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

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OCT 10 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA File No. 069001 - Pyrethrin: Review of Rat and Rabbit Teratology Studies.

TOX Chem No.: 715
TOX Project No.: 7-0898
Record No.: 201356

FROM: John Doherty 9/11/87
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Geraldine W. Werdig
Data Call-In Program
Registration Division (TS-767C)

THRU: Edwin R. Budd, Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769C)

The Pyrethrin Joint Venture/Chemical Specialties Manufacturers Association (CSMA) has responded to the Data Call-In Notice by providing rat and rabbit teratology studies. Toxicology Branch (TB) has reviewed these studies and is providing the following comments.

1. CORE classification of the rat teratology study is RESERVED. The study did not demonstrate any pharmacological effects of treatment in the dams. Such criteria are desirable for studies to be determined to be CORE MINIMUM or higher. TB, however, does not consider it necessary to request a second rat teratology study at this time because there were no indications of potential teratogenicity or developmental toxicity in this study or in the study with rabbits.

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TB requests that the registrant submit the results in detail for the range-finding study with rats. The submission should include all reactions at all dose levels together with an indication of the degree of severity where appropriate. On receipt and review of this information, TB will consider upgrading the study to CORE MINIMUM or higher.

2. The rabbit teratology study was determined to be CORE GUIDELINES.

TB requests, however, that the results of the range-finding study with rabbits also be submitted to the Agency.

Studies Reviewed

Study	Results	Core Classification
Rat Teratology IRDC 556-002 July 30, 1987	NOEL > 75 mg/kg/day (HDT) for maternal toxicity, teratogenicity, and fetotoxicity	[RESERVED]
Rabbit Teratology IRDC 556-004 July 22, 1987	Maternal Toxicity NOEL = 25 mg/kg/day Maternal LEL = 100 mg/kg/day (body weight decreases during dosing, one rabbit showed excessive salivation and head arched backward) Teratogenicity and fetotoxicity NOEL > 250 mg/kg/day (HDT).	GUIDELINES
Discussion of rat and rabbit teratology studies as prepared by Gerald P. Schoenig, Ph.D. (CSMA) (dated July 31, 1987).	[Document not reviewed in DER.] Dr. Schoenig summarizes the results of both the rat and rabbit teratology studies.	N/A

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Reviewed By: J.D. Doherty 9/11/87
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C) 10/2/87

DATA EVALUATION REPORT

Study Type: Teratology - Rat

TOX Chem No.: 715
MRID No.: N/A

Accession No.: 402882-02

Test Material: Pyrethrum Extract (57.574%) * FEK-99 (Task Force Blend)

Synonyms:

Study No.: IRDC 556-002

Sponsor: Pyrethrin Joint Venture/CSMA

Testing Facility: International Research and Development Corporation (IRDC)

Title of Report: Evaluation of Pyrethrum Extract in a Definitive Rat Teratology Study

Author(s): J.L. Schardein

Report Issued: July 30, 1987

Conclusions:

NOEL > 75 mg/kg/day (HDT) for maternal toxicity, teratogenicity, and fetotoxicity.

Classification: RESERVED

Special Review Criteria (40 CFR 154.7): N/A

Review:

Part I - Range-Finding Study

Only a brief description of the dose range-finding study was provided. In this study, rats were dosed with 37.5, 75, 150, 300, and 600 mg/kg/day. No information was provided as to the number of rats per group, condition as to pregnancy, and number of times they were dosed. It was reported that maternal toxicity in the form of tremors and/or convulsions and mortality were observed at 150, 300, and 600 mg/kg/day and that tremors were also noted at the 75 mg/kg/day dose level. Based on the results of

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the range-finding study, dosage levels of 5, 25, and 75 mg/kg/day were selected for the definitive study.

Part II - Definitive Study

Male and female Charles River COBS CD strain rats were mated (one male with one female) and the day of copulation (gestation day 0) noted by the presence of a vaginal plug. Mated females were assigned to one of four groups. The test article was administered by gavage following suspension in 0.5% methylcellulose on days 6 through 15 of gestation. [It was noted that ~~the~~ two rats receiving the low dose of 5 mg/kg/day were not dosed on gestation day 6; apparently they were accidentally omitted.]

The rats were sacrificed on gestation day 20 and the dams and pups necropsied; the pups were prepared for teratogenic and developmental toxicity evaluation.

1. Maternal Toxicity - None of the rats in the study died. A single female in the high-dose group delivered its litter on day 19, one day prior to scheduled delivery. There were no effects of pyrethrin administration with respect to body weight gain or behavioral reactions.

   There were no appearances of test chemical effects with respect to number of viable fetuses, postimplantation loss, total implantations, corpora lutea, mean fetal body weight, gravid uterine weight, or the sex ratio of the pups. There were 22, 21, 25, and 24 litters available for the control, low-, mid-, and high-dose test groups. There were also 334, 333, 357, and 341 pups available for the control, low-, mid-, and high-dose test groups.

   The NOEL for this study is > 75 mg/kg/day. This is not in agreement with the range-finding study which was reported to have demonstrated behavioral reactions at the dose level of 75 mg/kg/day.

2. Fetal Development - All of the available pups were reported to have been examined externally. Approximately one-half of the pups from each dose group were prepared for visceral examination and the remaining half were prepared for skeletal examination.

   There was no evidence of a test chemical related effect of pyrethrin on either external, visceral, or skeletal development presented. The anomalies that were reported were present in all dose groups except minor incidences of some variations, which were not present in some of the groups. One example is that "14th rudimentary ribs" were present in litters from dosed dams only. There were 5, 7, and 10 incidences in the low-, mid-, and

high-dose groups. The frequency of this type of lesion, however, did not exceed the historical control frequency.

The NOELs for both teratogenicity and fetotoxicity are > 75 mg/kg/day (HDT).

No positive control was included in this study but extensive historical control data were appended. The historical control data consisted of 25 control groups for a total of 572 dams and 3384 male and 3282 female pups from studies during the period from June, 1977 to August, 1984. The frequency of observations noted in this study were within the ranges noted for the historical controls.

[Note: Analysis of the test material as prepared for dosing was found to be 94 to 103% of the target dose levels. The dose levels are expressed as mg/kg/day of pyrethrin which was 57.574% of the weight of the test material.]

Conclusion:

CORE classification of this study is RESERVED. TB recognizes that there were no signs of maternal toxicity evident in this study as would be desirable for a CORE MINIMUM or higher study. TB, however, notes that the range-finding study reported that there were behavioral reactions in the dams at the dose level of 75 mg/kg/day, which was selected for the high-dose level in the definitive study. Since there were no indications of potential teratogenicity/developmental toxicity in this study or in the rabbit teratology study, TB does not consider it necessary at this time to request a second teratology study in rats.

The registrant is, however, requested to submit the results of the range-finding study which clearly demonstrates all the responses to the pyrethrin mixture at each of the dose levels in the range-finding study. Upon receipt and review of the data from the range finding study, TB will consider upgrading the study to CORE MINIMUM or higher.

Reviewed By: J.D. Doherty 9/11/87
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd
Section II, Toxicology Branch (TS-769C) 10/2/87

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DATA EVALUATION REPORT

Study Type: Teratology - Rabbit

TOX Chem No.: 715
MRID No.: N/A

Accession No.: 402882-03

Test Material: Pyrethrum Extract (Task Force #Blend, #FEK-99) 57.574% Pyrethrins

Synonyms:

Study Number: IRDC 556-004

Sponsor: Pyrethrin Joint Venture/CSMA

Testing Facility: International Research and Development Corporation (IRDC)

Title of Report: Evaluation of Pyrethrum Extract in a Definitive Rabbit Teratology Study

Author: J.L. Schardein

Report Issued: July 22, 1987

Conclusions:

Maternal NOEL = 25 mg/kg/day
Maternal LEL = 100 mg/kg/day, body weight gain decreased during dosing, one rabbit showed excessive salivation and head arched backward.

Teratogenicity and fetotoxicity NOEL > 250 mg/kg/day (HDT).

Levels tested 0, 25, 100, and 250 mg/kg/day.

Classification: Core-Guidelines

Special Review Criteria (40 CFR 154.7): N/A

Review:

Part I - Range-Finding Study

Only a brief description of the dose range-finding study was provided. In this study, groups of rabbits were dosed with the

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pyrethrin test material at dose levels of 37.5, 75, 150, 300, and 600 mg/kg/day. Neither the number of rabbits in each group, their condition as to pregnancy, nor the number of times they were dosed was provided. It was stated that maternal toxicity, "including tremors/convulsions, death and fetal toxicity in the form of high postimplantation loss, were observed at 600 mg/kg/day. At 300 mg/kg/day, tremors and weight loss were observed in the does during the treatment period. No obvious signs of fetal or maternal toxicity were observed at the lower levels." No data tables were provided. On this basis, the dose levels of 0, 25, 100, and 250 mg/kg/day were selected for the main definitive study. [Note: The dose is expressed in terms of pyrethrins and not total sample.]

Part II - Definitive Study

Four groups of sixteen female New Zealand White SPF (obtained from Hazleton Research Animals, Denver, Pennsylvania) rabbits were artificially inseminated with sperm obtained from bucks of the same strain. The sperm was obtained from eight bucks and pooled and diluted prior to insemination, such that the semen from one male was used to inseminate an equal number of females in each group. Immediately after insemination, ovulation was induced by an injection of 100 U.S.P units of human chorionic gonadotropin into the marginal ear vein.

The test material was administered to each doe on days 7 through 19 of gestation. Prior to administration, the test material was dispersed in 0.5% methylcellulose. The control group received the vehicle alone.

On gestation day 29, the surviving females were sacrificed with sodium pentobarbitol and their pups delivered.

Results:

1. Maternal Toxicity - None of the dams died. There were some signs of reaction to the test material in the high-dose group and in a single rabbit in the mid-dose group. These signs consisted of excessive salivation, head arched backward, and labored breathing. It should be noted that only two to three rabbits in the high-dose group and a single rabbit in the mid dose group exhibited these symptoms.

   Body weight gain was affected in the high- and mid-dose level groups during the dosing period. For example, the rabbits gained 201, 211, 129, and 38 grams for the control, low-, mid-, and high-dose test groups, respectively. Overall, for the 0 to 29 days of gestation, there was no marked effect on body weight gain.

Other indices of maternal toxicity, including viable fetuses, postimplantation loss, total implantations, or corpora lutea, did not show evidence of test chemical effects.

One doe in the high-dose group aborted near term, but there was no convincing evidence presented that this abortion was due to the test material. Another doe in the high-dose group had a totally resorbed litter, but again there was no evidence that this was due to the test material.

A NOEL for maternal toxicity is assigned as 25 mg/kg/day.

2. Fetal morphological observations (structural anomalies that alter general body conformity, disrupt or interfere with body function or are generally thought to be incompatible with life) and developmental variations (alterations in anatomic structure that are considered to have no significant biological effect on animal health or body conformity, representing slight deviations from normal).

There were 122, 103, 97, and 101 live fetuses available in the control, low-, mid-, and high-dose level test groups, respectively, which were examined externally, viscerally, and skeletally.

There were no patterns of test chemical-related increases in either morphological or developmental anomalies evident. There was no test chemical effect noted on either the sex ratio or the body weights of the fetuses.

The NOEL for both teratogenicity and fetotoxicity is assigned as > 250 mg/kg/day.

No positive control was included in this study but extensive historical control data were appended. The historical control data consisted of 17 control groups for a total of 290 dams and 950 male and 893 female pups from studies during the period May, 1985 to October, 1986. The frequency of observations noted in this study were within the ranges noted for the historical controls.

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Conclusion:

This study is CORE GUIDELINES. The following one-liner pertains:

Maternal Toxicity NOEL = 25 mg/kg/day
Maternal Toxicity LEL = 100 mg/kg/day; body weight gain during treatment decreased, one rabbit showed signs of excessive salivation and head arched backward.
Teratogenicity and Fetotoxicity NOEL > 250 mg/kg/day (HDT).

Note: The test material was analyzed for stability and for homogeneity in 0.5% methylcellulose. Data were presented to show that the pyrethrins were stable for 24 hours and that samples from the top, middle, and bottom were within ± 5% of the mean values. The test article concentrations were also reported to be 90 to 104% of the claimed concentrations of 25, 100, and 250 mg/kg/day.

The dose levels are expressed in terms of pyrethrins, which make up 57.574% of the actual sample.

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