports of deaths of persons entering sulfuryl treated houses. One entered the house illegally and was found dead in the morning, and a homeowner died of cardiac arrest after sleeping in the house overnight following fumigation. A plasma fluoride level of 0.5 mg/L (10 times normal) was found in this individual following exposure. (ACGIH, 1971; NIOSH, 1978; Nuckolls, 1987; PIMS, 1980; Taxay, 1966).

h. Data Requirements

A neurotoxicity study was not required by the Registration Standard for reregistration of this chemical. However, a 90-day neurotoxicity study in the rat submitted voluntarily by the registrant demonstrated slowing of the visual evoked response (VER) and somatosensory response (SER) wave forms in females and the auditory brain stem response (ABR) in males at 100 ppm, as well as lesions of the caudate-putamen nuclei at the high dose level. However, functional observation batteries and motor activities were not monitored adequately. Ninety-day inhalation toxicity studies in rats, rabbits and dogs at the same exposure concentration levels demonstrated similar neurohistologic lesions at similar (higher in dogs) doses. In addition, the dogs displayed signs consistent with neurologic toxicity. Because of concern that the chemical may produce other types of neurotoxicity, and because subchronic/chronic exposure of workers cannot be presently ruled out, a new 90-day neurotoxicity study in rats (GL # 82-5) is required using the Subdivision F Neurotoxicity Guidelines. An acute neurotoxicity battery in rats (GL # 81-8) also is required because acute neurotoxicity data are necessary for a realistic determination of short-term exposure risk following reentry into homes fumigated with sulfuryl fluoride (memo L. Hansen to SRRD dated 09/14/92). The requirement for an acute neurotoxicity battery has been satisfied recently (see under B.i.b.). The subchronic study is still outstanding. HED considers this required subchronic neurotoxicity study confirmatory.

2. Exposure Assessment

a. Dietary Exposure

No dietary exposure is expected from the use of sulfuryl fluoride as a non-food/non-feed use fumigant. Therefore, there

are currently no tolerances or exemptions from the requirements of a tolerance established for this chemical.

b. Occupational and Residential Exposure

Sulfuryl fluoride is a structural fumigant registered for use in closed, sealed buildings (dwellings, garages, barns, storage buildings, etc.) for control of numerous pests, including drywood termites, powder post beetles, old house borers, bedbugs, and clothes moths. Sulfuryl fluoride is not registered for the fumigation of stored grains or cereals. It is a gas at room temperature (25° C). All three registered end-use products are supplied as a liquefied gas in pressurized steel cylinders which contain 99% sulfuryl fluoride and 1% impurities which are present as part of the manufacturing process. Sulfuryl fluoride is classified as a restricted use pesticide based on inhalation toxicity and may only be used by trained individuals wearing a self-contained breathing apparatus (NIOSH approved).

b-1. Mixer/loader/applicator exposure

Based on the method of application, use pattern, and current label requirements for the use of respiratory protection, worker dermal and inhalation exposure to sulfuryl fluoride, if it occurs, will be intermittent and very low.

b-2. Residential/Occupational post application reentry exposure

Because of its physical nature (a gas at room temperature), oral and dermal exposure to residues of sulfuryl fluoride or its degradates which may remain on/in household contents or indoor air after the required aeration period are expected to be very low.

There is, however, a potential for inhalation exposure upon reoccupation/reentry of treated homes. The exposure may be either acute (residents and workers) or intermittent (workers during their working life span). In response to the Registration Standard, the registrant has submitted air monitoring data (GL # 133-4) for sulfuryl fluoride in 10 houses fumigated at 16 g/m³. After aeration to a level equal to or lower than 5 ppm, the houses were closed again, and the air concentration of sulfuryl fluoride measured. The results indicated that average concentrations of sulfuryl fluoride remained at or below 5 ppm (mean concentration = 4.5 ppm) during the monitoring period after aeration and closure; however, individual maximum concentrations ranged from 5 ppm immediately following aeration to approximately 16 ppm 60 minutes after aeration and closure. Data were not provided for airborne residues of sulfuryl fluoride remaining in homes at levels much below 5 ppm or beyond 120 minutes (MRID # 418177-01).

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In two more recent data submissions, a total of 22 houses were fumigated in the usual manner and at customary application rates, then aerated to a level equal to or lower than 5 ppm. Indoor air was monitored for 24 hours after closure. In the first project (four houses), of the 25 air samples collected at or near 24 hours after closure, three were at the 1-ppm level and all others at levels below the operational sensitivity of the detection devices (≤ 0.5 ppm) (memo D. Jaquith of OREB to SRRD dated 07/28/92). In the second project (eighteen houses) virtually all air samples measured at or near 24 hours after closure were at non-detectable levels (≤ 0.5 ppm) (memo D. Jaquith of OREB to SRRD dated 09/24/92).

Acute inhalation exposures of residents and workers reentering fumigated houses after aeration may be estimated using the following equation and assumptions:

$$\text{Daily Dose (mg/kg/day)} = \frac{\text{ppm} \times \text{MW}}{24450} \times \frac{\text{resp. vol. (L/day)}}{\text{Kg body weight}}$$

- Assumptions:
- MW = 102.07,
 - adult body weights of 70 kg/male and 60 kg/female,
 - respiratory volume (resp. vol.) based on 16 hours rest + 8 hours light work [ventilation rates (L/min) are respectively 7.4 (M) and 4.5 (F) at rest and 29 (M) and 16 (F) with light work,
 - 100% pulmonary absorption, and
 - various air levels [5 ppm as per current label, 4.5 ppm (mean value from DOW study MRID # 418177-01), or theoretically reduced values of 2, 1, and 0.25 ppm (LOD for Miran detector)].

Potential exposures are shown in the table below:

ESTIMATED DAILY DOSES AT VARIOUS LEVELS OF SULFURYL FLUORIDE

Exposure Scenario	Air level		Daily dose (mg/kg/day)	
	ppm	mg/m ³	Males	Females
Current label	5	20.87	6.27	4.17
DOW measurement	4.5	18.77	5.64	3.75
Exposure reduced to	2	8.34	2.51	1.67
Exposure reduced to	1	4.17	1.25	0.83
Exposure reduced to	0.25	1.04	0.31	0.21

Assessment of intermittent exposure of workers during their working life span will be addressed after the required 90-day inhalation neurotoxicity study is submitted and evaluated.

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Post fumigation desorption data (GL # 133-4), also submitted in response to the Registration Standard, indicated that sulfuryl fluoride is desorbed at low levels (ppb range) from various household materials for up to 40 days following fumigation and aeration and that there are no degradates desorbed from these materials (MRID # 403332-01).

Based on the overall indoor air monitoring and post fumigation desorption data, sulfuryl fluoride residues appear to dissipate to very low levels within 24 hours and the dissipation would be expected to continue. Therefore, HED believes that air levels of sulfuryl fluoride in homes fumigated at recommended label rates should be negligible within a short period of time after fumigation and aeration (memo D. Jaquith of OREB to SRRD dated 09/24/92). However, quantitation is limited by the sensitivity of the analytical instruments [Miran 101 infrared analyzer (LOD = 0.25 ppm) and/or Interscan gas analyzer (LOD = 0.3 ppm)].

b-3. Personal Protective Equipment (PPE) and Reentry Intervals (REIs)

In the sulfuryl fluoride Registration Standard, occupational reentry is permitted when air levels of sulfuryl fluoride in the treated areas are reduced to 5 ppm.

Current label requirements for the use of protective clothing and equipment while handling end use products containing sulfuryl fluoride are as follows:

Protective Clothing - Do not wear gloves or rubber boots. Do not reuse clothing or shoes that have become contaminated with liquid Vikane until thoroughly aerated and cleaned.

Respiratory Protection - If the concentration of sulfuryl fluoride in the fumigated area, as measured by a detector device with sufficient sensitivity such as an Interscan or Miran gas analyzer, does not exceed 5 ppm (20 mg/cubic meter), no respiratory protection is required. When this concentration is exceeded, all persons in the exposed area must wear a NIOSH or MSHA approved positive pressure self-contained breathing apparatus (SCBA) or combination air-supplied/SCBA respirator such as manufactured by Ranger, Survivair, Scott, or MSA. Before using any make or brand of SCBA, learn how to use it correctly. Determine that it has an adequate air supply for the job at hand, that it fits properly, providing an adequate seal around the face, and that it is in good working order. For more information on the source and use of air monitoring devices and respirators, consult the Vikane Fumigation Manual.

The above label statement requires that an air monitoring device with sufficient sensitivity, such as an Interscan or Miran gas analyzer, be used to monitor levels of sulfuryl fluoride at fumigation sites.

b-4. Recommendations

- 1) The registrant has proposed an additional label amendment to remove the following portion of the protective clothing statement from sulfuryl fluoride labels:

"Sulfuryl fluoride is heavier than air and may be trapped inside (clothing) and cause skin injury. Wear full body clothing and shoes or disposable protective clothing. Immediately after application, remove clothing, shoes, and socks."

Based on the method of application (i.e., introduction of sulfuryl fluoride into the target area via a hose), negligible exposure to the applicator would be expected until time of reentry into the fumigated structure to monitor air levels. Therefore, HED agrees that the above statement may be removed from sulfuryl fluoride labels.

- 2) The proposed label includes the statement "Wear goggles or full face shield for eye protection during introduction of the fumigant." HED believes that eye and nose protection are necessary against accidental liquid splash, and, therefore, supports inclusion of this statement on the label.

b-5. Data Requirements

- 1) To confirm HED's assumption of rapid dissipation of airborne residues and because the potential for subchronic/chronic neurotoxic effects cannot be presently ruled out, additional indoor air monitoring data to a level of 0.25 ppm (GL # 133-4), using more sophisticated analytical methods capable of detecting residues of sulfuryl fluoride in the ppb range, are required. The requirement is, however, reserved until the required 90-day inhalation neurotoxicity study has been submitted and evaluated.

- 2) Method validation data for the Miran and Interscan gas analyzers (also listed under GL # 133-4) and/or any other method used are also required. HED considers these data confirmatory.

3. Risk Assessment

a. Dietary Risk

Dietary risk is not expected since there are no food or feed uses for sulfuryl fluoride.

b. Residential/Occupational Risks

HED has a concern for neurotoxicity associated with inhalation exposure to sulfuryl fluoride. Histopathology of one or more brain anatomical structures has been a consistent observation in 90-day inhalation studies in several experimental animal species including the rat, rabbit, and dog (MRID #s 4080909-02, 4080909-01, and 422566-01). Neurologic signs such as tremor, incoordination, and tetany also were observed in the dog (MRID # 422566-01) as well as slowing of several electrophysiological evoked responses in the rat (MRID # 408399/02-03). In humans, poisonings and fatalities have been reported after sulfuryl fluoride exposure. Residents entering sulfuryl fluoride fumigated houses 2 to 5 hours after aeration experienced chest pains, dyspnea, nausea, and vomiting. There have been two reports of deaths of persons entering sulfuryl fluoride treated houses. One entered the house illegally and was found dead in the morning, and a homeowner died of cardiac arrest after sleeping in the house overnight following fumigation (ACGIH, 1971; NIOSH, 1978; Nuckolls, 1987; PIMS, 1980; Taxay, 1966).

Residents and workers reentering treated houses may be at risk for acute neurotoxic effects from exposure to sulfuryl fluoride. Workers, but not residents, may also be exposed intermittently over the course of their working life span. Using the potential exposures estimated above (B.2.b-2) for residents and workers, the margin of exposures (MOEs) for acute exposure may be estimated by the following equation:

$$\text{MOE} = \frac{\text{NOEL (mg/kg/day)}}{\text{Exposure (mg/kg/day)}}$$

- where - the NOEL is 300 ppm based on the 2-day inhalation neurotoxicity study, which HED toxicologists consider to be the most appropriate NOEL for determining acute/subacute exposure and
- conversion of rat ppm into mg/kg/day based on respiratory volumes ($\text{m}^3/24$ hours) of 0.37 (M) and 0.26 (F) and body weight (kg) of 0.4 (M) and 0.25 (F).

The MOEs for acute exposure are presented in the following table:

**MARGINS OF EXPOSURE FOR RESIDENTS REENTERING
HOMES TREATED WITH SULFURYL FLUORIDE**

Exposure Scenario	ppm	mg/m ³	Daily Dose (mg/kg/d) (16 hrs rest + 8 hrs light work/d)		NOEL ppm	NOEL mg/kg/d (M/F)	MOE	
			Males	Females			Males	Females
Current label	5	20.86	6.15	4.17	300	290/326	47	78
DOW measurement	4.5	18.77	5.54	3.75	300	290/326	52	96
If exposure were reduced to:	2	8.34	2.46	1.66	300	290/326	118	196
	1	4.17	1.23	0.83	300	290/326	236	382
	.25	1.04	0.31	0.21	300	290/326	935	1155

The MOEs are less than 100 for residents and workers reentering homes with air levels of 4.5 ppm and above. Acceptable MOEs (≥ 100) are obtained if air levels are reduced to levels equal to or lower than 2 ppm. Very young children (≤ 1 yr old) may be more susceptible than adults to sulfuryl fluoride neurotoxicity because the developing brain may be more vulnerable to chemical injury. According to a recent report by the National Research Council of the National Academy of Science, the central nervous system (CNS) continues to develop during the postnatal life (NAS Report, 1993). Lowering the air level to 0.25 ppm (LOD for Miran detector) should make reentry conditions acceptable for even young children since "quantitative differences in toxicity between children and adults are usually less than a factor of approximately 10-fold" (NAS Report, 1993). It should be noted that the MOEs were estimated using very conservative assumptions (e.g., 100% pulmonary absorption and a NOEL (300 ppm) which is the highest dose tested; the true NOEL may be higher than 300 ppm).

The MOEs for longer term exposure to sulfuryl fluoride will be addressed when the required 90-day inhalation toxicity study is submitted and evaluated. Although several inhalation 90-day studies are available, HED toxicologists do not consider them appropriate for long term risk assessment for the following reasons:

- the toxicological end-point of concern is neurotoxicity,
- the 90-day inhalation studies in rats, rabbits, and dogs were deficient (few animals on test, inadequate histopathology, lacking in functional observational battery/motor activity testing, or no positive control data), and
- the NOEL in the 2-generation reproduction study in rats was based on respiratory effects, not neurotoxic effects.

c. Recommendations

There is a concern for neurotoxic effects from acute exposure (residents and workers) and intermittent, but longer-term, exposure (workers during their working life span) upon reentry of treated homes.

To achieve acute MOEs higher than 100, the commonly acceptable level of exposure, HED recommends the following:

- for residents (including very young children) reoccupying treated homes, a permissible air level of sulfuryl fluoride of 0.25 ppm (currently permissible level = 5 ppm). At this indoor air level, MOEs are greater than 900 for adults and are most probably greater than 100 for even very young children. According to the available indoor air monitoring data, this level may be realized within 24 hours of aeration. With more vigorous aeration procedures, a level of 0.25 ppm (LOD of Miran detector) may possibly be realized within a few hours.
- for workers reentering the treated areas, although MOEs for acute exposure are greater than 100 at levels ≤ 2 ppm, HED recommends the use of currently required self-contained apparatus at all reentry air levels since workers may be intermittently exposed during their working life-span and the potential for neurotoxic effects associated with long term exposure will not be resolved until the required 90-day inhalation neurotoxicity study is submitted and evaluated. This decision may be subject to change, depending on the outcome of the toxicological evaluation.

The MOEs for long term exposure to sulfuryl fluoride will be addressed when the required 90-day inhalation toxicity study is submitted and evaluated.

REFERENCES

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STUDY

MRID

81-1	Acute oral toxicity/rat	00072289
81-1	Acute oral toxicity/guinea pig	40839901
81-3	1-hr inhalation toxicity/rat	41099001
81-3	4-hr inhalation toxicity/mouse	41769101
81-2	4-hr dermal vapor toxicity/rat	41712001
81-8	2-day inhalation neurotoxicity study/rat	427720-01
82-3	90-day inhalation toxicity/rat	4080909-02
82-3	90-day inhalation toxicity/rabbit	4080909-01
82-3	90-day inhalation toxicity/dog	4080909-01
82-5	90-day inhalation neurotoxicity/rat	408399/01-02
83-3	Developmental toxicity/rat	00090015
83-3	Developmental toxicity/rabbit	00090015
83-4	2-gen reproduction toxicity/rat	421798-01
84-2a	Mutagenicity (Ames)	41603001
84-2b	Mutagenicity (mouse micronucleus assay)	41448601
84-4	Mutagenicity (UDS assay in rat primary hepatocytes)	42179802
63-(2-17) and 63-20: Physical and Chemical Characteristics		00104291, 00104292, and 00106655
61-(1-3) and 62-(1-3) Product Identity and Analysis and Certification of Product Ingredients		47012303
133-4	Indoor air Monitoring Data	418177-01
133-4	Post fumigation Desorption Data	413332-01

Report of the National Research Council of the National Academy of Science, 1993: Perinatal and Pediatric Toxicity in *Pesticides in the Diets of Infants and Children*. National Academy Press, Washington, D.C., pps 49-125.

Report of the National Research Council of the National Academy of Science, 1993: Executive Summary in *Pesticides in the Diets of Infants and Children*. National Academy Press, Washington, D.C., pps 1-12.