5-19-86

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#2F2623: Cypermethrin: Registrant's request to Toxicology Branch to reconsider the NOEL for the dog 1-year dosing study set at 1.0 mg/kg/day based on increased incidences of liquid stools.

Tox. Chem. No. 271DD
Tox. Project No. 994
Record No. 162312

FROM: John Doherty 5/19/86
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: George LaRocca, PM 15
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

THRU: Edwin Budd 5/19/86
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Background:

In the original review of the dog 1-year dosing study with the synthetic pyrethroid cypermethrin (see J. Doherty review dated September 16, 1983 for PP#2F2623 and FAP#2H5334), Toxicology Branch (TB) assigned a NOEL of 1.0 mg/kg/day for this study based on increased incidences of passing of liquid stools. The net response over the 52-week period for the frequency of this effect of cypermethrin is as follows:

	Males	Females
Control	28	25
Low (1.0 mg/kg/day)	19	35
Mid (5.0 mg/kg/day)	133	254
High (15.0 mg/kg/day)	875	767

183

2

When the review was prepared, TB requested that some additional testing be conducted to help to determine if the increased incidences of liquid stools were the result of CNS stimulation or a direct action on the gastrointestinal system.

In subsequent correspondence, the ICI Corporation (refer to the letter from Dr. R.E. Ridsdale dated December 9, 1983) agreed to accept the NOEL of 1.0 mg/kg/day "for the present time and subject petition" and chose not to conduct additional testing at that time. The registrant, however, maintained the position that the proper NOEL for this study is 5.0 mg/kg/day.

In the current submission, the registrant is requesting that TB reconsider the assignment of the NOEL as 1.0 mg/kg/day based upon the following reasoning:

1. The liquid stools were not diarrhea and they were passed at normal frequency. In addition, the dogs maintained good clinical health throughout the study and there was no evidence of accompanying pathology or large changes in body weight.

2. There was also a predisposition to pass liquid stools among the control dogs and the cypermethrin dosing increased the number of occasions on which this phenomenon occured.

3. Some of the dogs eventually recovered. During the second half of the experiment the dogs in the 5.0 mg/kg dosing group were similar to the controls.

4. The phenomenon was related to the method of dosing and occurs when the cypermethrin is given by capsule but not by incorporation into the diet. The phenomenon is thus related to a local irritation caused by the chemical in the gastrointestinal system.

TB Discussion of the Registrant's Submission

The registrant has not provided a sufficient basis for reassignment of the NOEL from 1.0 mg/kg/day to the higher level of 5.0 mg/kg/day.

1. The increased incidences of liquid stools could still be the result of stimulation of the CNS by cypermethrin.

2. Although the phenomenon was not frank diarrhea, the 4 (males) to 10 (females) fold increases in incidences noted in the mid-dose groups (5 mg/kg/day) indicate that the test chemical has an effect.

2

3. Although the dogs in the mid-dose appear to recover, the study shows that they were affected for about 6 months.

4. Not all agents which cause moderate irritation of the skin also result in the passing of liquid stools in dog studies. Moreover, the non-cyano-substituted pyrethroids are about the same as skin irritants, but do not result in similar disturbances of the gastrointestinal tract.

5. TB notes that the dog-90 day feeding study (where the test material was incorporated into the feed) with cypermethrin (see J. Doherty review dated October 28, 1981 for EPA Reg. No. 10182-EUP-19 and PP 1G2461 and FAP 1H5287) has a NOEL of 500 ppm (approximately 12.5 mg/kg/day) and an LEL of 1500 ppm (approximately 37.5 mg/kg/day). At the LEL the dogs had increased incidences of diarrhea. Thus, response at 5.0 mg/kg/day in the dogs in the 1-year study when the test material was administered by capsule may be related to the method of administration.

6. Since exposure to humans will be better approximated by the feeding studies, the dog 1 year dosing study with a NOEL of 1.0 mg/kg/day possibly may not be the most appropriate study to be used in setting the ADI.

In conclusion, TB cannot change the NOEL for this 1-year dog dosing study from 1.0 mg/kg/day to 5.0 mg/kg/day as requested by the registrant. However, the dog 1-year study may not be the most appropriate study for setting the ADI.

Reassessment of the ADI

The setting of the ADI for cypermethrin will soon be re-evaluated by the TB/ORD RFD/ADI committee. At that time the study deemed to be most appropriate for setting the ADI will be selected.

Note to product manager: Please request that the ICI Company provide verification of the content of cypermethrin in the diet for the 90 day dog feeding study mentioned above.

3

4