

US EPA ARCHIVE DOCUMENT

5-19-94



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

MICROFILM

010986

MAY 19 1994

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)

Marion P. Copley
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)

1337



Recycled/Recyclable
Printed with Soy/Canola Ink on paper that
contains at least 50% recycled fiber

Q

010986

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'
84-2	Mutagenicity: <u>In Vivo</u> Micronucleus Assay in Mice	431876-02/427702-25'

- Initially submitted for EUP

III. STUDIES REVIEWED:

STUDY/CLASSIFICATION	TB-1 COMMENTS
84-2 Mutagenicity-(HGPRT) Species: CHO cells American Cyanamid Co. 91-05-001; 03/25/93 MRID # 431876-02/42770-24 core-Acceptable	<p>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).</p> <p>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.</p> <p>The study is upgraded from Unacceptable to Acceptable. The study satisfies the guideline requirement for a gene mutation study (84-2).</p>
84-2 Mutagenicity-Micronucleus assay Species: mice American Cyanamid Co. 91-18-001; 3/17/93 MRID #431876/427702-25 <u>Core - Unacceptable</u>	<p>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).</p> <p>This study is classified as an Unacceptable study. It does not satisfy the guideline requirement for Structural Chromosomal Aberration Assay (84-2).</p>

②

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. *12-92*
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Irving Mauer, Ph.D. *J. Mauer*
Tox. Branch I (7509C) *05-12-92*

010986

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 #: 34-2

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).

No+ 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

010986

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 $\mu\text{g}/\text{mL}$ and relative survival for the 500 $\mu\text{g}/\text{mL}$ 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 $\mu\text{g}/\text{mL}$ in the presence of S-9 activation the test substance precipitated; and the RS at 250 $\mu\text{g}/\text{mL}$ 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 $\mu\text{g}/\text{mL}$. The sponsor explained that doses higher than 500 $\mu\text{g}/\text{mL}$ could not be repeated due to precipitation of the chemical. We agree with the Sponsor's explanation and upgrade the study from **Unacceptable** to **Acceptable**.

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.
 - FIFRA registration data.
 - _____ The document is a duplicate of page(s) _____.
 - _____ 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.

010986

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)

J. Sharma
2-16-93

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 \approx 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.