

US EPA ARCHIVE DOCUMENT



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

Microfiche

JUN 10 1993

010323

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id. No.: 000279-03124. S-Cypermethrin (Fury):
Review of a in vivo chromosomal aberrations study
in rat bone marrow.

TOX CHEM No.: 268AA
PC No.: 129064
Barcode No.: D191134
Submission No.: S440499

FROM: John Doherty, Ph.D., D.A.B.T. *John Doherty 6/4/93*
Section IV, Toxicology Branch
Health Effects Division (H7509C)

TO: George LaRocca/Adam Heyward
Product Manager #13
Registration Division (H7505C)

THROUGH: Marion Copley, DVM, Section Head *Marion Copley 6/7/93*
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

I. CONCLUSION

The chromosomal aberrations study in rat bone marrow in vivo (MRID No.: 427586-01) was reviewed and determined to be ACCEPTABLE. Since this is the only series 84-2 study with s-cypermethrin, additional mutagenicity studies are necessary to meet the series 84-2 requirements.

II. Action Requested

The FMC Corporation (refer to letter from Linda A. Dansbury dated April 27, 1993) has submitted an in vivo rat bone marrow chromosomal aberrations study to meet part of the requirements for the series 84-2 testing. The study was reviewed and a copy of the DER is attached. The following comments apply.



1810

010323

III. Toxicology Branch Comments

1. This study meets current criteria for acceptability for regulatory purposes. Under the conditions of the study which was conducted at a dose level at which some of the animals died, there was no evidence of Fury induced chromosomal aberration. The study however, is considered a "non-test" for mutagenicity because there is no firm evidence that the test material actually reached the target cells in the bone marrow in effective concentrations to elicit a mutagenic effect. This is an inherent problem with in vivo rat and mouse bone marrow mutagenicity assays.

The need for additional chromosomal aberrations studies will be reassessed as other series 84-2 studies are submitted and evaluated.

2. The study author used a constant concentration of test material in the vehicle corn oil and dosed each test group with a different volume of corn oil to achieve the desired dosage levels. TB-I does not consider this a good practice because the corn oil volume can affect the bioavailability of the test material. This practice alone does not invalidate the study but the laboratory should be advised that the dosing volume should be constant in gavage studies of multiple dose levels.

IV. Studies Reviewed.

Study Identification	Material	MRID No.:	Results	Classification
<p>84-2. Chromosomal aberrations <u>in vivo</u> in rat bone marrow. Hazleton Washington, Inc. Study Nos: HWA 15265-0-452 and FMC A92-3675, March 3, 1993</p>	<p>zeta-cypermethrin technical (86.26% s-isomer Reference PL92-81</p>	<p>427586-01</p>	<p>No evidence of induction of chromosomal aberrations. (Additional chromosomal aberrations studies may be required pending further review of mutagenicity /genetic toxicity testing for s-cypermethrin) Sprague-Dawley rats. Acute dose levels tested: 0, 31.25, 62.5 and 125 mg/kg.</p>	<p>ACCEPTABLE</p>

010323

Reviewed by: John Doherty *John Doherty 6/4/93*
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley, DVM *MC 6/1/93*
Section IV, Toxicology Branch I (H7509C) *Jan. L. L. 06-04-93*

DATA EVALUATION REPORT

010323

STUDY TYPE: 84-2. Chromosome aberrations in vivo in rat bone marrow.

MRID NO.: 427586-01

TOX. CHEM. NO.: 268AA
PC Code: 129064

TEST MATERIAL: FMC 56701 Technical. Zeta cypermethrin. 82.6% s-isomer, 91.9% cypermethrin isomers. Reference PL92-81. Fury.

STUDY NUMBER(S): HWA 15265-0-452 and FMC No.: A92-3675

SPONSOR: FMC Corporation

TESTING FACILITY: Hazleton Washington, Inc.

TITLE OF REPORT: "Measuring Chromosomal Aberrations in vivo in Rat Bone Marrow Cells"

AUTHOR(S): Hemalatha Murli, Ph.D.

REPORT ISSUED: March 3, 1993

STUDY DATES: Sept 4, 1992 to December 4, 1992

CONCLUSIONS:

No evidence of structural chromosomal aberrations was demonstrated at either 6, 18 or 30 hours post dosing.

Sprague-Dawley strain rat. Acute dose levels tested: 0, 31.25, 62.5 and 125 mg/kg in corn oil.

Classification: ACCEPTABLE. Additional chromosomal aberration studies may be required since there is no evidence that the test material actually entered the bone marrow.

Quality Assurance Statement: Provided.

Good Laboratory Practice Statement: Provided.

REVIEW

Experimental Constants:

010323

Test Chemical: FMC 56701-technical. Zeta cypermethrin or cypermethrin-s. Stated as being 82.6% s-isomer, 91.9% total isomers. Reference: PL92-81.

Appendix II of the study report provided a report that the chemical was stable for 30 days. No data on the concentration of the test material in the dosing solutions were presented.

Test System: Male and female Sprague-Dawley strain rats obtained from the Harlan Sprague-Dawley Co, Frederick, Maryland. This strain is reported to be randomly bred to maximize genetic heterogeneity and at the same time assure access to a common source. The animals were stated as being 8 weeks of age at the time of dosing.

The rats were dosed by once by gavage with the test material dissolved in corn oil. The desired dose was achieved by giving various volumes of a constant concentration of 10 mg/ml of the test material. Thus for the main study the rats received 3.125, 6.25 and 12.5 ml/kg of corn oil solution while the controls were dosed with 12.5 ml/kg of corn oil. This practice of varying the dosing volume to vary the dose level of a test material is not considered a good experimental procedure. The varying amounts of corn oil can interfere with the bioavailability of the test material. This practice alone, however, does not invalidate the study.

Basic Experimental Design

A. Determination of the Dose Levels for the Definitive Chromosomal Aberration Study.

Three sets of preliminary experiments were run to determine the appropriate dose levels for the main study. The first study dosed 5 groups of 3 male and 3 female rats with either 10, 45, 80, 115 or 150 mg/kg of Fury in corn oil and the rats were observed for three days. No toxic signs were noted. No deaths resulted. The second study a single group of 2 male and 2 female rats with 300 mg/kg and both females and one male died. The surviving male appeared languid and ataxic and with dyspnea. The third study assessed 5 groups of 3 male and 3 female rats each dosed with 100, 150, 200, 250 or 300 mg/kg. Only 5 of the 15 females survived. Two deaths were in the female 150 mg/kg dose group but only a single death was found in the 200 mg/kg dose group. Four males died, 2 in the high dose group but one each in the 150 and 200 mg/kg dose groups. Symptoms of ataxia and languid appearance were evident in all survivors except for two in the lowest male dose group. On this basis, dose levels of 0, 31.25, 62.5 and 125 mg/kg were selected for the definitive study. No explanation was provided as to why the rats in the first trial did not respond to the test material at dose levels similar to the third trial.

B. Main Study.

010323

Single groups of 5 male and 5 female rats were dosed with the corn oil vehicle or the positive control (cyclophosphamide, 60 mg/kg in water and administered by gavage). The vehicle control group was sacrificed after 30 hrs and the positive control group was sacrificed after 18 hours. The groups receiving the three dose levels of Fury consisted of 15 males and 15 females per dose level. Groups of 5/sex were sacrificed at 6, 18 and 30 hours post dosing. A "secondary" dose group of 10 males and 10 females was also dosed with 125 mg/kg in order to replace any mortalities at this dose level.

Approximately 1.5 to 2.5 hours prior to euthanasia (by CO₂) the rats were dosed with 2 mg/kg colchicine. The tibiae were removed and the bone marrow collected. The preparation of the bone marrow cells for staining by Giemsa was described. The scoring called for reading 50 spreads from each animal and only cells containing 2n ± 2 chromosomes were scored. A mitotic index was also calculated by scoring the number of cells in mitosis per 500 cells observed at each experimental point.

The Kruskal-Wallis test for non-parametric data was performed to determine whether any of the means from the treatment groups differed from the vehicle control.

Principle of the method. The objective of the study was to determine if the test article or its metabolites can interact with the bone marrow cells to produce gross lesions and whether these changes could survive more than one mitotic cycle of the cell. The detectable aberration figures would be breaks in the chromatin which either failed to repair or were repaired in an atypical combination. Analyses were thus performed on a per animal basis for the following variables:

1. Number of cells with at least one structural chromosomal aberration.
2. Number of cells with 2 or more structural chromosomal aberrations.

Results

1. Reactions to treatment.

One male and one female in the high dose group died. The symptoms in the treated animals were reported as either languid in appearance (reported in all dose groups) or having ataxia or with diarrhea. Ataxia was reported in only one animal in the low dose group. Although the languid appearance is a rather inexact symptom, the presence of ataxia and the deaths indicate that the dose levels used were resulted in systemic toxicological responses.

2. Chromosome aberrations.

Tables 1, 2 and 3 photocopied from the study report illustrate the results of the bone marrow analysis for evidence

010323

34-2. Chrom. Abber. in vivo Fury/19931

of chromosomal aberrations. The positive control produce the expected positive results in both sexes with respect to increases in frequency of structural aberrations, percent of cells per animal with structural aberrations, percent of cells per animal with > 1 structural aberration and mitotic index per animal. These parameters were equivalent to the control for all animals dosed with Fury.

CONCLUSION. This study is ACCEPTABLE. The following "one liner" is supported.

No evidence of structural chromosomal aberrations was demonstrated at either 6, 18 or 30 hours post dosing.

Sprague-Dawley strain rat. Acute dose levels tested: 0, 31.25, 62.5 and 125 mg/kg in corn oil.

Note: This study meets current criteria for acceptability for regulatory purposes. Under the conditions of the study which was conducted at a dose level at which some of the animals died, there was no evidence of Fury induced chromosomal aberration. The study however, is considered a "non-test" for mutagenicity because there is no firm evidence that the test material actually reached the target cells in the bone marrow in effective concentrations to elicit a mutagenic effect. This is an inherent problem with in vivo bone marrow mutagenicity assays.

Cypermethrin Review

Page _____ is not included in this copy.

Pages 8 through 10 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.
