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

005089

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPTAM/EPTC - Toxicology Data Submitted in Response to Registration Standard - Accession No. 258242 - Registration Nos. 476-2140, 476-2165

Caswell No. 435

FROM: Irving Mauer, Ph.D.
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04-30-86

TO: Robert Taylor, PM 25
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THRU: Jane E. Harris, Ph.D., Head
Section VI
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Hazard Evaluation Division (TS-769C)

J E Harris 5/2/86

5/4/86

Registrant: Stauffer Chemical Co.

Action Requested:

Review the following studies submitted in response to the Data Call-In (DCI) from the EPTC Registration Standard:

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Title	40 CFR 158.135 Guideline Reference Numbers	Appendix
EPTAM® Technical - Mutagenicity Evaluation in Bone Marrow Micronucleus (T-11906)	84-4	1
Project 148170 - Thiocarbamate Herbicides EPTAM Rat Metabolism - Interim Report No. 3 (March 1979)	85-1	2
Project 148170 - Thiocarbamate Herbicides EPTAM Rat Metabolism - Interim Report No. 5 (April 1979)	85-1	3
Project 148170 - Thiocarbamate Herbicides EPTAM Rat Metabolism - Interim Report No. 6 (June 1979)	85-1	4

TB Evaluation/Conclusions:

The mouse micronucleus assay (reported as negative) was judged Acceptable (see Data Review attached to this memorandum). The three interim reports on rat metabolism (Stauffer Project 148170) were not reviewed, pending submission of the final report.

Attachment

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TOXICLOGY BRANCH: DATA REVIEW

Chemical: EPTC

Caswell: 435
Chem. # 041401

Study Type: Mutagenicity: Micronucleus assay in mice.

Citation: EPTAM Technical - Mutagenicity Evaluation in Bone Marrow Micronucleus

Accession No.: 258242

Sponsor/Testing Lab.: Stauffer (Europe Chemical Division)/ Environmental Health Center, Stauffer.

Study No./Date: T-11906/November 28, 1984

Test Material: EPTAM technical (Lot # 4291-4-10), a pale yellow liquid, 98.6% ai, dissolved in corn oil for oral gavage.

Procedures:

Following two range-finding studies at doses up to 3000 mg/kg, adult male and female CD1 mice (5/sex/group) were intubated with the test material in a constant volume of 0.5 mL per animal in two trials, and sacrificed 24, 48, and 72 hr after dosing. Trial 1 males and females received a single dose of 0 (corn oil vehicle), 250, 500 and 1000 mg/kg. For Trial 2, it was intended that both sexes be dosed twice at 0, 1000, 1200, and 1400 mg/kg each 24 hours apart, but only males received the full dosage schedule; females were judged to be more sensitive to the first dose of EPTC (reduced activity), consequently only the 1000 mg/kg dose was repeated.

Cyclophosphamide (CPA, in distilled water) by oral gavage served as the positive control in both trials. CPA-treated animals were routinely sacrificed 48 hr postdose.

Bone marrow was prepared for microscopic slide analysis by standard methodology, and 1000 polychromatic erythrocytes (PCE) per animal scored for micronuclei. The frequency of PCE to total erythrocytes was also determined as a measure of cytotoxicity. The incidence of micronuclei for each dose/timed sacrifice group was compared to that of its concurrent control group within each trial, and statistical significance calculated from the Kastenbaum-Bowman tables. According to the authors of this report, a substance is considered positive if it induces a response reaching the $p < 0.01$ level of significance compared to solvent controls, and shows dose and/or time related activity.

A Quality Assurance Statement was included in the report.

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Results:

In the first range-finding assay (single dose schedule), all animals died following doses ≥ 2500 mg/kg; deaths and severe clinical toxicity were observed at 1500 and 2000 mg/kg. The PCE frequency of 1500 mg/kg females as well as that of both sexes given 1000 mg/kg were reported to be reduced, but these data were not included in the report. In the second range-finding study (single doses of 0, 1000, or 1200 mg/kg, or two treatments at these levels 24 hr apart), bone marrow slides were stated to have been prepared and (selected slides) evaluated, but neither clinical nor microscopic data were presented.

Based upon the results of the first range-finding study, 1000 mg/kg was considered the MTD, and hence was the highest dose tested in the first of the two main (micronucleus) assays.

[NB: "Some deaths and clinical signs. . ." were said to have occurred at this dose level, and not at lower levels, but no data were presented. Inspection of Table 1 of the Report however, reveals that at the 72-hour sacrifice, only 3 control males were analyzed, and only 4 at each of the 250 and 500 mg/kg doses (in addition to one female at this middose); further, only 4 low-dose females and 4 low-dose males are entered for the 48-hour sacrifice. Elsewhere in the Report, it was stated that additional animals were treated at 1000 mg/kg because of deaths prior to harvest ". . . to insure that 5 animals per high dose group/sacrifice time were available."]

Although there was apparently no reduction in PCE frequency at any dose level in this Trial, increased incidences of micronuclei compared to control values (= 0.8 to 1.3 for males; 2.0 to 3.8 for females) were found at all dose levels in treated males sacrificed at 72 hours (but were not dose-related), as well as in HDT females sacrificed at both 48 hours and 72 hours (time-related increase).

In the second micronucleus assay (Trial 2), the number of deaths were reported as percentages at 1000 mg/kg (the only dose evaluated.)

[NB: As with Trial 1, it was stated (in another part of the Report) that animals were added to replace these losses, and further that animals ". . . were reassigned to sacrifice times to permit the maximum number of groups with a minimum of 3 animals . . .," so that " . . some of the scheduled groups were eliminated . . . ," with the exception of the 1000 mg/kg group.

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A reduction in PCE frequency was found in females sacrificed 48 hours after the second 1000 mg/kg dose. (As noted, because of high loss and clinical toxicity in females after the first doses of 1200 and 1400 mg/kg, a second treatment was not administered; however, no cytogenetic values from survivors were included in the Report.) Compared to control values of micronuclei for males (1.2, 0.4, and 1.4 at respectively, the 24-hr, 48-hr, and 72-hr harvests), there were no significant increases in any dose or time group of either sex, contradicting the Trial 1 results which showed an increase in micronuclei in EPTC-treated animals, but no dose-relationship.

The results with the positive control, CPA, were variable; two different lots had to be used (because the first had reportedly "lost activity;" but no other evidence to support this statement was provided). Further, the dose to achieve a positive response had to be increased from 50 to 100 (and up to 200) mg/kg in the first trial, and to 2 x 100 (and 2 x 200) mg/kg for the double-dose Trial 2. Significant increases in micronuclei (at the $p < 0.01$ level) were finally achieved, accompanied by drastic reductions in PCE frequency, evidence of marked toxicity.

Conclusions:

The authors conclude that ". . . EPTAM technical is not clastogenic when tested in the mouse micronucleus assay to doses that reduced animal survival by 45%."

TB Evaluation: Acceptable.

Although there appeared to be contradictory results between Trials 1 and 2, and the positive controls had to be repeated (because of apparent inactivity of one batch of CPA), Trial 2 was sufficiently adequate to support a negative result, i.e., no increase in induction of micronuclei with EPTAM, administered to mice at toxic levels (MTD).

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