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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

FCR 1272 (Cyfluthrin) **Developmental Toxicity (Rat)**

EPA Reviewer: Laurence D. Chitlik, D.A.B.T. .
Toxicology Branch I (7509C)
EPA Secondary Reviewer :Pamela M. Hurley
Registration Action Branch 2 (7509C)

Laurence D Chitlik, Date 2/13/01
Pamela M Hurley, Date 2/15/01

Note: This supplement provides an executive summary and additional information not included in the original DER for MRID 00157794.

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental toxicity Study in the Rat

TEST MATERIAL (PURITY): FCR 1272 (93.4%) (Lot 816 170 019) administered as a suspension in distilled water with 1% Cremophor EL

SYNONYMS: Cyfluthrin

CITATION: Becker, H. (1983) Embryotoxicity (Including Teratogenicity) Study with FCR 1272 in the Rat. Research and Consulting Company AG.,Itingen, Switzerland. Project No. 019348. December 14, 1983. MRID 00157794. Unpublished.

Becker, H. (1983) Dose-Finding Embryotoxicity (Including Teratogenicity) Study with FCR 1272 in the Rat (Preliminary Study). Research and Consulting Company AG., Itingen, Switzerland. Project No. 021508. December 8, 1983. MRID 00157794.Unpublished.

Holzum, B. (1993) Justification for the Dose Selection for the Oral Embryotoxicity Study With FCR 1272 in Rats. Project No. 019348. Supplemental Submission to EPA MRID No. 00157794. March 12, 1993. Unpublished.

SPONSOR: Bayer AG

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 00157794), FCR 1272 (93.4%) was administered by gavage to 25 Wistar KFM-Han rats/dose as a suspension in distilled water and 1% Cremophor EL at dose levels of 0, 1, 3, or 10 mg/kg/day from days 6-15 of gestation.

Dose related maternal toxicity was not observed at any dose level in this study and animal data were remarkably consistent in all dose levels as compared to controls. As well, in the range-finding study (only 5 females/dose level), no consistent clear maternal toxicity was apparent at dose levels as high as 10 mg/kg/day although some minimal transient findings in only a few animals (likely not associated with treatment) were noted at the beginning of the dosing period. These data clearly supported higher dose levels in the definitive study but none were utilized.

Marked levels of maternal toxicity must be apparent in a developmental study if the study is to be capable of assessing potential developmental toxicity. In response to this issue which was apparently raised by the Agency in the early 1990's , the registrant submitted supplemental information (March 12, 1993) in an attempt to justify dose levels. These data demonstrated FCR 1272 to have a deep dose response curve when administered in more polar suspensions such as water with 1% Cremophor. This information did not negate the necessity for an agent to be tested at high enough dose levels to produce maternal toxicity but clearly indicated the need to have more accurate rangefinding data to use for dose selection. An Ad Hoc HED committee reviewed the registrant submission (May 18, 1993) and confirmed that no maternal toxicity was present in the definitive study. They also recognized the slight and transient maternal findings in the rangefinding study (which are likely unrelated to the test material), and concluded that these findings were not adequate to define a maternal LOAEL since none was referenced in their review. Clearly, it is not appropriate to conclude that maternal effects might be seen at higher dose levels and recommend that such studies should then be accepted as the committee did at that time. Marked maternal toxicity must be observed for a test to be considered capable of fulfilling a data requirement or testing at the limit dose level must be performed. **The maternal LOAEL is >10 mg/kg/day and dose levels are considered inadequate in this study.**

No developmental toxicity was observed at any dose level. However, recent examination of the visceral and skeletal data raise questions about the adequacy of the original examination. To begin with, complete individual animal data are not available for these examinations in the test report. Those data that are present do not support the conclusion that a full skeletal and visceral examination was performed. For example, very few soft tissue findings were noted in this study and these only relate to coagulated blood in the abdominal cavity or in the renal pelvis. Those are the only soft tissue findings and normal background incidences of visceral findings are expected to be much higher and more diverse in a study of this type. In addition, the investigators do not report any decreases in ossification or partial ossification. They only note the presence or absence of structures. As well, although the head should receive a full and complete soft tissue and skeletal exam, the report does not include a single finding associated with the skull, eye or brain or associated tissues. Variations are expected and typically should be observed here as well. Questions such as these can typically only be resolved by a laboratory audit and this is an old study to consider for audit. **The NOAEL for developmental toxicity is > 10 mg/kg/day, but questions relative to the conduct of this study preclude acceptability of these data at this time.**

An additional issue was identified during review of study data which also renders this study unacceptable at this time. Lot number 816 170 019 was used in both the rangefinding and the primary studies and both were conducted during the same time frame. However, in the primary study the purity for this lot is specified to be 93.4% while in the rangefinding study it is reported to be only 90%. In addition, analytical and stability results for the two studies are identical.

This developmental toxicity study is classified as **Unacceptable** and does not satisfy the guideline requirements for a developmental toxicity study (**§83-3a**) in rats.

COMPLIANCE: An unsigned and undated GLP statement was included. A signed and dated Quality Assurance statement was provided.

TERATOLOGY STUDY OF FCR 1272 IN RATS

Research & Consulting Company AG; Report No. 019348; December 14, 1983; Accession No. 261771

PROTOCOL: One hundred Wistar KFM-Han female rats (181-230 g, 12-13 weeks old) were assigned to four groups of 25 rats, and mated overnight with sexually mature males. Vaginal plugs and smears were used to establish gestation day 0. All mated dams were orally dosed with the test article (93.4% purity) once daily by intubation on days 6 through 15 at doses of 0 (vehicle control), 1, 3, and 10 mg/kg/day. The test article was formulated daily by mixing it with a vehicle of 1% Cremophor EL in distilled water. The test article was analyzed for homogeneity and dose concentration. The dams were observed twice daily for clinical signs, and weighed daily. Food consumption was measured on gestation days 6, 11, 16, and 21. The dams were asphyxiated, and their ovaries, uteri, uterine contents, and other organs examined. The fetuses were removed by caesarean section, sexed, weighed, and grossly examined. One third of the live fetuses from each litter were examined for visceral and brain lesions by the technique of Wilson (1965). The remaining live fetuses were clarified, stained with Alizarin red, and examined for skeletal lesions by the technique of Dawson (1926).

RESULTS: No dams died during this study. There were no clinical signs, except for vaginal bleeding (colporrhagia), abortion, and weight loss in one mid-dose dam on gestation day 18. Weight gain and food consumption were similar in all groups. The litter data were as follows:

Dose (mg/kg/d)	Pregnant/ Mated	Abortions	Live litters	Fetuses			Resorptions (%)	
				Fetuses/dam	% Live	Wt (g)	Embryonic	Fetal
0	25/25	0	25	10.2	100	4.9	7.2	0
1	25/25	0	25	10.7	100	5.0	3.3	0
3	22/25	1	21	11.0	100	5.0	4.6	0
10	24/25	0	23	11.7	100	4.9	1.8	0

All groups had similar mean values for corpora lutea/dam, embryonic resorptions, implantations, live litters, fetuses/dam, male:female ratios, and fetal weights. There were no dead fetuses, and no fetal resorptions. There was however the one dam which aborted on day 18, but this was probably not a compound-related event.

Visceral lesions included coagulated blood in the abdominal cavity of one control and one high-dose fetus, and coagulated blood in the kidney pelvis of one low-dose and one high-dose fetus. Skeletal malformations and anomalies included absent sternebrae in 2 control, 3 low-dose, and 3 high-dose fetuses; longitudinally split sternebrae in 1 control, 1 low-dose, and 1 high-dose fetuses; and wavy ribs (all) in 1 control fetus. None of the visceral or skeletal findings are considered to be compound-related. Thus, there were no compound-related teratogenic effects at the doses tested. The defined NOEL for teratogenic, maternal toxicity, and fetotoxicity effects was $\geq$10 mg/kg/day in rats (the highest dose tested).

This study is CORE GUIDELINE. This study received Quality Assurance review.

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CASWELL FILE

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

MAY 26 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Submission of Supplemental Information to Aid in the Review of the Cyfluthrin Developmental Toxicity Database

Barcode: D189407
Submission: S437356
PC Code: 128831
Tox Chem No.: 266E

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

K. Hamernik 5/18/93

TO: George Larocca/ Adam Heyward
PM Team #13
Registration Division (H7505C)

THRU: Karl Baetcke, Ph.D.
Chief, Toxicology Branch I
Health Effects Division (H7509C)

5/24/93

ACTION REQUESTED

The following Cyfluthrin developmental toxicity data/information was submitted by Miles, Inc. so that it would be available to Toxicology Branch I during a review of the Cyfluthrin developmental toxicity database:

1. MRID 426754-01, a developmental (oral) toxicity study entitled, " Embryotoxicity Study (Including Teratogenicity) with FCR 1272 [Cyfluthrin technical] in the Rabbit, conducted by RCC, Research and Consulting Co., LTD, Switzerland, for Miles, Inc., RCC project number 309914 and Miles number 103980, report date 12/3/92;

2. MRID 426989-01, a supplemental submission to EPA MRID No. 00157794 (Lab Project ID 019348 and Miles report No. 86477-1), dated 3/12/93. MRID 426989-01 included:

(a) a dose-finding study (called Attachment II) entitled, "Dose-Finding Embryotoxicity (Including Teratogenicity) Study with FCR 1272 [Cyfluthrin technical] in the Rat, conducted by RCC Research and Consulting Company AG, Switzerland, for Bayer AG, Germany, RCC project number 021508 and Bayer number 86477, report date 12/8/83; and,

(b) a justification for the dose selection for the oral embryotoxicity study with FCR 1272 in rats (MRID 00157794).

CONCLUSIONS

1. MRID 426754-01, a developmental (oral) toxicity study in the rabbit, had been previously submitted under project D188797. The study is currently under review.

2. MRID 426989-01, supplemental submission to MRID 00157794:

(a) The dose-finding study (MRID 00157794), which originally had been submitted to the Agency many years ago, was reevaluated for its adequacy to support dose selection in the main study (also MRID 00157794) during a recent review of the Cyfluthrin developmental toxicity database (see the attached memorandum entitled, "Cyfluthrin: Meeting of Ad Hoc Committee to Discuss Developmental Toxicity Database");

(b) the justification for dose selection (copy appended with exception of Attachment II) in the rat oral embryotoxicity study (MRID 00157794) was evaluated during the review of the Cyfluthrin developmental toxicity database. It was concluded that dose-selection in the main study was supported by the dose-finding study (see 2(a) above).

3. No further action is required at this time.

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
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CONCURRENCE:

James N. Rowe — James Rowe Toxicology Branch II
Stephen C. Dapson — Steven Dapson Toxicology Branch II
David Anderson — 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.

In addition, concerns had been expressed about the adequacy of the Cyfluthrin developmental toxicity database to support its use in combination with Phostebupirim on corn (PP #1F04026 and ID# 003125-URR) (memo of A. Levy, TBII, dated 3/29/93).

COMMITTEE RESPONSE

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. 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)

Registrant Response 86477-1

DISCUSSION

The first oral embryotoxicity study with FCR 1272 in FB 30 rats was performed using dose levels of 0, 3, 10 or 30 mg/kg b.w./day, respectively. The vehicle, polyethylene glycol 400, was used. (1) A comparison of the absorption of FCR 1272 in formulations of polyethylene glycol 400 and Cremophor EL in distilled water (5 drops in 10 ml) after single oral administration of 10 mg/kg b.w. to male fasted Wistar rats revealed distinct differences between these two vehicles. When 10 mg FCR 1272/kg b.w. was administered in Cremophor EL/distilled water, the four enantiomer pairs were detectable in blood after only 30 minutes and maximal values were obtained after one hour. But, when FCR 1272 was administered in polyethylene glycol 400, the concentration did not peak until after 6 hours, and the values were five times lower than the maximal values measured after one hour in the rats treated with FCR 1272 dissolved in Cremophor EL/distilled water. (2,3) Correlating to these differences in blood levels of FCR 1272 after single oral administration when using the two different vehicles, great differences were evident in the LD_{50} values of FCR 1272 using polyethylene glycol 400 and Cremophor EL/distilled water. The oral LD_{50} of FCR 1272 for male rats was 653 or 590 mg/kg b.w. when using polyethylene glycol 400 and only 16.2 mg/kg b.w. when using Cremophor EL/distilled water. (2,4) Within approximately 3 hours after administering a single dose of 13 mg/kg b.w./day in Cremophor EL/distilled water, 1 out of 5 animals died. (4)

Because of higher blood levels after oral administration of FCR 1272 in Cremophor EL in distilled water when compared with polyethylene glycol 400, an additional oral embryotoxicity study including range finding was performed in Wistar rats using Cremophor EL/distilled water as the vehicle.

The dose range finding study was performed with dose levels of 0, 1, 3 or 10 mg/kg body weight/day. In this range finding study, the 10 mg/kg b.w./day dose produced a transient decrease of body weight at the beginning of the treatment period and a decrease in body weight gain from day 6 to day 11 p.c. as well as a decrease in food consumption during the treatment period. In addition, single females of the 3 and 10 mg/kg group exhibited slight transient dyspnea after administration on single days. (5)

Thus, the dose of 10 mg/kg body weight/day which was chosen as high dose for the main-oral embryotoxicity study in rats revealed maternal toxicity in the range finding study and was only slightly below the beginning lethal range after acute oral administration in rats. Higher dose levels did not appear reasonable with respect to the high blood levels after the oral administration of 10 mg/kg b. w. and because of the high toxicity after single oral administration of FCR 1272 in Cremophor EL/distilled water.

Pages 13-14 - *Access to FIFRA health and safety data is restricted under FIFRA

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HED File Code	***13000 Tox Reviews***
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