5/18/93

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

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Cyfluthrin: Meeting of Ad Hoc Committee to Discuss Developmental Toxicity Database

Tox.Chem No.: 266E
PC Code: 128831

From: John C. Redden, Toxicologist
Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

To: File

Thru: Karen L. Hamernik, Ph.D.
Acting, Section Head Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

CONCURRENCE:

James N. Rowe — James Rowe Toxicology Branch II
Stephen C. Dapson — Steven Dapson Toxicology Branch II
David McAnderson — David Anderson Toxicology Branch I
Roger Gardner — Roger Gardner Toxicology Branch I

An ad hoc committee meeting was convened on 4/22/93 to discuss concerns raised about the suitability of the Developmental Toxicity database for Cyfluthrin. The committee members were: James Rowe, TBII, Steven Dapson, TBII, David Anderson, TBI, and Roger Gardner, TBI. Karen Hamernik, TBI and John Redden, TBI presented the studies to the committee. The major issues discussed and committee comments/recommendations are presented below.

ISSUE 1.

The adequacy of the highest dose tested had been questioned for the Rat (Oral) Developmental Toxicity Study, MRID 00157794, ACC 261771.

COMMITTEE RESPONSE

1. Although no maternal toxicity was reported at 10 mg/kg/day (HDT), a dose range-finding study (also MRID 00157794), could be used to support the sponsor's dose selection in the main study. Indications of maternal toxicity reported in the dose range-finding study at 10 mg/kg/day (HDT) included decreased body weight gain from day 6 to day 11 post coitus, decreased food consumption during the treatment period, and single instances of slight dyspnea after test material administration in one female each from the 3 and 10 mg/kg/day dose groups.

2. The Rat (Oral) Developmental Toxicity Study, along with the dose range-finding study (MRID 00157794), can be used to support the requirement for developmental toxicity testing in one of two species with Cyfluthrin. The NOEL for Maternal Toxicity in this study is > 10 mg/kg/day (HDT) and the NOEL for Developmental Toxicity is > 10 mg/kg/day (HDT). The vehicle used in the study was 1% Cremophor in H_2O.

ISSUE 2

A Rabbit Oral Developmental Toxicity Study, MRID 426754-01, had been recently submitted under FIFRA Section 6(a)(2) adverse effects data. The committee was asked to look over the study and provide an opinion about the magnitude of the "so-called" adverse effects and to give a preliminary assessment of whether the study could be used to fulfill the requirement for a second species developmental toxicity study for Cyfluthrin.

[redacted]

COMMITTEE RESPONSE PENDING REGISTRATION INFORMATION IS NOT INCLUDED

1. A preliminary analysis of the study, in which doses of 0 (corn oil vehicle), 20, 60, and 180 mg/kg/day were administered, indicated a preliminary NOEL and LOEL for maternal toxicity at 20 mg/kg/day and $\geq$ 20 mg/kg/day (based on body weight loss) respectively and a preliminary NOEL and LOEL for developmental toxicity at 20 and 60 mg/kg/day (based on increased fetal resorptions) respectively. A full review of the study is needed before these values can be confirmed.

2

2. Using the preliminary NOEL for developmental toxicity in the rabbit of 20 mg/kg/day and some available residue information for corn commodities (memo of M. Nelson, CBI, dated 3/9/93), a rough calculation of an Acute Dietary MOE was made using a worst case scenario. (CBI reported that residues of Cyfluthrin on corn grain were not detected at the limit of detection of 0.01 ppm and were not detected past the limit of detection of 0.01 ppm on corn fodder).

Therefore:

0.01 ppm cyfluthrin residue = 0.01 mg residue/kg diet

Assuming a 1.5 kg diet of corn/day:

1.5 kg corn diet/day x 0.01 mg residue/kg diet

= 0.015 mg residue/day

Assuming a 60 kg human body weight:

Maximum Permissable Intake (MPI_{daily}) = $\frac{0.015 \text{ mg residue/day}}{60 \text{ kg body weight}}$

= 0.00025 mg residue/day/kg

The Margin of Exposure (MOE) = $NOEL/MPI_{daily}$

= $\frac{20 \text{ mg/kg/day}}{0.00025 \text{ mg/day/kg}}$ = 80,000

A normally acceptable margin of exposure is 100.

3. The current RfD of 0.025 mg/kg/day based on a 2-year rat chronic/oncogenicity feeding study is not expected to be affected by the new rabbit developmental toxicity study.

4. Since preliminary analysis of the rabbit developmental toxicity study does not indicate that a pressing toxicological concern exists, the study will not be reviewed as adverse effects data.

5. It would appear that the requirements for developmental toxicity testing in two species for Cyfluthrin could be satisfied with the rat oral and the rabbit oral developmental toxicity studies (pending a completed and satisfactory final review of the rabbit study).

ISSUE 3

With regard to the Rat (Inhalation) Developmental Toxicity Study, MRID Nos. 40780401 and 40968501, concerns had been raised about the low NOELs and LOELs in the study. The Maternal NOEL and LOEL were set respectively at 0.0011 mg/l and 0.0047 mg/l (based on reduced motility, dyspnea, piloerection, ungroomed coats, and eye irritation) and the Developmental Toxicity NOEL and LOEL were set respectively at 0.00059 mg/l and 0.0011 mg/l (based on unspecified sternal anomalies and increased runt incidence). The vehicle used was 1:1 polyethylene glycol E 400 (Lutrol) and ethanol.

Although the study had been graded Core Minimum and NOELs and LOELS had been established for maternal and developmental toxicity, comments had also been made that developmental anomalies in the study had not been adequately reported (memo J. Whalen, dated 11/28/89).

COMMITTEE RESPONSE

The committee recommended that the study should be reexamined if it was to be used as a regulatory endpoint (i.e. if OREB determined that inhalation is a probable route of exposure for a given use of Cyfluthrin).

cc: Elizabeth Doyle (TBII)
Alan Levy (TBII)