MEMORANDUM

SUBJECT: RfD/Peer Review Report of Cypermethrin [(±)-α-Cyano-3-phenoxymethyl (±)-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate]

CASRN: 52315-07-8
EPA Chem. Code: 109702
Caswell No.: 268AA

FROM: George Z. Ghali, Ph.D. Manager, RfD/QA Peer Review Committee Health Effects Division (7509C)

THROUGH: William Burnham Chairman, RfD/QA Peer Review Committee Health Effects Division (7509C)

TO: George LaRocca, PM 13 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 6, and again on July 11, 1996 to discuss and evaluate the existing and/or recently submitted toxicology data in support of Cypermethrin re-registration and to re-assess the Reference Dose (RfD) for this chemical.

It should be noted that some of the studies included for review by the RfD Committee were conducted with technical Cypermethrin (a mixture of approximately equal parts of 8 isomers) and others were conducted with Cypermethrin-S (PC Code: 129064, Tox Chem. No. 271DE, also referred to as Cypermethrin minus), an insecticidally active isomer enriched preparation. The Committee was requested to address a question posed by the respective branch as whether studies conducted with Cypermethrin-S can fulfill the Guideline requirement series 83-3a.
(developmental toxicity with rats), 83-4 (reproductive toxicity in rats), and 84-2 (mutagenicity) for technical Cypermethrin. It was the Committee's position that sufficient data are available on technical Cypermethrin to preclude the need to use data generated with Cypermethrin-S to support the requirements for technical Cypermethrin reregistration.

Material available for review with technical Cypermethrin included data evaluation records (DERs) for a chronic toxicity/carcinogenicity study in rats (83-5), a chronic toxicity study in dogs (83-1b), a carcinogenicity study in mice (83-2b), reproductive toxicity studies in rats (83-4), developmental toxicity studies in rats and rabbits (83-3a and -3b), subchronic toxicity studies in rats and dogs (82-1a and -1b), acute neurotoxicity studies in rats (81-8), a subchronic neurotoxicity study in rats (82-7) and mutagenicity studies (84-2).

The respective branch requested the Committee to determine the need for a new HED Cancer Peer Review evaluation (see Carcinogenicity Section Below).

In the first meeting (June 6, 1996), the Committee could not make a definitive conclusion on this chemical and recommended updating/upgrading some of the DERs. The following are the conclusions made by the Committee in the second meeting (July 11, 1996) on this chemical.

A. Chronic and Subchronic Toxicity:

The Committee reviewed the chronic feeding aspects of the combined chronic toxicity/carcinogenicity study in rats (83-5, MRID No. 00112910, 92027041). In the first meeting the Committee recommended that the data be reevaluated and the DER (HED Doc. No. 003249) be updated and summary data tables and an executive summary be added. In the second meeting, the study was considered acceptable and the updated/upgraded DER (HED Doc. No. 012057) was considered adequate. The NOEL/LOEL were 150 and 1500 ppm (~7.5 and 75 mg/kg/day respectively) based on reduced body weight gain, increased liver weights in females, slight effects on several hematological parameters and clinical chemistry parameters, decrease in urine volume, pH and an increase in the specific gravity in both males and females.

The Committee discussed the chronic toxicity study in dogs (83-1b, MRID No. 00112909, 42068503, 92027037). In the first meeting the Committee recommended that the data be reevaluated and the DER (HED Doc. No. 003249, 003647, 005159) be updated and summary data tables and an executive summary be added. In the second meeting, the study was considered acceptable and the updated DER (HED Doc. No. 012057) was considered adequate. The NOEL/LOEL were 1 and 5 mg/kg/day, respectively, based on gastrointestinal effects. At 15 mg/kg/day there were additional
neurological effects as indicated by clinical signs.

There were subchronic toxicity studies in rats and dogs (82-1a and -b, MRID No. 00056802, 92027034; 00112929, HED Doc. No. 004825) on technical Cypermethrin available for review, but were not reviewed by the Committee in the first meeting. The DERs for these studies were subsequently updated (HED Doc. No.: 012057). The rat and dog chronic feeding studies were considered by the RfD Committee to supplant the information provided by the subchronic studies.

B. Carcinogenicity:

The Committee did not discuss the carcinogenicity studies in rats (83-5, MRID No. 00112910, 92027041, HED Doc. No. 003249, 003647 and 012057) and in mice (83-2b, MRID No. 00112911, 92027038, HED Doc. No. 003249, 003647 and 012057) although updated and upgraded DERs were prepared for these studies. The carcinogenicity issue had been already addressed by the HED-Carcinogenicity Peer Review Committee and technical Cypermethrin was classified as C, possible human carcinogen, based on increases in the lung adenomas in female CD-1 mice. The evidence (being common tumor, one species, one sex, no proportional increase in malignancy or decrease in the time to tumor) was not considered strong enough to warrant a quantitative estimation of human risk using a Q1* (HED-CPR report dated February 17, 1988). An RfD approach was recommended for human risk assessment purposes.

The respective branch requested the Committee to advise as whether the carcinogenicity issue should be brought back to the HED-Carcinogenicity Peer Review Committee (HED-CPRC). The RfD Committee determined that since there were no new data to impact the previous CPRC decision, technical Cypermethrin should not be reconsidered by the CPRC.

C. Developmental and Reproductive Toxicity:

The Committee considered the 3-generation reproductive toxicity study in rats (83-4, MRID No. 00112912, 42068504, 92027040) to be acceptable and the updated/upgraded DER (HED Doc. No. 012057) to be adequate. The NOEL/LOEL for parental/systemic toxicity were considered to be 2.5 and 7.5 mg/kg/day, respectively, based on decreased body weight gain in both sexes. The NOEL for reproductive toxicity was considered to be 37.5 mg/kg/day, the highest dose level tested.

There was an older reproductive toxicity study in rats (83-3b, 1979, MRID No. 00090040, HED Doc. No. 012057 updated/upgraded version) available for review and was considered to be supplementary.
The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 00056804, 92027039, 92027061) to be acceptable and the updated/upgraded DER (HED Doc. No. 012057) to be adequate. The NOEL/LOEL for maternal toxicity were considered to be 17.5 and 35 mg/kg/day, respectively, based on body weight gain decrease. No effects on either skeletal or visceral structures were reported. The NOEL for developmental toxicity was considered to be 70 mg/kg/day, the highest dose level tested.

The Committee considered the developmental toxicity study in rabbits (83-3b, MRID No. 43776301-pilot study, 43776302-main study) to be acceptable and the DER (HED Doc. No. 012056) to be adequate. The NOEL/LOEL for maternal toxicity were considered to be 100 and 450 mg/kg/day, respectively, based on decreased body weight gain. There were no indications of developmental toxicity. The NOEL and LOEL for developmental toxicity was considered to be 700 mg/kg/day, the highest dose level tested.

There was an older developmental toxicity study in rabbits (83-3b, 1978, MRID No. 00056807, HED Doc. No. 012057 updated/ upgraded version) available for review by the Committee and was considered to be supplementary.

D. Mutagenicity:

The mutagenicity issue has already been addressed in conjunction with the Carcinogenicity Peer Review (HED-CPR report dated February 17, 1988). Additional mutagenicity studies were submitted subsequent to the Carcinogenicity Peer Review and found to be acceptable and were reported to be negative.

E. Neurotoxicity:

There were three neurotoxicity studies with rats available for review by the Committee: 1) an acute neurotoxicity screening study in rats (81-8, MRID No. 43152001, HED Doc. No. 010888); 2) a non-guideline neurotoxicity screening study in rats (HED Doc. No.: 010888); and 3) a subchronic neurotoxicity study in rats (82-7, MRID No.: 43152002, HED Doc. No.: 010888). The DERs for all three studies were considered adequate by the Committee. The first listed acute study and the subchronic study were considered ACCEPTABLE but the non-guideline acute study was considered SUPPLEMENTARY.

The NOEL and LOEL for the first listed study were considered to be 30 and 100 mg/kg/day, respectively, based on ataxia and related conditions (described as staggered or impaired gait, decreased activity and splayed hind limbs), decreased motor activity and salivation and lacrimation. The non-guideline study which was classified as SUPPLEMENTARY primarily because no histopathology was included, however, demonstrated a NOEL and
LOEL of < 20 mg/kg based on decreased motor activity and gait abnormalities and this study should be used for risk assessment.

The NOEL and LOEL for subchronic neurotoxicity were considered to be 31 and 77 mg/kg/day, respectively, based on ataxia, splayed hind limbs, impaired gait, decreased motor activity and decreased body weight gain.

F. Reference Dose (RfD):

The Committee recommended that the RfD for this chemical remain unchanged. The RfD was originally established based on a one-year oral dosing study in dogs with a NOEL of 1 mg/kg/day. Gastrointestinal tract disturbances were reported at the next higher dose level of 5 mg/kg/day. An Uncertainty Factor of 100 was used to account for both interspecies extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.01 mg/kg/day.

It should be noted that this chemical has been reviewed by the WHO/FAO Joint Meeting on Pesticide Residue (JMPR) and an ADI of 0.05 mg/kg/day has been established in 1981.
G. **Individuals in Attendance:**

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Acting Chief, TB II), Kit Farwell, Nancy McCarroll, Guruva Reddy, James Rowe, William Sette, Henry Spencer, and Rick Whiting.

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

- John Doherty
- Marion Copley

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated):

- Karl Baetcke

CC: Stephanie Irene
Debra Edwards
Albin Kocialski
Karl Baetcke
Marion Copley
John Doherty
Beth Doyle
Amal Mahfouz (OW)
RfD File
Caswell File
H. Material Reviewed:


2. Lindsay, S. et al. (1982). Cypermethrin: Lifetime Feeding Study in Mice: MRID No. 00112911, 92027038, HED Doc. No. 003249, 003647, 012057 (updated/upgraded DER). Classification: Acceptable (according to the DER). This study was evaluated by the Carcinogenicity Peer Review Committee and it satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.


5. Hend, R. W. et al. (1979). Toxicity study on the insecticide WL 43467: A three generation reproduction study in rats. MRID No. 00090040, HED Doc. No. 002391, 012057. Classification: Supplementary. This study does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

6. Hoberman, A. (1991). Multigeneration Study with FMC 56701 Technical Administered Orally via Diet to Crl:CD (SD) BR Rats. MRID No. 41968205, HED Doc. No. 009347. Classification: Core guideline data. This study was conducted with Cypermethrin-S, the enriched preparation, and therefore was not used in support of the Cypermethrin re-registration.

8. Hoberman, Alan M. (1990). Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of FMC 56702 Technical Administered Orally Via Gavage to® (SD) BR Presumed Pregnant Rats. MRID No. 41776102, HED Doc No. 009347. Classification: Core guideline data. This study was conducted with Cypermethrin-S, the enriched preparation, and therefore was not used in support of the Cypermethrin re-registration.


12. McCarty, Jane D. (1990). Ninety-Day Feeding Study in Rats. MRID No. 41776101, HED Doc No. 008865. Classification: Acceptable. This study was conducted with Cypermethrin-S, the enriched preparation, and therefore could not be used in support of the Cypermethrin re-registration.


Effects of Two Pyrethroids Permethrin and Cypermethrin.
MRID No. (none), HED Doc. No. 010888. Classification: Supplementary. This study does not satisfy data requirement 81-7 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in rats.
