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

MAY 19 1994

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: PIRATE® Insecticide-Miticide (AC 303,630): Review of additional information in support of gene mutation and structural chromosome aberration studies

P.C.#: 129093
Submission #: S462967
Project No. D201696
EPA ID#: 3G04223

From: Guruva B. Reddy, D.V.M., Ph. D.
Section 4
Toxicology Branch I
Health Effects Division (7509C)

5/18/94

To: Dennis Edwards/Meredith Johnson
Project Manager 19
Registration Division (7505C)

Thru: Marion P. Copley, D.V.M., D.A.B.T.
Section Head
Section 4, Toxicology Branch I
Health Effects Division (7509C)

5/18/94

I. **CONCLUSIONS:**

Additional information in support of mutagenicity CHO/HGPRT Assay has been reviewed and is acceptable (MRID # 431876-01). The information presented for the micronucleus assay (MRID # 431876-02) is not sufficient to change our initial assessment as **NON-TEST and UNACCEPTABLE**, pending review of the final report of metabolism study.

A copy of the supplemental DERs are attached.

cc: CCB, OREB (Dorsey)

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II. ACTION REQUESTED:

American Cyanamid Company, has submitted additional information to upgrade the gene mutation study and the structural chromosome aberration study.

Guideline #	Study Type	MRID #
84-2	Mutagenicity: Gene mutation in cultured Chinese hamster ovary cells (CHO/HGPRT)	431876-01/427702-19[1]
84-2	Mutagenicity: In Vivo Micronucleus Assay in Mice	431876-02 /427702-25[1]

1. Initially submitted for EUP

III. STUDIES REVIEWED:

STUDY/CLASSIFICATION	TB-I COMMENTS
84-2 Mutagenicity-(HGPRT) Species: CHO cells American Cyanamid Co. 91-05-001; 03/25/93 MRID # 431876-02/42770-24 core-Acceptable	In two independently conducted trials, Pirate™ was exposed to chinese hamster ovary cells at nonactivated doses of 2.5 - 250 µg/mL or S9-activated doses of 5 - 500 µg/mL. S9 fraction was derived from Aroclor 1254 induced rat livers. Compound was delivered in DMSO (MRID #s 427702-24 and 431876-01). Not mutagenic up to 500 µg/mL. Cytotoxicity was observed at 500 µg/mL and above with and without S9 activation in a preliminary range finding study. Test article precipitated in the test system at 250 - 500 µg/mL with S9 and 100 - 250 µg/mL without S9 activation. Relative survival (RS) at the highest dose yielding was 36.7% or 40.1% at 250 µg/mL in the nonactivated trials or 23.9% or 38.5% at 250 µg/mL in the S9-activated trials. The positive controls were adequate. The study is upgraded from Unacceptable to Acceptable. The study satisfies the guideline requirement for a gene mutation study (84-2).
84-2 Mutagenicity-Micronucleus assay Species: mice American Cyanamid Co. 91-18-001; 3/17/93 MRID #431876/427702-25 Core - Unacceptable	Additional information indicates that 168 hours post oral dose ≈ 12% - 15% of radioactivity was present in bone marrow compared to radioactivity present in the blood, however, pending review of the metabolism study, our earlier assessment as **NON-TEST and UNACCEPTABLE** remains (MRID #431876-02). This study is classified as an Unacceptable study. It does not satisfy the guideline requirement for Structural Chromosomal Aberration Assay (84-2).

(2)

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D.
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Irving Mauer, Ph.D.
Tox. Branch I (7509C)

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SUPPLEMENTARY DATA EVALUATION REPORT
(HED Doc. # 010651)

STUDY TYPE: Mutagenicity: Gene mutation in cultured Chinese hamster ovary cells (CHO/HGPRT)

TOX. CHEM. No.: 962

MRID No.: 431876-01/427702-24

GUIDELINE #: 84-2

TEST MATERIAL: Pirate™; AC 303,630

SYNONYMS: Pyrrole-3-carbonitrile, 4-bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)

STUDY NUMBERS: American Cyanamid No. 91-05-001

SPONSOR: American Cyanamid Co.
Princeton, NJ

TESTING FACILITY: American Cyanamid Co.
Princeton, NJ

TITLE OF REPORT: Evaluation of CL 303,630 in the Mammalian Cell CHO/HGPRT Mutagenicity Assay

AUTHORS: R.K. Sharma

REPORT ISSUED: 3/25/93; resubmitted 4/7/94

EXECUTIVE SUMMARY: In two independently conducted trials, Pirate™ was exposed to chinese hamster ovary cells at nonactivated doses of 2.5 - 250 µg/mL or S9-activated doses of 5 - 500 µg/mL. S9 fraction was derived from Aroclor 1254 induced rat livers. Compound was delivered in DMSO (MRID #s 427702-24 and 431876-01).

Not mutagenic up to 500 µg/mL. Cytotoxicity was observed at 500 µg/mL and above with and without S9 activation in a preliminary range finding study. Test article precipitated in the test system at 250 - 500 µg/mL with S9 and 100 - 250 µg/mL without S9 activation. Relative survival (RS) at the highest dose yielding valid data was 36.7% or 40.1% at 250 µg/mL in the nonactivated trials or 23.9% or 38.5% at 250 µg/mL in the S9-activated trials. The positive controls were adequate.

The study is upgraded from **Unacceptable** to **Acceptable.** The

study satisfies the guideline requirement for a gene mutation study (84-2).

DISCUSSION: The current submission is in response to the Agency's classification of the study as **supplementary**, based on that cytotoxic levels were not tested. The submission included additional data and explanation in support of upgrading the study from **Unacceptable to Acceptable** category. The data from the dose-range finding study indicates that the compound precipitated from 500 to 3000 μg/mL and relative survival for the 500 μg/mL with S-9 was 29.9% (meets the guideline requirements; see Tables 1 & 2). In addition, in the confirmatory studies, at doses of 250 to 500 μg/mL in the presence of S-9 activation the test substance precipitated; and the RS at 250 μg/mL was 38.5%, which was marginally higher than the preliminary results. Further, in the absence of S-9 the test material precipitated at 100 to 250 μg/mL. The sponsor explained that doses higher than 500 μg/mL could not be repeated due tc precipitation of the chemical. We agree with the Sponsor's explanation and **upgrade the study from Unacceptable to Acceptable.**

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CHLORFENAPYR

Page _____ is not included in this copy.

Pages 5 through 6 are not included in this copy.

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.

X FIFRA registration data.

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_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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Reviewed by: Guruva B. Reddy, D.V.M., Ph.D.
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Irving Mauer, Ph.D.
Tox. Branch I (7509C)

SUPPLEMENTARY DATA EVALUATION REPORT
(HED Doc. #: 010651)

STUDY TYPE: Mutagenicity: In Vivo Micronucleus Assay in Mice

TOX. CHEM. No.: 962

MRID No.: 431876-02/427702-25

GUIDELINE #: 84-2

TEST MATERIAL: Pirate™; AC 303,630

SYNONYMS: Pyrrole-3-carbonitrile, 4-bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)

STUDY NUMBERS: American Cyanamid Co. 91-18-001

SPONSOR: American Cyanamid Co.
Princeton, NJ

TESTING FACILITY: American Cyanamid Co.
Princeton, NJ

TITLE OF REPORT: Evaluation of CL 303, 630 in the In Vivo Micronucleus Assay in Mouse Bone Marrow Cells

AUTHORS: R.K. Sharma

REPORT ISSUED: March 17, 1993; resubmitted April 7, 1994

EXECUTIVE SUMMARY: Additional information indicates that 168 hours post oral dose ≈ 12% - 15% of radioactivity was present in bone marrow compared to radioactivity present in the blood, however, pending review of the metabolism study, our earlier assessment as **NON-TEST and UNACCEPTABLE** remains (MRID #431876-02).

This study is classified as an **Unacceptable** study. It does not satisfy the guideline requirement for Structural Chromosomal Aberration Assay (84-2).

DISCUSSION: Additional information presented as a single summary tabulation indicates that bone marrow drug concentrations reached about 12% - 15% of the levels present in blood 168 hours post oral dosing. This information is considered supportive, however, pending review of the final report of this metabolism study our earlier assessment as **NON-TEST and UNACCEPTABLE** remains.

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