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

JUN 4 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: VIKANE (Sulfuryl Fluoride) - Company Response
Submitted Under EPA MRID Nos. 417691-01 and
417691-02
ID No. 078003.

Chemical (Caswell) No.: 816A
RD Record No.: S-391185
HED Project No.: 1-0754

FROM: Irving Mauer, Ph.D., Geneticist 5/15/91
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Don Mackey/Lois Rossi, PM Team 50
Reregistration Branch
Special Review and Reregistration Division (H7508C)

THRU: Karl P. Baetcke, Ph.D., Chief 5/30/91
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

Registrant: DowElanco, Indianapolis, IN

Request

Appraise company response to the Agency's evaluation of a previously submitted toxicity study, namely:

Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test, Lab. Project TXT:K-016399-033 (EPA MRID No. 414486-01)

which was judged UNACCEPTABLE because of insufficient dosage, in addition to lacking information in chamber design, animal

exposure, and sampling method (see: DER attached to memorandum: Mauer to Mackey, stamp-dated August 24, 1990, HED Doc. No. 008067).

Company Submission

Under cover letter of January 25, 1991, the registrant has submitted the following:

A. Nitschke, K.D. and J.F. Quast: Sulfuryl Fluoride: Acute LC_{50} Study with CD-1 Mice, performed at the Toxicology Research Lab, Health and Environmental Science, Dow Chemical, Midland, MI, Project No. K-016399-031, Final Report dated December 21, 1990 (EPA MRID No. 41769101).

B. Nitschke, K.D. and B.B. Gollapudi: Response to U.S. EPA Comments on the Study Entitled "Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test," Laboratory Project ID: TXT:K-016399-033 (EPA MRID No. 41769102).

As part of the response to the first deficiency (insufficient dosage), the registrant-authors submitted an acute toxicity study indicating LC_{50} values of 660 and 642 ppm sulfuryl fluoride in male and female CD-1 mice, respectively [This study is reviewed here; see attached DER]. The highest exposure level used in the subject micronucleus assay was 520 ppm, which the authors claim to be "80% of the LC_{50}" and thus ". . . a generally acceptable upper limit for the micronucleus test (according to Heddle et al., 1983). Since 2 of 15 high-dose females died shortly after exposure, the respondents state that ". . . it is reasonable to assume that these deaths were treatment-related." Therefore, the authors maintain that the 520 ppm level used in this micronucleus assay represented a MTD.

In response to the issues of chamber design and operations, methods for animal exposure and test article sampling, the authors offer the following:

1. The exposure chamber was described in Section D of the original report, where it was stated to be a commercially available, Rochester-type chamber (as illustrated again here, as Figure 1 of this response).

2. Reaffirmation of their confidence in infrared spectrophotometry (IR) as the most reliable and dependable method for analyzing chamber concentrations of sulfuryl fluoride. The IR instrument was calibrated prior to animal exposure (at a

wavelength specific for detecting sulfur-fluorine bonds, namely, 11.8 microns, as in Figure 2 of this response), air standards reanalyzed by IR as a follow-up, and the calibration curve checked at least one test article concentration on the day of exposure.

3. Maintain that they have already described the distribution of test article within the chambers in the original report (on p. 11 therein, "Section F: Chamber Monitoring"), but they enlarge on that description with new illustrations regarding location of sampling devices in relation to reference point values (Figures 3(a) and 3(b) of the present response). Since animals were exposed to only one concentration of test article on any given day, and chamber air was continuously drawn through the IR device from the chamber, it is the respondent's contention that the chamber was continuously monitored during the 4-hour exposure. Chamber concentration reported was then an average taken over a 30-minute interval.

4. The animals were placed 1 to 2 per cage in five-cage units with four units fully occupying the chamber at any one time (see Figures 3(a) and 3(b), although not drawn to scale).

TB Conclusions

A. The Acute LD_{50} Study (K-016399-031, EPA MRID No. 417691-01) is assessed as CORE-MINIMUM DATA, demonstrating approximate LC_{50}'s of 660 and 642 ppm for males and females, respectively.

B. Response to Evaluation of TXT:K-016399-033 (EPA MRID No. 417691-02): Although details on the cause of the two high-dose females in the micronucleus study have still not been provided, causes of deaths were provided with gross pathological examination of animals dying-on-study in the LC_{50} assay (K-016399-031, EPA MRID No. 417691-01). Hence, the HDT used in the muta study (= 80% of the LC_{50}) would appear to satisfy the regulatory guidelines for this type of study.

Since the additional information submitted here also satisfies apparent deficiencies in describing critical parameters of chamber design and sampling, this study is upgraded to ACCEPTABLE.

Attachment (DER)

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Reviewed By: Irving Mauer, Ph.D., Geneticist 05/01/91
Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief 5/30/91
Toxicology Branch I - IRS (H7509C)

DATA EVALUATION RECORD

I. SUMMARY

MRID No.: 41769101
ID No.: 078003
RD Record No.: S-391185
Caswell No.: 816A
Project No.: 1-0754

Study Type: Acute inhalation LC_{50} - mice

Chemical: Sulfuryl fluoride (SO_2F_2)

Synonyms: VIKANE gas fumigant

Sponsor: DowElanco, Indianapolis, IN

Testing Facility: Health/Environmental Services, Dow Chemical, Midland, MI

Title of Report: Sulfuryl Fluoride: Acute LC_{50} Study in CD-1 Mice.

Authors: K.D. Nitschke and J.F. Quast

Study Number: K-016399-031

Date of Issue: December 21, 1990

TB Conclusions:

Approx. LC_{50} = 660 ppm (males); and
= 642 ppm (females)

Classification (Core-Grade): MINIMUM

II. DETAILED REVIEW

A. Test Material - SO_2F_2 (Dow Chemical)

Description: Colorless gas
Batch (Lot): 880329 752MAR/88
Purity (%): 99.6
Solvent/Carrier/Diluent: Compressed (sterile) air

B. Test Organism - Rodent

Species: Mouse
Strain: CD-1
Age: 7 weeks (on receipt)
Weights - Males: 33.0 - 34.4 g
Females: 25.3 - 28.0 g
Source: Charles River, Kingston, NY

C. Study Design (Protocol) - This study was designed to assess the acute toxicity potential of sulfuryl fluoride when administered by inhalation to CD-1 mice (LC_{50} Study).

Statements of both Quality Assurance measures (inspections/audits) as well as of adherence to Good Laboratory Practice were provided.

D. Procedures/Methods of Analysis - Following a 1-week acclimation, groups of mice (5/sex/group) were exposed to three target concentrations of the test substance (600, 700, and 800 ppm) for 4 hours under dynamic airflow conditions (225 L/min) in a Rochester inhalation chamber, and observed daily for 2 weeks. Animals were weighed on test days 1, 2, 4, 8, 11 and 15, and survivors necropsied on study day 15. Airflow through the chamber was monitored with a Series 830 Mass Flow Meter (Sierra, Carmel Valley, CA) at 30-minute intervals. Analytical concentration of test article was determined at 30-minute intervals with a MIRAN 1A infrared sphectrophotometer (Foxboro/Wells, South Norwalk, CT) at a wavelength of 11.8 um. Prior to animal exposure, distribution of Vikane was determined from five sample points within the animal breathing zone, and a reference point within the chamber (approximately 15 cm from the anticipated breathing zone). Concentrations of test material within the breathing zone ranged from 97 to 100 percent of the mean reference value. Animals that died prior to study termination were also necropsied.

At necropsy, all animals were examined for gross pathological alterations, which included in situ status of eyes by glass-slide fluorescent illumination.

Means and SDs were calculated for animal body weight, chamber concentrations, temperature, RH and airflow, and the LC_{50} determined by nonlinear interpolation.

E. Results - [See DER Table A on following page for summary results.] Analytical concentrations for the targets were determined as 596, 692, and 806 ppm SO_2F_2, respectively (Report Table 1).

Five of the 10 high-dose animals died 30 minutes after the 4-hour exposure, and 2 more within 2 days (Report Table 2). A total of nine mid-dose animals* died within 5 days of exposure. Body tremors and/or lethargy were observed shortly after removal from the exposure chamber. At the LDT, all animals survived and did not manifest any clinically visible effects during the 14-day postexposure period.

Body weights decreased in most mid-dose and high-dose animals following exposure (Report Tables 3 and 4). There were no body weight changes in mice exposed to the LDT. Although there were no observed treatment-related gross pathologic changes indicative of organ or systemic damage in animals exposed to the test article, animals that died showed visceral congestion, accompanied by evidence of starvation, i.e., lack of normal feed in the gastroinstestinal tract, and decreased fat in the abdominal cavity (Report Table 5, and APPENDICES).

The authors concluded that the approximate LC_{50} in CD-1 mice is 660 ppm for males, and 642 ppm for females.

F. TB Evaluation - MINIMUM

*As indicated in Report Table 2 and APPENDIX, and not "8" as stated in text (page 13).

DER Table A: Acute Effects of Sulfuryl Fluoride in CD→1 Mice (5/sex/group)[1]

Observation	Dose (Analytical/Target) ppm					
	569/600		692/700		806/800	
	Males	Females	Males	Females	Males	Females
Deaths	0	0	5	4	4	3
Body weight gain[2] (g)	0.7	1.8	(- 6.1)	0.1	(- 1.8)	1.7
Pathology: Congestion (visceral)	0	0	5	4	4	3

[1]Extracted from Tables 1-5 and APPENDICES of the Final Report
[2]Calculated by the reviewer