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

JUN 12 1995

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Pyrethrins

CASRN. 121-21-1
EPA Chem. Code: 069001
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FROM: George Z. Ghali, Ph.D. *G. Ghali*
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THRU: William Burnam
Chairman, RfD/Peer Review Committee
Health Effects Division (7509C)

TO: Rick Keigwin, PM 10
Insecticide-Rodenticide Branch
Registration Division (7505C)

Chief, Reregistration Branch
Special Review and Reregistration Division (7508W)

The Health Effects Division RfD/Peer Review Committee met on June 1, 1995 to discuss and evaluate the existing and recently submitted toxicology data in support of Pyrethrins re-registration and to assess the Reference Dose (RfD). Pyrethrins (Pyrethrum) are a mixture of botanical pesticides the active principles of which are **PYRETHRINS I and II** (esters of pyrethrolone and chrysanthemic acid and pyrethroic acid), **CINERINS I and II** (esters of cinerolone and chrysanthemic and pyrethroic acids), and **JASMOLIN I and II** (esters of jasmolin and chrysanthemic and pyrethroic acids), collectively known as pyrethrins.

Material available for review included data evaluation records (DERs) for a 2-year chronic toxicity/carcinogenicity study in rats (83-1a and -2a or 83-5), a carcinogenicity study in mice (83-2b), a one-year feeding study in dogs (83-1b), a reproductive toxicity study in rats (83-4), developmental toxicity studies in rats (83-3a) and rabbits (83-3b), an acute neurotoxicity study in rats (81-8) and a subchronic inhalation toxicity study in rats (82-4).



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A. Chronic and subchronic Toxicity

The Committee considered the chronic toxicity phase (83-1a, MRID No. 41559501) of the combined chronic toxicity/carcinogenicity study in rats to be acceptable and the data evaluation record (HED Doc. No. 010798) to be adequate. The Committee recommended revising the NOEL/LOEL in males from 4.37 and 42.9 mg/kg/day to 42.9 and 130 mg/kg/day, respectively. The Committee discounted the accentuated lobulation of the liver. The NOEL/LOEL were mainly based on body weight decreases in males and females and the increased incidences of liver spongiosis hepatitis in males at 3000 ppm (130 mg/kg/day in males and 173 mg/kg/day in females). Otherwise, the Committee agreed with the evaluation and interpretation of the data. The Committee recommended downgrading the study from Core-minimum to Core-supplementary until the rereading of the histopathological slides is completed and a report is submitted to the Agency for reevaluation of the histopathological changes. Therefore, the NOEL/LOEL established for this study should be regarded as tentative values until the requested histopathological information are made available to the Committee. The request for histopathological information was originally made by the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC) and is being again reiterated by the HED-RFD/Peer Review Committee.

The Committee did not discuss the chronic toxicity phase of the mouse carcinogenicity study (83-2b, MRID No. 41559401, HED Doc. No. 010798). Again, the RfD Committee reiterated a recommendation made by the HED-CPRC with respect to rereading of histopathological slides. Without this information it would be difficult to accurately determine the overall NOEL/LOEL for systemic effects observed in this study.

The Committee deferred to the respective branch to determine the appropriate action once the slides rereading reports for the rat and mouse studies are received. The respective branch, at its discretion, may refer the matter again to the RfD/Peer Review Committee for consideration.

The Committee considered the chronic toxicity study in dogs (83-1b, MRID No. 41496501) to be acceptable and the data evaluation records (HED Doc. No. 011395) to be adequate. The NOEL/LOEL in this study were considered to be 13.7 and 66.4 mg/kg/day, respectively, based on liver weight increase in males (30%, $P < 0.05$) and females (25%, not significant). The Committee agreed with the evaluation and interpretation of data and classification of the study.

The Committee did not discuss the subchronic inhalation toxicity study in rats (MRID No. 42478201, HED Doc. No. 011068). The toxicity issue in this study will be addressed elsewhere and when inhalation exposure data are made available.

B. Carcinogenicity

The Committee did not discuss the carcinogenicity phase (83-2a, MRID No. 41559501) of the combined chronic toxicity/carcinogenicity study in rats and the carcinogenicity study in mice (83-2b, MRID No. 41559401). The carcinogenic potential of pyrethrins has been addressed by the HED-CPR Committee. Although the chemical was not classified as to carcinogenicity, a Q1* was assigned based on thyroid follicular cell tumors in female rats. Additional information were deemed necessary before a classification could be designated.

C. Reproductive and Developmental Toxicity

The Committee considered the reproductive toxicity study in rats (83-4, MRID No. 41327501) to be acceptable and the data evaluation record (HED Doc. No. 008639) to be adequate. The Committee recommended revising the systemic toxicity NOEL/LOEL from 6.4 and 65 mg/kg/day to 65 and 196 mg/kg/day, respectively, based upon body weight decreases in F1 adult males and in F1 adult females during the premating period and day 0 and 6 of gestation and during lactation for the F2a and F2b pups. The data evaluation record of this study should be altered to reflect the recommendations made by the Committee regarding the changes in the systemic NOEL/LOEL. Otherwise, the Committee agreed with the evaluation and interpretation of the data and classification of the study. The reproductive toxicity NOEL/LOEL were considered to be 6.4 and 65 mg/kg/day based upon decreased pup weights of F1b female observed on post-partum day 14, 21 and 28. Pup birth weight decreases were also observed at 196 mg/kg/day in F2a and possibly F2b.

The Committee considered the developmental toxicity study in Sprague-Dawley rats (83-3a, MRID No. 40288202, 40603701), when viewed together with the range finding study, to be acceptable and the data evaluation record (HED Doc. No. 006348, 006824) to be adequate. The maternal toxicity NOEL was considered to be 75 mg/kg/day, the highest dose tested in the main developmental toxicity study. The developmental toxicity NOEL was considered to be 75 mg/kg/day. It should be noted that doses up to 150 mg/kg/day tested in the range finding study did not cause maternal or developmental toxicity.

The Committee considered the developmental toxicity study in rabbits (83-3b, MRID No. 40288203, 40603702) to be acceptable and the data evaluation record (HED Doc. No. 006348, 006824), except for minor additions, to be adequate. The Committee recommended that summary data tables on body weight, body weight gain at the mid- and high-dose levels in addition to litter data be included to support the conclusions made in the data evaluation record of this study. The maternal toxicity NOEL/LOEL were considered to be 25 and 100 mg/kg/day based on decreased body weight gain, excess

salivation in 1 dam and arched backward head in 1 dam. In the range-finding study, tremors/convulsions and death occurred at 600 mg/kg/day. The developmental toxicity NOEL/LOEL were set at 250 and 600 mg/kg/day, respectively. No developmental effects were observed at 250 mg/kg/day, the highest dose level tested in the main study. Post-implantation loss was observed at 600 mg/kg/day in the range-finding study.

The Committee did not recommend for a developmental neurotoxicity study.

D. Acute and Subchronic Neurotoxicity

The Committee considered the acute neurotoxicity study in rats (81-7, MRID No. 42925801, 42930401) to be acceptable and the data evaluation record (HED Doc. No. 010883) to be adequate. The study demonstrated a NOEL/LOEL for neurotoxicity of 20 and 63 mg/kg/day based on the presence of tremors in females. The treatment was associated with neuropathy at 200 mg/kg/day in females and 400 mg/kg/day in males, the highest dose levels tested.

No subchronic neurotoxicity study (82-7) was available for review by the Committee.

E. Reference Dose (RfD)

The Committee recommended that an RfD be established based on the reproductive toxicity study in rats with a NOEL of 100 ppm (6.4 mg/kg/day). Treatment related effects including decreased pup weights in F1b females were observed on post-partum days 14, 21 and 28 at 1000 ppm (65 mg/kg/day). An Uncertainty Factor (UF) of 100 was applied to account for both interspecies extrapolation and intraspecies variability. On this basis, the RfD was calculated to be 0.064 mg/kg/day.

F. Individuals in Attendance

Peer Review Committee members and associates present were William Burnam (Chief, SAB; chairman, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), George Ghali (Manager, RfD/Peer Review Committee), Rick Whiting, William Sette, Henry Spencer, and David Anderson.

Scientific reviewer (Committee or non-committee member(s) responsible for data presentation; signature (s) indicate technical accuracy of panel report).

John Doherty

W. Copley for JD

Marion Copley

Marion Copley

Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke

Karl D. Baetcke

CC: Stephanie Irene
Debra Edwards
Karl Baetcke
John Doherty
Marion Copley
Karen Whitby
Albin Kocialski
Kerry Dearfield
Beth Doyle
RfD File
Caswell File

G. Material Reviewed

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1. Goldenthal, E. I. (1990). Evaluation of pyrethrum extract in a two-year dietary toxicity and oncogenicity study in rats. MRID No. 41559501, HED Doc. No. 010798. Classification: Core-supplementary data as downgraded by the Committee. This study as presented does not satisfy data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.
2. Goldenthal, E. I. (1990). Evaluation of pyrethrum extract in an eighteen month dietary oncogenicity study in mice. MRID No. 41559401, HED Doc. No. 010798. This study has not been discussed by the RfD Committee.
3. Goldenthal, E. I. (1990). Evaluation of pyrethrum extract in one year chronic toxicity study in dogs. MRID No. 41496501, HED Doc. No. 011395. Classification: Guideline data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
4. Schardein, J. L. (1989). Two-generation reproduction study in rats with pyrethrum extract. MRID No. 41327501, HED Doc. No. 008639. Classification: Guideline data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.
5. Schardein, J. L. (1987). Evaluation of pyrethrum extract in a definitive rat teratology study. MRID No. 40288202, 40603701, HED Doc. No. 006348, 006824. Classification: Core-minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.
6. Schardein, J. L. (1987). Evaluation of pyrethrum extract in a definitive rabbit teratology study. MRID No. 40288203, 40603702, HED Doc. No. 006348, 006842. Classification: Guideline data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.
7. Hermansky, S. J. and Hurley, J. M. (1993). Acute oral neurotoxicity study with pyrethrum. MRID NO. 42925801, 42930401, HED Doc. no. 010883. Classification: Guideline data. This study satisfies data requirement 82-7 of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity testing in rats.
8. Newton, P. E. (1992). Subchronic (3-month) inhalation toxicity study of pyrethrum extract in the rat via whole-body exposure. MRID No. 42478201, HED Doc. No. 011068. Classification: Core-minimum data (according to the data evaluation record). This study was not discussed by the Committee.