UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 6 1992

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Updated Toxicology Review for the Reregistration Eligibility Document on Sulfuryl Fluoride

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Chemical: Sulfuryl fluoride.

Case # 0176/Chemical # 078003
Tox Chem # 816A
HED Project # 2-8R0176

Considerations: Sulfuryl fluoride is registered for non-food uses for the fumigation of closed (sealed) structures and their contents, such as buildings, dwellings, garages, barns, storage buildings, and other structures infested with a variety of pests such as drywood termites, powder post beetles, old house borers, bedbugs, and clothes moths. It is marketed as a liquified gas in pressurized steel cylinders. A Registration Standard for this chemical was completed in June 1985. Since there are no registered food uses, the minimum data requirements for reregistration are:

Acute Toxicity Studies
Teratology study in one species
Subchronic study in one species
Battery of mutagenicity studies (gene mutation, chromosomal Aberration, and DNA damage)

Although not required for in the 1985 Registration Standard of this chemical, the registrant has submitted a 90 day subchronic neurotoxicity study and a 2-generation study in rats, administered by inhalation.

Toxicology Data Base

The toxicology data base on sulfuryl fluoride is adequate and will support reregistration eligibility.

a. Acute Toxicity (MRID 00072289; 40839901; 41099001; 41769101; 41712001)

Test	Result (mg/kg)	Category
Acute oral rat	100	
Acute oral guinea pig	100	
Acute inhalation rat		
1 hr LC_{50}	= 17.5 mg/L	III
Acute inhalation mouse		
4 hr LC_{50}	= 660 ppm (2.56 mg/L)M	
	= 642 ppm (2.49 mg/L)F	IV
Dermal vapor rat 4 hr LC_{50}	=9599 ppm (37.27 mg/L)	

Sulfuryl fluoride causes freezing of skin and eye tissue on contact, therefore no dermal or eye irritation studies are required.

b. Subchronic Toxicity.

Administration of sulfuryl fluoride to rats by inhalation for 6 hours/day for 90 days (routine study) (MRID 4080909-02) at doses of 30, 100, and 300 ppm (M - 29, 97, 290 mg/kg/day; F - 33, 109, 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).

An inhalation neurotoxicity 90-day study in rats (MRID 408399-02, 408909-03) 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 visual evoked response and somato-sensory 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.

Administration of sulfuryl fluoride by inhalation for 90 days to rabbits (MRID 4080909-01) at doses of 30, 100, and 300 ppm (11, 38, 114 mg/kg/day) by inhalation for 90 days resulted in similar signs of toxicity although brain lesions occurred at lower levels. The NOEL was 30 ppm. The LEL of 100 ppm was 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.

Preliminary review of a new 90-day inhalation dog study (6 hours/day exposure) (MRID 422566-01) resulted in the histologic lesions in the caudate nucleus of the mid brain (M,F) at 200 ppm. In addition, one male also had transient clinical neurologic signs including lateral recumbency, tremors, incoordination, salivation and tetany followed by inactivity.

There was no developmental of overt maternal toxicity associated with administration of sulfuryl fluoride by inhalation to pregnant rats for six hours/day on gestation days 6-15 doses of 0, 25, 75, and 225 ppm (27, 81, 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 to pregnant rabbits at doses of 0, 25, 75 and 225 ppm (10, 28, 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 of 225 ppm for maternal toxicity was reduced body weight gain and for developmental toxicity was reduced fetal body weights and crown rump length (MRID 00090015).

c. Chronic Toxicity

A two-generation study in rats (MRID 421798-01) administered sulfuryl fluoride by inhalation at doses of 0, 5, 20, or 150 ppm (M - 4, 17, 130 mg/kg/day; F - 5, 20, 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.

d. 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 up to 80% of the acute LC_{50}. (MRID 41448601)

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

42179802).

e. Other Toxicology Information

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 death in 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).

f. Toxicological Issues

The 1971 Documentation for Threshold Limit Values (TLV's) set the TLV's at 5 ppm. New studies with NOEL's at or below 30 ppm indicate that the occupational exposure standard (TLV or PEL = 5 ppm) does not provide an adequate margin of safety for repeat exposure. It is necessary to assure that the dissipation curves for sulfuryl fluoride fumigation under labeled use directions do in fact dissipate rapidly after the PEL = 5 ppm is reached and to be certain that the off-gassing concentrations in structures are low enough to allow habitation.

A neurotoxicity study was not required by the Registration Standard for re-registration of this chemical. However, a 90 day neurotoxicity study submitted 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, a new 90 day neurotoxicity study in rats is required using Subdivision F Neurotoxicity Guidelines. The acute neurotoxicity battery is also required.

Exposure is purported to be acute. However, since the data base for dissipation of Sulfuryl Fluoride is incomplete, the duration of exposure in the animal studies needed to adequately define the neurotoxicity is not known. Following evaluation of dissipation data additional time points may be required in the 90-day neurotoxicity study. The protocol should be discussed with the agency at that time.

The registrant has supplied information on the residues which remain on surfaces following fumigation. The toxicological significance of these residues are unknown at present.

Hazard Assessment.

The NOEL from the Hazard Assessment for use in the Risk Assessment based on acute exposure to humans, is 30 ppm (1.3 mg/kg/day). This is based on the 90-day rabbit which has most sensitive and appropriate endpoint (neurohistologic signs). The use of the subchronic data is necessary since there is no data to demonstrate the earliest time point when the neurophysiologic and neurohistologic signs are present. Neurohistologic signs occur at slightly higher levels in rats. In the dog, neurohistologic and related clinical signs occur only at higher doses. The NOELs for neurologic effects protect for developmental effects observed in the rabbits. Other endpoints in the 90 day and reproduction studies at lower or similar dose levels are not relevant for the risk assessment since it is unlikely they would result from acute exposure or due to dose spread.

Data Gaps.[1]

(81-7 ss) Acute neurotoxicity
(82-7 ss) 90-day neurotoxicity

References.

See OPP/PDMS printout is attached listing with MRID Nos. (circled) which apply to this summary. These need to be included with the open literature references listed below:

--ACGIH (1971). Documentation of TLVs. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

--NIOSH (1978). Occupational Health Guide for Sulfuryl Guide. National Institute of Occupational Safety and Health/ Department of Labor. NIOSH Pub. 81-123.

--Nuckolls, J.G.(1987). Fatalities resulting from sulfuryl fluoride exposure after home fumigation- Virginia. J Am. Med Assoc. 258: 2041-44.

--PIMS (1980). Summary of Reported Pesticide Incidence Involving Sulfuryl Fluoride. Pesticide Incident Monitoring Systems Report no.289. USEPA, Office of Pesticide Programs. February 1980.

--Taxay, E.P. (1966). Vikane Inhalation. J. Occup. Med. 8:425-426.

[1] It is strongly recommended that protocols be discussed with the Agency prior to initiation of the studies.

May 6, 1992

Assumptions and Calculations for Sulfuryl Fluoride and Methyl Bromide

Molecular weight
Sulfuryl Fluoride = 102.07
Methyl Bromide = 95.0

$$\text{Dose} = \frac{\text{PPM x mol wt}}{24450} \times \frac{\text{Vol}}{\text{Wt/}}$$

$$= \text{Conc[mg/L]} \times \frac{\text{Vol[L/6hr]}}{\text{weight[kg]}}$$

[] - units to be used in equation.
All animal exposures were for 6 hours.

See table 1 below for respiratory volumes for the different species and strains. Body weights used in calculations were either taken from the table below or the actual study.

Table 1 - assumptions used in PPM to mg/kg/day conversions[1]

Species - Strain	Vol/24 hr (m^3/24hr)	Body Weight (Kg)	
		♂	♀
Rat-Fisher	0.37	0.4	0.25
Sprague Dawley	0.50	0.6	0.35
Rabbit-NZW	0.34	4.1	

[1] Values taken from EPA RfC workgroup committee, RTP, phone conversation between Annie Jarabek's office and Henry Spencer, 3/30/92.

Sulfuryl Fluoride

SPECIES-STRAIN	♂	♀
RAT - 2-gen repro Sprague Dawley MRID 4201798-01	Wt = **0.6 kg** Vol/24hr = 0.5 m^3 Vol/6hr = 0.125 m^3 = **125 L** $\frac{5 \times 102.07}{24450} \times \frac{125}{.6} = 4.35$ **5 ppm = 4.35 mg/kg/day** **20 ppm = 17.4 mg/kg/day** **150 ppm = 130.5 mg/kg/day**	Wt = **0.35 kg** Vol/24hr = 0.34 m^3 Vol/6hr = 0.085 m^3 = **85 L** $\frac{5 \times 102.07}{24450} \times \frac{85}{.35} = 5.07$ **5 ppm = 5.07 mg/kg/day** **20 ppm = 20.3 mg/kg/day** **150 ppm = 152.1 mg/kg/day**
RAT - subchronic Fisher MRID 4080909-02 4080909-03	Wt = **0.4 kg** Vol/24hr = 0.37 m^3 Vol/6hr = 0.0925 m^3 = **92.5 L** $\frac{30 \times 102.07}{24450} \times \frac{92.5}{0.4} = 29.0$ **30 ppm = 29.0 mg/kg/day** **100 ppm = 96.7 mg/kg/day** **300 ppm = 290 mg/kg/day**	Wt = **0.25 kg** Vol/24hr = 0.26 m^3 Vol/6hr = 0.065 m^3 = **65 L** $\frac{30 \times 102.07}{24450} \times \frac{65}{.26} = 32.6$ **30 ppm = 32.6 mg/kg/day** **100 ppm = 108.7 mg/kg/day** **300 ppm = 326 mg/kg/day**
RAT - develop Fisher MRID 00090015		Wt = **0.25 kg** Vol/24hr = 0.26 m^3 Vol/6hr = 0.065 m^3 = **65 L** $\frac{25 \times 102.07}{24450} \times \frac{65}{.26} = 27.1$ **25 ppm = 27.1 mg/kg/day** **75 ppm = 81.4 mg/kg/day** **225 ppm = 244.3 mg/kg/day**
RABBIT - subchronic New Zealand White MRID 4080909-01	Wt = **4.1 kg** Vol/24hr = 1.49 m^3 Vol/6hr = 0.3725 m^3 = **372.5 L** $\frac{30 \times 102.07}{24450} \times \frac{372.5}{4.1} = 11.4$ **30 ppm = 11.4 mg/kg/day** **100 ppm = 37.9 mg/kg/day** **300 ppm = 114 mg/kg/day**	Wt = **4.1 kg** Vol/24hr = 1.49 m^3 Vol/6hr = 0.3725 m^3 = **372.5 L** $\frac{30 \times 102.07}{24450} \times \frac{372.5}{4.1} = 11.4$ **30 ppm = 11.4 mg/kg/day** **100 ppm = 37.9 mg/kg/day** **300 ppm = 114 mg/kg/day**
RABBIT - developmental New Zealand White MRID 00090015		Wt = **4.1 kg**[2] Vol/24hr = 1.49 m^3 Vol/6hr = 0.3725 m^3 = **372.5 L** $\frac{25 \times 102.07}{24450} \times \frac{372.5}{4.1} = 9.5$ **25 ppm = 9.5 mg/kg/day** **75 ppm = 28.5 mg/kg/day** **225 ppm = 85.4 mg/kg/day**

CALC1.SFL

[2] value estimated from study