8-25-93

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

25 AUG 1993 FILE

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Cyhalothrin / Karate

CASRN. 68085-85-8
EPA Chem. Code: 128867
Caswell No. 271F

FROM: George Z. Ghali, Ph.D. G. Ghali 7.19.93
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: George La Rocca, PM 13
Insecticide-Rodenticide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on February 12, 1993 to reassess the Reference Dose for Cyhalothrin in light of additional information provided by the respective branch.

Cyhalothrin and karate are basically the same chemical, the differences are found in their stereo chemistry and the number of isomers in each mixture. Cyhalothrin consists of four stereo isomers while karate is a mixture of two isomers. The two karate isomers are contained in cyhalothrin, they represent 40% of the cyhalothrin mixture. The major studies submitted to the Agency were conducted with cyhalothrin. However, these studies are used in support of registration for both mixtures. There is some evidence, based on subchronic studies in rats, that the two mixtures are not biologically different with respect to their mammalian toxicity.

In an attempt to establish a Reference Dose (RfD) for this chemical in the meeting of 1986, and because of the complexity of the issue at hand, the Health Effects Division RfD Committee was confronted with three options: a) to establish a reference dose for cyhalothrin and then derive a separate reference dose for karate accounting for the fact that only 40% of the cyhalothrin was actually karate, b) to establish a reference dose for cyhalothrin and request all pivotal studies with karate before establishing a separate reference dose for karate, or c) to establish one reference dose for both cyhalothrin and karate based on studies conducted with cyhalothrin.

1/8

The consensus of the RfD Committee was to generate one reference dose for both chemicals using data from studies conducted with cyhalothrin since there is evidence that there is no significant difference in the toxicity of different stereo isomeric mixtures of this chemical. For some regulatory reasons, establishing separate reference doses constitutes underestimation of risk by exposing the population to excessive levels of residues. Furthermore, setting two separate reference dose for stereoisomers of the same compound might be inconsistent with the practice of setting combined tolerances on salts, acids and esters of the same chemical; the basic biological/toxicological properties remain the same even though these different forms of the same compound are not chemically identical.

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on May 19, and May 29, 1986 and verified by the Agency RfD Work Group on July 15, 1987. At that time the RfD was based on a NOEL of 10 ppm (0.5 mg/kg/day) for decreased weight gains in pups and parents observed at 30 ppm (1.5 mg/kg/day) in a three-generation reproduction study in rats. An Uncertainty Factor (UF) of 100 was used to account for the interspecies extrapolation and intraspecies variability.

Subsequently, in the meeting of February 12, 1993 the Committee decided to increase the NOEL for the reproductive/ systemic toxicity in the multi-generation reproduction study in rats conducted with cyhalothrin from less than 0.5 mg/kg/day to 1.5 mg/kg/day, and the LOEL was changed from 1.5 mg/kg/day to 5 mg/kg/day, based upon decreased parental and pup body weights. In addition, the developmental NOEL was to be set at 100 ppm, the highest dose tested. Furthermore, the Committee lowered the NOEL for the dog study to 0.1 mg/kg/day.

The RfD/Peer Review Committee recommended that the RfD should be revised accordingly. The RfD is currently based upon a NOEL of 0.1 mg/kg/day for clinical signs of neurotoxicity and other effects observed at 0.5 mg/kg/day in a long-term study in dogs using an uncertainty factor (UF) of 100 to account for the inter-species extrapolation and intra-species variability. **On this basis the RfD was calculated to be 0.001 mg/kg/day.**

The Committee considered the high dose tested in the rat carcinogenicity study to be approaching adequate dose. Based on the range finding study in the same strain of rats, it is evident that the animal could have tolerated higher doses. Data from the range finding study indicated that body weight gain in males and females was reduced by 10 and 6% respectively. Generally, the highest dose tested in the mouse carcinogenicity study appears to be approaching an adequate dose for carcinogenicity testing in males based upon decreased body weight gain. On the other hand, several questions were raised concerning the adequacy of doses tested and the incidence of mammary tumors in females. The

Committee requested any relevant data supporting the dose levels selected for the carcinogenicity testing in mice and any available historical control data for the mammary tumors observed in this study before any final decision can be made with respect to this study. The chemical was classified, tentatively, as a "Group D" carcinogen.

A. Individual in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Marcia Van Gemert

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

James Rowe

George Ghali

Rick Whiting

2. Scientific Reviewer(s) (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Pam Hurley

Roger Gardner

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Roger Gardner
Pam Hurley
Rick Whiting
James Kariya

B. Material Reviewed

Material available for review included a chronic toxicity study in rats (83-5 or 83-1a and -2a), a long-term toxicity study in dogs (83-1b), developmental toxicity studies in rats and rabbits (83-3a and -3b), a reproductive toxicity study in rats (83-4) and a tox. one-liner. The deliberation was mainly focused on the following studies:

1. Hext, P. et al. (1986). One-year oral dosing study in dogs. MRID No. 40027902, HED Doc No. 006004.

Core Classification: According to the data evaluation record, the study is classified as Guideline.

Committee's Conclusions and Recommendations:

In this study the chemical was tested at 0.1, 0.5 and 3.5 mg/kg/day. Generally the Committee agreed with the reviewer's evaluation and interpretation of data. However, the Committee felt that the no-observable effect level can be set best at 0.1 mg/kg/day and not at 0.5 mg/kg/day. Some neurotoxicity signs were evident at 0.5 mg/kg/day. The Committee considered the study to be acceptable and the data evaluation record to be adequate. This study fulfills data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in non-rodent species.

2. Piggot, G. H. et al. (1984). Two-year feeding study in rats. MRID No. 00154803, HED Doc. No.005100.

Core Classification: According to the data evaluation record, the study is classified as Guideline.

Committee's Conclusions and Recommendations:

In this study the chemical was tested at 10, 50, 250 ppm. Generally, the Committee agreed with the reviewer's evaluation and interpretation of data. Based on the range finding study in the same strain of rats, it is evident that the animal could have tolerated higher doses. Data from the range finding study indicated that body weight gain in males and females was reduced by 10 and 6% respectively. However, the Committee considered the high dose tested in the rat carcinogenicity study to be, at least, approaching adequate dose. This study fulfills data requirement 83-1a and -2a (or 83-5) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

3. Colley, J. et al. (1984) Cyhalothrin: potential tumorigenic and toxic effects in prolonged dietary administration to mice. MRID No. 00150842, 00153035, HED Do. No. 005100.

Core Classification: According to the data evaluation record, the study is classified as Core-minimum.

Committee's Conclusions and Recommendations:

In this study the chemical was tested at 20, 100, 500 ppm. There was no rationale provided for dose selection in this study. Generally, the highest dose tested in the mouse carcinogenicity study appears to be approaching an adequate dose for carcinogenicity testing in males based upon decreased body weight gain. On the other hand, several questions were raised concerning the adequacy of doses tested and the incidence of mammary tumors in females. The Committee requested any relevant data supporting the dose levels selected for the carcinogenicity testing in mice and any available historical control data for the mammary tumors observed in this study before any final decision can be made with respect to this study.

4. Milburn, G. M. et al. (1984). Cyhalothrin: three-generation reproduction study in the rat. MRID No. 00154802, HED Doc No. 005100, 005161.

Core Classification: According to the data evaluation record, the study is classified as Guideline.

Committee's Conclusions and Recommendations:

In this study the chemical was tested at 10, 30, 100 ppm. Generally, the Committee agreed with the reviewer's evaluation and interpretation of data. However, the Committee decided to increase the NOEL for the reproductive/ systemic toxicity in the multi-generation reproduction study in rats conducted with cyhalothrin from less than 0.5 mg/kg/day to 1.5 mg/kg/day, and the LOEL was changed from 1.5 mg/kg/day to 5 mg/kg/day, based upon decreased parental and pup body weights. In addition, the developmental NOEL was to be set at 100 ppm, the highest dose tested. The study is acceptable and the data evaluation record, except for the revision of the no-observable levels, is considered adequate. This study fulfill data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

C. Conclusions and Recommendations

1. Data Base

The Committee recommended to increase the NOEL for the reproductive/ systemic toxicity in the multi-generation reproduction study in rats conducted with cyhalothrin from less than 0.5 mg/kg/day to 1.5 mg/kg/day, and the LOEL was changed from 1.5 mg/kg/day to 5 mg/kg/day, based upon decreased parental and pup body weights. In addition, the developmental NOEL was to be set at 100 ppm, the highest dose tested. Furthermore, the Committee lowered the NOEL for the dog study to 0.1 mg/kg/day.

2. Reference Dose (RfD)

The RfD is currently based upon a NOEL of 0.1 mg/kg/day for clinical signs of neurotoxicity and other effects observed at 0.5 mg/kg/day in a long-term study in dogs using an uncertainty factor (UF) of 100 to account for the inter-species extrapolation and intra-species variability. **On this basis the RfD was calculated to be 0.001 mg/kg/day.**

3. Carcinogenicity

The Committee considered the high dose tested in the rat carcinogenicity study to be approaching adequate dose. Based on the range finding study in the same strain of rats, it is evident that the animal could have tolerated higher doses. Data from the range finding study indicated that body weight gain in males and females was reduced by 10 and 6% respectively. Generally, the highest dose tested in the mouse carcinogenicity study appears to be approaching an adequate dose for carcinogenicity testing in males based upon decreased body weight gain. On the other hand, several questions were raised concerning the adequacy of doses tested and the incidence of mammary tumors in females. The Committee requested any relevant data supporting the dose levels selected for the carcinogenicity testing in mice and any available historical control data for the mammary tumors observed in this study before any final decision can be made with respect to this study. The chemical was classified, tentatively, as a "Group D" carcinogen.

4. Acute and Subacute Concern

There was no evidence, based on the available data, that the chemical can be considered a reproductive or developmental toxicant under the testing conditions. The chemical did not produce frank

developmental or reproductive toxicity under the testing conditions.

There were no data available for review to address or characterize the hazard of a one-time or one-day exposure for other toxicological end-points. However, data available for review did not indicate that a one-day exposure to the chemical would be of such concern as to warrant the need for acute exposure studies to be used in an acute dietary risk assessment.