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

099506

MAY 18 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM **EXPEDITE**

SUBJECT: ID No. 062719-00004. Sulfuryl fluoride, technical. Expedited review of 13-week inhalation study in beagle dogs.

PC. No.: 078003
Tox. Chem. No.: 816A
Proj. No.: D177175
Submission No.: S416259

FROM: Linnea J. Hansen, Ph.D.
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CONCLUSIONS:

The subchronic inhalation study of sulfuryl fluoride in dogs satisfied guideline requirements and is acceptable for regulatory purposes.

Dogs were administered 0, 30, 100 and 200 ppm sulfuryl fluoride by inhalation.

NOEL: 100 ppm
LEL: 200 ppm

At 200 ppm, decreased mean body weight/body weight gain and slight histopathology of the caudate nucleus of the basal ganglia was observed in males and females (single incidence of histopathology per sex). The male with this brain lesion also showed transient neurological symptoms (lateral recumbency, tremors, incoordination, salivation and tetany, followed by inactivity).

Classification: ~~Core-guideline~~ minimum

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ACTION REQUESTED:

DowElanco submitted for review a 13-week inhalation study of sulfuryl fluoride in beagle dogs (MRID No. 422566-01). This data was intended to support registration of sulfuryl fluoride (Vikane®). An expedited review was requested by the Registration Division.

Reviewed by: Linnea J. Hansen, Ph.D. Linnea J. Hansen
Toxicology Branch I, Section IV (H7509C) 5/18/92

Secondary review: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley
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DATA EVALUATION REPORT

STUDY TYPE: Subchronic 90-Day Inhalation Dog (82-1) TOX. CHEM NO: 816A

MRID NO.: 422566-01 PC NO: 078003

TEST MATERIAL: Sulfuryl Fluoride

SYNONYMS: Vikane®, CAS No. 2699-79-8

STUDY NUMBER: K-016399-041, -041A

SPONSOR: DowElanco, 9002 Purdue Rd., Indianapolis, Indiana 46268-1189

TESTING FACILITY: The Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland, MI 48674

TITLE OF REPORT: Sulfuryl Fluoride: 13-Week Inhalation Toxicity Study in Beagle Dogs

AUTHOR: K.D. Nitschke, M.J. Beekman and J.F. Quast

REPORT ISSUED: February 24, 1992

CONCLUSION:

Doses administered: 0, 30, 100 and 200 ppm sulfuryl fluoride administered by inhalation (6 hr/day, 5 days/week) to young adult male and female beagle dogs for 13 weeks.

NOEL: 100 ppm.

LEL: 200 ppm, based on decreased mean body weight/body weight gain and slight histopathology of the caudate nucleus of the basal ganglia in males and females (single incidence of histopathology per sex), and transient neurological symptoms (lateral recumbency, tremors, incoordination, salivation and tetany, followed by inactivity) in one male.

Classification: Core-minimum

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This study appeared to have been properly conducted and is considered acceptable for regulatory purposes.

A signed quality assurance statement was present.

Special Review Criteria (40 CFR 154.7): None

A. MATERIALS:

1. Test compound: Sulfuryl fluoride, technical. Description - odorless and colorless gas, Batch # - Lots WP880329 752 and WP901011 907, Purity - 96.26%.

2. Test animals: Species: dog, Strain: beagle, Age: 24 - 27 weeks (at start of dosing), Weight: 9.17 - 11.99 kg, males; 8.47 - 10.74 kg, females, Source: Marshall Research Laboratory, North Rose, NY

B. STUDY DESIGN:

1. Animal assignment

After a 7 week acclimation period, animals were assigned randomly to the following test groups:

TABLE 1: TEST GROUP ASSIGNMENT

Test Group	Dose in atmosphere (ppm)	Sacrifice at 13 Weeks male	female
1 Cont	0	4	4
2 Low (LDT)	30	4	4
3 Mid (MDT)	100	4	4
4 High (HDT)	200	4	4

Doses were chosen based on the results of a 2-week study in dogs (Nitschke and Quast, 1991, "2-Week Inhalation Toxicity Study with Beagle Dogs", Dow Chemical Company; data not included with this report). All animals were housed individually during exposure in the chambers and two per run during the rest of the study. Animals received food (Purina Certified Canine Chow #5007) and tap water ad libitum.

2. Exposure Conditions:

Animals were exposed to sulfuryl fluoride in a 14.5 m^3 chamber with dynamic airflow conditions (2900 liters/min).

Sulfuryl fluoride was introduced into the chambers and metered at a constant rate via a glass J-tube. Compressed air diluted the test gas in the tube and further mixing and dilution occurred in the main chamber airstream.

The following parameters were monitored once every 60 minutes: air flow in each chamber was monitored with a Universal Venturi tube with a Setra Differential Pressure Transmitter; temperatures with thermometers or resistance temperature devices and relative humidities with relative humidity gauges or humidity sensors.

Analytical concentration of sulfuryl fluoride in each chamber was measured every 30 min using a MIRAN 1A infrared spectrophotometer at 11.8 μm, which was calibrated with air standards of sulfuryl fluoride. The cylinder of test material was weighed before and after each exposure. Samples were taken from at least 8 different points within the breathing zone and from the reference point prior to initial animal exposure.

Results - Airflow: Airflow was actually somewhat lower than intended due to manometers that had not been zeroed. Actual airflows were 2570, 2530, 2370 and 2330 liters/min in the 0, 30, 100 and 200 ppm chambers, respectively. The study authors considered this flow adequate and felt that it did not adversely affect oxygenation for the dogs.

Test compound concentrations: The reduced airflow resulted in slightly reduced time-weighted nominal concentrations of sulfuryl fluoride. Analytically measured averages were 0.0, 29.9, 99.9 and 197.9; when corrected for airflow, these values were still within 10% of the target concentrations (recalculations not presented by the study authors) and were therefore acceptable.

Temperature and Humidity: Temperatures ranged from 22.8°C to 26.5°C (means for each chamber about 24 - 25°C) and humidity ranged from 24.1% - 56.3% (means for each chamber 37.3 to 43.4).

4. Statistics - Means and standard deviations only were calculated for chamber concentrations, temperatures, relative humidities, airflows, differential leukocyte counts and nucleated red blood cell counts. Other parameters were tested for equality of variance using Bartlett's test. For values with equality of variances, parametric analysis were performed. Log and inverse transformation was applied to data where there was inequality of variances.

3-way repeated measure ANOVA was used for time, sex and dose; terminal body weights, organ weights and urine specific

gravities were analyzed with a 2-way ANOVA with the factors of sex and dose (most differences between groups were detected by the time-dose interaction). Ovary and testes weights were analyzed using one-way ANOVA. Where significant dose effects were determined, separate doses were compared to controls using separate one-way ANOVA's.

Where 2-way ANOVA was used, data was first examined for significant sex-dose interaction, then done separately if this was positive. If not but a dose effect was identified, the appropriate ANOVA was repeated for each exposure group with control separately. For 3-way ANOVA, examination was performed using time-sex-dose interaction. If present, each sex was analyzed. This was followed by a sex-dose interaction examination (where identified, data reexamined for each sex). Time-dose interaction was then examined and when identified, analysis repeated for each dose against controls.

Bonferroni's correction was used to compensate for the multiple comparisons with controls and was applied only when comparisons to the control group were made (for the dose factor in 1 and 2-way ANOVA and the time-dose factor in 3-way ANOVA).

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected once or twice daily for signs of toxicity and mortality. A complete physical exam was conducted weekly.

Results: No mortality occurred during the study.

One male at 200 ppm developed lateral recumbency, tetany, tremors, salivation and incoordination on Day 19, 75 minutes following initiation of exposure, followed by decreased activity relative to controls 1 hour later. An incidence of salivation by one female dog was also noted on Days 19 - 25 of the study. No other treatment-related clinical symptoms were noted during the study.

2. Body weight

Animals were weighed weekly during the study. Mean body weight gains and percent change during specified intervals (compared to controls) for males and females are presented below in Table 2:

TABLE 2: BODY WEIGHT GAIN, G (% OF CONTROL GROUP WEIGHT GAIN)[1]

		SULFURYL FLUORIDE, PPM			
INTERVAL:		0	30	100	300
DAYS 1 - 26	♂	928	515 (-44.2%)	676 (-24.4%)	793 (-8.1%)
	♀	429	719 (+71.1%)	488 (+11.1%)	178 (-57.8%)
DAYS 26 - 61	♂	1114	1136 (+2.1%)	878 (-17.9%)	712 (-30.5%)
	♀	686	1086 (+70.6%)	611 (-16.2%)	599 (-19.3%)
DAYS 61 - 94	♂	800	666 (-16.1%)	619 (-16.1%)	521 (-27.4%)
	♀	389	711 (+83.3%)	335 (-16.7%)	342 (-8.3%)
DAYS 1 - 94	♂	2842	2717 (-4.2%)	2173 (-20.2%)	2026 (-23.3%)
	♀	2592	2516 (+60.8%)	1844 (-13.9%)	1118 (-30.1%)

1 Data taken from Tables 6 and 7 of study

Body weights but not body weight gains were analyzed statistically by the study authors. At 200 ppm in males, mean body weight at termination was about 11.5% lower at high dose than controls and overall body weight gain about 23% lower than controls (initial mean body weight of high dose males was slightly lower than controls). Mean body weight of females at 200 ppm was slightly lower than controls (about 3.8%) and overall body weight gain was decreased by about 30%. The study authors determined that combined male and female body weights for the 200 ppm group were statistically significantly lower than controls when examined for time-dose interaction. TB-I considers the slightly decreased body weights likely to be treatment-related.

3. Food consumption and compound intake

Food consumption was not determined during this study since administration was via inhalation.

4. Ophthalmological examination

Ophthalmological examination was performed prior to the initiation of dosing and within 1 week of scheduled 13 week sacrifice. No treatment-related effects were observed at any dose.

5. Blood was collected on 3 occasions pre-test, at 6 weeks and at termination for hematological analysis (including differential leukocyte count) and clinical chemistry analysis from all animals (fasted overnight). The CHECKED (X) parameters were examined.

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a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
X	Platelet count*		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - There were no apparent hematological effects of sulfuryl fluoride at any dose.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
X	Magnesium*	X	Blood urea nitrogen*
X	Phosphorous*	X	Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total serum Protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatinine phosphokinase*^		Serum protein electrophoresis
	Lactic acid dehydrogenase (LAD)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies
^ Not required for subchronic studies

Results - Parameters showing statistically significant effects in animals at 200 ppm are presented below in Table 3:

TABLE 3: CLINICAL CHEMISTRY PARAMETERS AT 13 WEEKS[1]

	SULFURYL FLUORIDE, PPM			
PARAMETER:	0	30	100	200
Aspartate Aminotr. ♂	27	26	23	22*
♀	23	25	21	20*
Albumin ♂	3.7	3.6	3.6	3.5*
♀	3.6	3.6	3.8	3.6*

1 Data taken from Tables 40 and 50 of study
* $p < 0.05$; statistics performed on combined male and female incidences, analysis of time-dose interaction

No significant treatment-related effects on clinical chemistry parameters were observed at any dose. The statistically significant decreases (calculated for combined male and female values, time-dose interaction) in aspartate aminotransferase activity and albumin concentration at 200 ppm after 13 weeks in were small and probably not biologically important.

6. Urinalysis

Urine was collected directly from the bladder at necropsy. The checked parameters were examined:

X	Appearance	X	Glucose
	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

Results - No apparent treatment-related effects on urinalysis parameters were observed at any dose.

7. Sacrifice and Pathology

All animals were subject to gross pathological examination at necropsy (sacrifice performed using sodium pentobarbital) and CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	Digestive system	X	Cardiovasc./Hemat.	X	Neurologic
X	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	XX	Heart*	X	Periph. nerve*#
X	Esophagus*	X	Bone marrow*	X	Spinal cord*#
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen	X	Eyes (optic n.)*#
X	Jejunum*	X	Thymus*		Glandular
X	Ileum*		Urogenital	XX	Adrenal gland*
X	Cecum*	XX	Kidneys*+		Lacrimal gland#
X	Colon*	X	Urinary bladder*	X	Mammary gland*#
X	Rectum*	XX	Testes*	X	Parathyroids*
XX	Liver*	X	Epididymides	X	Thyroids*
X	Gall bladder*	X	Prostate		Other
X	Pancreas*	X	Seminal vesicle	X	Bone*#
	Respiratory	XX	Ovaries*	X	Skeletal muscle*#
X	Trachea*	X	Uterus*	X	Skin*#
XX	Lung*			X	All gross lesions/ masses*
X	Nose				
X	Larynx				
	Pharynx				

* Required for subchronic and chronic studies.
# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement.
+ Organ weight required in subchronic and chronic studies.

a. Organ weight - No apparent treatment-related differences in absolute or relative organ weights were observed at any dose.

b. Gross pathology - No apparent treatment-related macroscopic pathology was observed.

c. Microscopic pathology -

1) Non-neoplastic - One male and female dog at 200 ppm showed small bilaterally symmetrical focal microscopic changes in the putamen of the midbrain. The lesion consisted of a slight vacuolization, gliosis, perivascular cuffing, hypertrophy of endothelial cells, individual cell pyknosis and karyorrhexis, and was slightly more pronounced in the male. The male with this lesion was the same animal that developed neurological symptoms on Day 19 of treatment. Since this rather specific lesion was seen in two high dose animals and was accompanied in one by neurological symptoms, it is considered a likely treatment-related effect. No other treatment-related histopathology was noted.

2) Neoplastic - No neoplastic lesions were observed in any animals.

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D. DISCUSSION:

At 200 ppm males and females showed decreases in body weight/body weight gain when compared to controls. Body weights of high dose males and females were statistically significantly lower than controls. Although the decreases in body weight gain were not statistically significant, they did appear to be treatment-related, and the overall % weight gains were markedly decreased at high dose. A single male developed clinical symptoms shortly after initiation of dosing on Day 19 and the same animal showed slight histopathological lesions of the putamen in the midbrain at necropsy. One female developed the same type of lesion but clinical symptoms were not observed. It is not clear whether salivation noted in another female was due to treatment. Although only single incidences of brain histopathology were noted per sex and were classified as "slight" by the study authors, TB-I agrees with the authors that they were probably related to treatment with sulfuryl fluoride. Similar lesions and clinical symptoms have been observed in rats given sulfuryl fluoride at comparable doses.

Study deficiencies: serum lactic dehydrogenase not determined, no mention of food consumption.

These deficiencies were not considered sufficient to alter the conclusions of the study and it is considered acceptable for regulatory purposes.

Core-grade: Core-minimum

009506

Sulfuryl fluoride
PC# 078003
MRID 422566-01
D177175

82-1 Subchronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 10 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. ✓ Dosing duration daily for 90-days or 5 days/week for 13 weeks.
4. ✓ Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1000 mg/kg).
5. ✓ Doses tested include a NOEL.
6. • ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
7. ✓ Individual daily observations.
8. ✓ Individual body weights.
9. ✓ Individual or cage food consumption.
10. • ✓ Opthalmoscopic examination (at least pretest and at term) control and high dose.
11. ✓ Clinical pathology data of 12 & 13 at termination for rodents, before, monthly or midway and at termination for nonrodents.
12. ✓ Hematology.
    - ✓ Erythrocyte count
    - ✓ Hemoglobin
    - ✓ Hematocrit
    - ✓ Leucocyte count
    - • ✓ Differential count
    - ✓ Platelet count (or clotting measure)
13. ✓ Clinical chemistry.
    - ✓ Alkaline phosphatase
    - ✓ Aspartate aminotransferase
    - • ✓ Creatinine kinase
    - Lactic dehydrogenase
    - ✓ Glucose
    - ✓ Bilirubin
    - ✓ Cholesterol
    - • ✓ Creatinine
    - ✓ Total Protein
    - ✓ Albumin
    - ✓ Urea
    - ✓ Inorganic phosphate
    - ✓ Calcium
    - • ✓ Potassium
    - ✓ Sodium
    - • ✓ Chloride
14. • ✓ Urinalysis, only when indicated by expected or observed activity. As scheduled in 11.
    - ✓ Blood
    - ✓ Protein
    - ✓ Ketone bodies
    - ✓ Appearance
    - ✓ Glucose
    - ✓ Total bilirubin
    - • ✓ Urobilirubin
    - ✓ Sediment
    - ✓ Specific gravity (osmolality)
    - • Volume
15. ✓ Individual necropsy of all animals.
16. ✓ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

Criteria marked with a • are supplemental and may not be required for every study.

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aorta	jejunum	peripheral nerve
eyes	bone marrow	kidneys†
caecum	liver†	esophagus
colon	lung†	ovaries†
duodenum	lymph nodes	oviduct
brain†	stomach	pancreas
skin	mammary gland	rectum
heart†	spleen†	spinal cord (3x)
testes†	musculature	thyroid / parathyroids
pituitary	epididymis	salivary glands
ileum	adrenals†	thymus
trachea	uterus	urinary bladder

† organs to be weighed

Criteria marked with a * are supplemental and may not be required for every study.