CASWELL FILE

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

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MAY 21 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: PROMETRYN - Toxicology Data Submitted under MRID Nos. 404662-02/-03; 404575-18/-19/-20/-21/-22: ID No. 080805

Chemical No.: 097 (080805)
RD Records: S-402942, S-402941, S-402936
Project Nos.: 1-2485, 1-2486, 1-2487

FROM: Irving Mauer, Ph.D., Geneticist
Toxicology Branch I
Health Effects Division (H7509C)

03-11-92

TO: Carol Peterson/Walter Waldrop, PM 71
Reregistration Branch
Special Review and Reregistration Division (H7508W)

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

5/18/92

Registrant: CIBA-GEIGY, Greensboro, NC

Request: Review and evaluate the following seven mutagenicity studies (Gdln 84-2/4):

1. Mouse Lymphoma Mutagenicity Test (LS178/TK), performed by CIBA-GEIGY, Basle; Lab. Study No. 831384, Final Report dated December 6, 1985 (MRID No. 40466202).

2. Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster Structural Chromosomal Aberration Test (in vivo CA), performed by CIBA-GEIGY, Basle; Lab. study No. 831382, Final; Report dated October 17, 1984 (MRID No. 40466203).

3. Gene Mutations Test (Ames), performed by CIBA-GEIGY, Summit, NJ; Lab. Study No. 872346, Final Report dated, November 6, 1987 (MRID 40457518).

4. In Vitro Microbial Assays for Mutagenicity Testing of Prometryn (Ames/E. coli), performed by the Nomura Research Institute (Japan); Lab. study No. NRI-79-2884, Final Report dated November 1979 (MRID 40457519).

5. Chromosome Studies on Human Lymphocytes in vitro (HLC/CA), performed by CIBA-GEIGY Basle; Lab. Study No. 860126, Final Report dated November 26, 1986 (MRID 40457521).

6. Autoradiographic DNA Repair Test on Human Fibroblasts (CRL-1121/UDS), performed by CIBA-GEIGY Basle; Lab. Study No. 831383, Final Report dated May 29, 1984 (MRID 40457521).

7. Autoradiographic DNA Repair Test on Rat Hepatocytes (HPC/UDS), performed by CIBA-GEIGY Basle; Lab. Study No. 34161-TECH, Final Report dated May 24, 1984 (MRID 40457522).

Tox Branch Conclusions: These studies have been assessed as follows (detailed reviews are appended to this memo):

HED Project	Study (MRID)	Reported Results	TB Evaluation
1-2485	L5178Y/TK (40466202)	Negative for inducing forward mutations in mouse lymphoma cells exposed up to 100 ug/mL, a non-toxic dose	UNACCEPTABLE
	in vitro CA (40466203)	Negative for chromosomal damage in hamsters treated orally up to 5000 mg/kg, the limit dose.	ACCEPTABLE
1-2486	Ames (40457518)	Negative for reverse mutation in Salmonella (Ames) strains exposed to concentrations up to toxicity/solubility limits (1000-2000 ug/plate).	ACCEPTABLE
	Ames/E. coli (40457519)	Negative for recombination repair as well as for reverse gene mutation in bacterial cultures exposed up to precipitating levels (10,000 ug/plate)	ACCEPTABLE

	HLC/CA (40457520)	Negative for inducing structural chromosome damage in lymphocytes from a single (unidentified) donor but only at concentrations limited to 50% relative mitotic index.	UNACCEPTABLE
1-2487	CRL-1121/UDS (40457521)	Negative for DNA repair in human fibroblast cultures treated up to 156.25 ug/mL, but too few experimental details to validate conclusions.	UNACCEPTABLE
	HPC/UDS (40457522)	Negative for DNA repair in rat hepatocytes cultured in vitro up to cytotoxic levels (156.25 ug/mL).	ACCEPTABLE

cc: Myron Ottley (cover, plus DERs)

Attachments (DERs)

PROMETRYN.IM/LCA

CASWELL FILE

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)

DATA EVALUATION RECORD

I. SUMMARY

MRID No.: 404662-03
PC No.: 080805
RD Record No.: S-402942
EPA ID No.: 080805
Tox Chem. No.: 097
Project No.: 1-2485

Study Type: (84-2) Mutagenicity - Chromosome damage in vivo (CH/CA)

Chemical: Prometryn technical

Synonym: G 34 161

Sponsor: Ciba-Geigy, Greensboro, NC

Testing Facility: Ciba-Geigy, Basel

Title of Report: Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster (Structural Chromosomal Aberration Test)

Author: H. Loos

Study Number: 831382

Date Issued: October 17, 1984

Conclusions:

Reported negative for inducing any nuclear anomalies in femoral bone marrow of Chinese hamsters dosed orally up to 5000 mg/kg.

TB-I Evaluation:

ACCEPTABLE.

II. DETAILED REVIEW

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A. Test Material - G 34 161 techn.

Description: [Not stated]
Batch (Lot): 1045
Purity (%): 100
Solvent/carrier/diluent: 0.5 percent (Aq) CMC + 0.1 percent Tween 80

B. Test Organism - Rodent

Species: Chinese hamster (Cricetulus griseus)
Strain: "Random outbred"
Weights - males: 23-30 g (4-9 wk)
females: 22-29 g (6-10 wk)
Source: Ciba-Geigy Tierfarm, Sisseln (Schweiz)

C. Study Design (Protocol) - This study was designed to determine the clastogenic (chromosome-damaging) potential of prometryn in bone marrow cells when administered orally to Chinese hamsters, according to recognized procedures (referenced in the Final Report).

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

D. Procedures/Methods of Analysis - Following toxicity testing, groups of hamsters (6/sex/group) were dosed orally by gavage on 2 successive days, animals sacrificed 24 hr after the second dose, bone marrow removed from both femurs, and processed as cell smears onto microscope slides by conventional cytological techniques. In addition to solvent (negative) control (CMC-Tween 80), a positive control group was run concurrently, namely, animals treated with cyclosphosphamide (ENDOXAN, 128 mg/ml). Air-dried slide preparations were stained with May-Grümwald Solution, then in Giemsa, cleared, and mounted.

One thousand bone marrow cells on slides of three males and three females from each dose group were scored for the following nuclear anomalies:

1. Jolly bodies
2. Fragmented erythrocyte nuclei
3. Micronuclei in PCEs
4. Micronuclei in leucocytes
5. Polyploidy

Data were analyzed by X^2.

E. Results: No differences between test and CMC groups in any of the signal characteristics were recorded even at applied oral test doses up to 5000 mg/kg (Report Table 1, attached to this DER). By contrast, Endoxan-treated cells showed an increase in anomalies (= 10.02) some 100 times solvent value (0.1), a highly significant ($p < 0.05$) finding.

F. TB Evaluation: ACCEPTABLE. Although no evidence was presented that prometryn transported from the g.i. tract to the target tissue (femoral bone marrow cells), which could have been provided by direct or indirect measures of cytotoxicity, the limit dose was applied.

Attachment (Data Tables)

RIN # 0615-00

MRID # 40466203

Page 7 is not included in this copy.

Pages _____ through _____ are not included.

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