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

MAY 17 1993

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: S-Ethyl dipropylthiocarbamate (EPTC), EPTAM®): Tox.
Data Submitted Under MRID #42397001.
ID#041401

Chemical: 435 (041401)
RD Record: S-422805
HED Project: D181185

FROM: Irving Mauer, Ph.D., Genetic'st
Toxicology Br[illegible]ch-I
Health Effects Division (H7509C)

05-13-93

TO: Walter Waldrop/Terri Stowe, PM #71
Reregistration Branch
Special Review and Reregistration Division (H7508W)

THRU: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I
Health Effects Division (H7509C)

5/14/93

Registrant: ICI Americas, Inc., Wilmington, DE

Request: Review and evaluate the following mutagenicity study:

EPTC: An Evaluation in the Mouse Micronucleus Test, performed at ICI's Central Toxicology Laboratory (CTL), Alderley Park, Cheshire (UK), Study No. SMO612, Report No. CTL/P/3724, dated June 3, 1992 (MRID 423970-01)

TB CONCLUSION: This study has been judged UNACCEPTABLE (see attached DER).

[No further toxicological data are required at this time.]

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ATTACHMENT: DER

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

05-14-93

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DATA EVALUATION RECORD

MRID NUMBER No.: 423970-01
PC No.: 041401
RD Record No.: S422805
Tox Chem. No.: 435
Project No.: D181185

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity - in vivo cytogenetics (mouse micronucleus)

CHEMICAL: S-Ethyl dipropylthiocarbamate (EPTC)
SYNONYMNS: EPTAM®

SPONSOR: ICI Americas, Wilmington, DE

TESTING FACILITY: ICI Central Toxicology Laboratory (CTL), Alderley Park (UK)

TITLE OF REPORT: EPTC: An Evaluation in the Mouse Micronucleus Test

AUTHOR(S): V. Randall and J. M. Mackay

STUDY NUMBER: SMO612 (Report # CTL/P/3724)

DATE ISSUED: June 03, 1992

CONCLUSIONS: Reportedly negative for inducing micronuclei in polychromatic erythrocytes of mice treated once orally at 800 mg/kg. No cytotoxicity observed.

TB-I EVALUATION: UNACCEPTABLE, due to insufficient dosage.

II. DETAILED REVIEW

A. TEST MATERIAL: EPTC (from ICI, Fernhurst UK)

Description:	Pale yellow liquid
Batches (Lots):	P4/D7534/10; T3102A
Purity (%):	98.6
Solvent/carrier/diluent:	Corn oil

B. TEST ORGANISM: Rodent

Species:	Mice
Strain:	C57BL/6J
Age:	7-12 weeks
Weights - males:	19-24 g
females:	16-24 g
Source:	Barried Animal Breeding Unit, ICI, Alderley Park (UK)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the clastogenic potential of the test article when administered in a single oral dose to mice, and bone marrow polychromatic erythrocytes examined for the presence of micronuclei, according to established (published) procedure and OECD Test Guideline 474.

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

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Following preliminary toxicity testing to determine the MTD (at doses up to 2000 mg/kg), groups of animals (5/sex/group) were dosed orally once with diluent (corn oil control) or 800 mg/kg test substance, and sacrificed 24 and 48 hours later. A positive control group of five males and five females was given 65 mg/kg cyclophosphamide and sacrificed at 24 hours.

Bone marrow smears were prepared from the tibia of all animals, and stained with methylene blue and eosin. One thousand polychromatic erythrocytes (PCE) per coded slide were scored for the presence of micronuclei (m-PCE). An additional 1000 erythrocytes were examined to determine the ratio of PCE to total erythrocytes, as an indication of cytotoxicity. Cellular data were analyzed by ANOVA and, following transformation by natural logs, one-sided Student's t-test based on error mean squares.

E. RESULTS: In preliminary MTD testing, 2000 mg/kg was totally lethal, while 1250 mg/kg resulted in approximately 50% mortality (2/5 males, 3/5 females). Dose-related reduced activity, piloerection and hunched posture were observed in animals treated at 500, 800 and (surviving) 1250 mg/kg. Based upon this pattern of clinical signs and mortalities, 800 mg/kg (only) was chosen as the MTD for the main assay.

In the main assay, 800 mg/kg of the test substance caused mild decrease in activity ("subdued nature") as the "only observed adverse reaction to treatment." Compared to statistically significant increased micronuclei among CP-treated animals sacrificed at 24 hours (Report Tables 1 and 2, attached here), no increased incidence of m-PCE over vehicle control was found in treated males at either sampling time (24 or 48 hours), although a small but statistically significant increase in m-PCE was observed among females treated with 800 mg/kg EPTC and sacrificed at 24 hours. This apparent increase at 24 hours was considered by the authors not to be of biological relevance because of: (i) the low vehicle control value, and (ii) no such increase persisted to the 48 hours samp ing (Report Table 2).

Finally no significant change in ratios of PCE to total erythrocytes was observed among EPTC-treated animals compared to control values (Report Tables 3, 4 - attached here).

The investigators concluded that EPTC was not clastogenic in bone marrow cells of mice administered the test article once orally at the MTD (as defined).

F. TB EVALUATION: UNACCEPTABLE in its present form. The selection of 800 mg/kg may not represent the MTD, considering the fact that only mild hypoactivity was observed in all mice; customarily, the highest dose of a test compound administered is 80% of the LD_{50} (which would approximate 1000 mg/kg in this study). Secondly, and more important, there is no assurance, the test substance transported to the target. since no effect on the PCE/total erythrocyte ratio was obtained.

ATTACHMENTS: (Data Tables)

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