UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

008067

AUG 24 1990

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OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Vikane Fumigant (sulfuryl fluoride) - Toxicology Data Submitted under MRID No. 41448601 - ID No. 078003 - (EPA Reg. No. 62719-4)

Chemical (Caswell) No.: 861A
RD Record No.: 264,026
HED Project No.: 0-1235

FROM: Irving Mauer, Ph.D., Geneticist 7-10-90
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THRU: Karl P. Baetcke, Ph.D., Chief 7/21/90
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

Registrant: DowElanco, Indianapolis, IN

Request

Review and evaluate the following mutagenicity study, performed by the Health and Environmental Sciences (Toxicology Research) Laboratories of Dow Chemical Company (Freeport, TX and Midland, MI):

Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test (MNT), Lab Project No. TXT:K-016399-033, Final Report dated February 16, 1990 (EPA MRID No. 41448601).

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TB Conclusion

The study is judged UNACCEPTABLE, since no evidence is provided that the animals were exposed to the test article at concentrations affecting the target cells. In addition, critical information on chamber design and operation, animal exposure and sampling methods has not been provided. (See detailed review attached to this memorandum.)

Attachment (DER)

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

7-16-90

4/21/10

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DATA EVALUATION RECORD

I. SUMMARY

MRID (Acc) No.: 41448601
ID No.: 078003
RD Record No.: 264,026
Caswell No.: 816A
Project No.: 0-1235

Study Type: Mutagenicity - Chromosome aberration in vivo (mouse micronucleus)

Chemical: Sulfuryl fluoride (SO_2F_2)

Synonym: Vikane® Gas Fumigant

Sponsor: DowElanco, Indianapolis, IN

Testing Facility: Dow, Freeport, TX and Midland, MI

Title of Report: Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test.

Authors: Gollapudi, B.B; McClintock, M.L.; Nitschke, K.D.

Study Number: TXT:K-016399-033

Date of Issue: February 16, 1990

TB Conclusions:

Although recorded as negative for inducing micronuclei in bone marrow PCE of mice exposed by inhalation up to 520 ppm, no evidence is provided that a MTD was reached; additionally, critical information on exposure and sampling has not been provided.

Classification (Core-Grade): UNACCEPTABLE

II. DETAILED REVIEW

A. Test Material - Sulfuryl fluoride (SO_2F_2)

Description: Colorless gas
Batch (Lot): WP880329 752 Mar/88
Purity (%): 99.6
Solvent/Carrier/Diluent: Compressed air

B. Test Organism - Rodent

Species: Mice
Strain: CD-1
Age: 8 to 9 weeks
Weights - Males: 25 to 37 g
Females: 23 to 29 g
Source: Charles River, Kingston, NY

C. Study Design (Protocol) - This study was designed to assess the clastogenic potential of sulfuryl fluoride when administered by inhalation to CD-1 mice (4-hour exposures under dynamic air flow conditions).

A statement affirming compliance with Agency GLPs was provided.

A Statement of Quality Assurance measures (inspections/ audits) was also provided.

D. Procedures/Methods of Analysis - Groups of five male and five female mice were exposed for 4 hours in pyramidal inhalation chambers to compressed air (negative control) or to three time-weighted average (TWA) analytical concentrations of the test compound, and sacrificed 24, 48, and 72 hours later. Another group was exposed to a single TWA concentration of heated benzene (as positive inhalation control), while a final group of animals was given cyclophosphamide (CP, 120 mg/kg) once by oral gavage (to serve as an additional positive control); all positive controls were sacrificed 24 hours after treatment.

Animals were weighed prior to treatment and again just before sacrifice. At scheduled sacrifice times, bone marrow was collected from both femurs of each animal, cell smears prepared on microscope slides by conventional cytological techniques, and stained with 5% Giemsa.

One thousand polychromatic erythrocytes (PCE) per animal were examined on coded slides for the presence of micronuclei (MN-PCE), and the ratio of PCE to normochromatic erythrocytes (NCE) also recorded (expressed as: PCE x 100/PCE + NCE).

The raw individual animal data (counts of MN-PCE) were first transformed to natural logs, and percent PCE analyzed by three-way ANOVA (sex, dose, time), then subjected to conventional two-way analyses for statistical significance (e.g., pairwise, of treated vs. controls, by t-test with the Bonferroni correction for multiple comparisons). The alpha level of significance was set at $p \leq 0.01$.

E. Results - The TWA concentrations of the test substance were 0 (compressed air), 48, 180, and 520 ppm of SO_2F_2, closely corresponding to the target concentrations of 50, 175, and 520 ppm, whereas positive control groups were actually exposed to 8696 and 8872 ppm benzene for the expected target of 9000 ppm (Report Table 1 attached here). Two test females died shortly after exposure to 520 ppm SO_2F_2, but all other treated test animals survived without visible clinical effects (Report Table 2, attached); three benzene-exposed males also died, while several others showed transient respiratory deficits. No adverse clinical effects were found in CP-treated animals.

In neither males nor females treated with SO_2F_2 were any significant differences from negative controls (= 0.08) in MN-PCE counts found (summary Report Tables 3 and 4, attached here; based on individual animal data in Report Tables 5 to 15), nor in ratios of PCE to NCE (a measure of exposure or toxicity to target cells). In contrast, significantly ($p < 0.01$) elevated MN-PCE counts (10.7) were recorded among benzene-exposed males (Table 4), but the slight increase registered in benzene-treated females (1.9) did not reach the chosen level of significance (Table 3). The authors consider this sex-differential cytogenetic response to benzene to be consistent with other published results.* On the other hand, both sexes responded with highly significant positive results to orally-administered CP (Tables 3 and 4).

The authors conclude that SO_2F_2 did not induce micronuclei in CD-1 mice exposed acutely to inhalation concentrations up to 520 ppm, and hence was judged negative in this test.

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*E.g.: B.J. Dean, MUTATION RES, 154: 153-181, 1985.

F. TB Evaluation - UNACCEPTABLE. Although reportedly conducted according to established procedures for inhalation studies, no evidence has been presented that the test substance was administered at an MTD or, in the absence of adverse clinical effects, to the limit concentration of 5 mg/L. No details on the deaths of the two females exposed to the HDT (520 ppm) were provided (no other clinically adverse effects were noted in the remaining eight survivors treated at this dosage), hence these deaths were not definitively stated to be compound-related (no LC_{50} data for dose-selection were provided).

In addition, several critical parameters of chamber design, as well as methods for animal exposure and sampling were not provided in the report; for example:

1. Nature and identity of inhalation chamber.

2. Miran-1A Infrared Spectrophotometry is not the optimal method of analyzing chamber concentration of SO_2F_2. In any event, neither the location of such sampling devices nor the method of sampling the "animal's breathing zone" were indicated.

3. Placement of animal(s) within the chambers was not described, specified, or illustrated.

Attachment (Summary Data Tables)

ATTACHMENT

Summary Data Tables

VIKANE (Sulfuryl fluoride) TK Review 008067

Page ____ is not included in this copy.

Pages 8 through 13 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

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