12-2-91

MRID 41776102

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

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DEC 2 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Cypermethrin-S: Experimental Use Permit for the Use of FMC 56701 1.5 EC/EW Insecticide on Cotton, Lettuce and Beans - FINAL REPORT (EPA ID No. 279-EUP-REA)

TOX Chem No.:	268AA
Shaughnessy No.:	109702
Project No.:	1-0771
Submission No.:	S391759

FROM: William B. Greear, M.P.H. William B. Greear 11/19/91
Review Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Adam Heyward/George LaRocca, PM Team #15
Insecticide-Rodenticide Branch
Registration Division (H7505C)

THRU: Marion P. Copley, D.V.M., Section Head
Review Section IV, Toxicology Branch I
Health Effects Division (H7509C)

I. CONCLUSIONS:

The two remaining toxicity studies, i.e. 90-day study feeding in rats (#P9-2880) and developmental toxicity study in rats (#89-2958) that were not reviewed under Proj. #1-1713 have been evaluated and found to be acceptable in satisfying the requirements for a Guideline series 82-1 90-day feeding-study and 83-3 developmental toxicity study.

II. REQUESTED ACTION:

RD has requested that TB-I evaluate the data submitted in support of the EUP request.

III. DISCUSSION:

EUP Program

The program involves the spraying of FMC 56701 1.5 EC and FMC 56701 1.5 EW by broadcast-foliar by ground rig and aircraft at a rate of 0.016-0.05 lb ai/acre for a maximum of 0.30 lb ai/acre to a total of 3985 acres in Alabama, Arizona, California, Georgia, Louisiana, Mississippi, North Carolina, New Mexico, Oklahoma, South Carolina, Tennessee, Texas, Colorado, Florida, Michigan, New Jersey, New York, Ohio and Wisconsin. A maximum of 797 gal of FMC 56710 1.5 EC/EW (1195.5 lb ai) will be required.

The EUP request was initially evaluated under Project No. 1-1713 (Expedite - see memorandum of W. Greear dated July 31, 1991). Under Project No. 1-1713 only the acute toxicity studies necessary for labeling FMC 56701 1.5 EC and FMC 56701 1.5 EW were reviewed. The data adequately supported the EUP. The remaining toxicity data, i.e. the 90-day feeding study in rats #A89-2880 and the developmental toxicity study in rats #A89-2958, have been evaluated herein (DERs attached). The results of the two studies are summarized below:

- FMC 56701 Technical: Ninety-Day Feeding Study in Rats #A89-2880, April 20, 1990, MRID #417761-01

  NOEL = 250 ppm (M = 13.8 mg/kg/day; F = 16.3 mg/kg/day)a.i.
  LEL = 500 ppm (M = 28.2 mg/kg/day; F = 32.2 mg/kg/day)a.i. based on decreased body weight and body weight gain, decreased food consumption, and "interference" with the estrous cycle in females

  In addition, males in the 900 ppm group (55.7 mg/kg/day)a.i. had decreases in RBC, WBC, HGB and HCT and increases in BUN. Females in the 900 ppm group (65.2 mg/kg/day)a.i. had decreases in glucose. Mortality was observed in both sexes.

  Classification: Minimum (satisfies the requirement for a Guideline Series 82-1 90-Day Feeding Study.)

- Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of FMC 56701 Technical Administered Orally Via Gavage to Crl: CD(SD) BR Presumed Pregnant Rats #A89-2958, October 2, 1990, MRID# 417761-02

  NOEL (maternal) = 12.5 mg/kg/day
  LEL (maternal) = 25 mg/kg/day based on ataxia, urine-stained abdominal fur, decreased food consumption and decreased weight gain
  NOEL (developmental) $\geq$ 35 mg/kg/day

Classification: Guideline (satisfies the requirement for a Guideline Series 83-3 Developmental Toxicity Study.)

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GUIDELINE: 83-3

Primary Reviewer: Guruva B. Reddy, DVM, PHD 10/29/91
Section IV , Tox.Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, DVM, DABT 10/29/91
Section Head, Review Section IV , Tox.Branch I (H7509C)

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rat
Guideline: 83-3

EPA Identification No.s: EPA MRID (Accession) No. 417761-02
EPA Shaughnessy No.
Caswell No.

Test Material: FMC 56701 Technical

Synonyms: Cypermethrin

Sponsor: FMC Corporation

Study Number(s): A89-2958

Testing Facility: Argus Research Laboratories, Inc.
Horsham, PA 19044

Title of Report: Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of FMC 56701 Technical Administered Orally Via Gavage to Crl:CD® (SD) BR Presumed Pregnant Rats

Author(s): Alan M. Hoberman, PH.D., DABT

Report Issued: October 2, 1990

Conclusions: The maternal NOEL = 12.5 mg/d the maternal LEL = 25 mg/d based on ataxia, urine-stained abdominal fur, fecal-stained perineal fur, decreased food consumption and decreased weight gain. The developmental NOEL = ≥ 35 mg/d

Core Classification: Guideline

The information presented for this developmental toxicity study satisfies the criteria set forth in Subdivision F, Series 83-3.

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A. **Materials**

Test Compound: Purity: 89.6%
Description: Dark brown viscus liquid
Lot No.: E-6539-78

Vehicle(s): Corn Oil, Wesson®, Lot No.: M98WI

Test Animal(s):

Species:	rat
Strain:	Charles River Crl:CD® (SD) BR
Source:	Charles River Laboratories, Inc Raleigh, NC and Charles River Laboratories, Inc. Portage, MI
Age:	95 to 97 days
Weight:	Males: 510 - 914 g Females: 266 - 337 g

B. **Study Design**

This study was designed to assess the developmental toxicity potential of FMC 56701 Technical when administered by gavage to female rats on gestation days 6 through 15, inclusive.

Mating

Natural. Male and female rats were paired and cohabitated in individual cages for a maximum of 4 days.

Group Arrangement:

Test Group	Dose Level (mg/kg/d)	Number Assigned
Control	0	25
Low Dose	5	25
Mid Dose (low)	12.5	25
Mid Dose (high)	25	25
High Dose	35	25

Dosing:

All doses were in a volume of 5 ml/kg of body weight/day prepared once during the dosing period. The dosing solutions were analyzed for concentration and stability. Recovery ranged from 91 to 106%. Dosing was based on individual body weights recorded daily.

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Observations

The animals were checked for mortality or abnormal condition from day 0 to day 20. Dams were sacrificed on day 20 of gestation. Examinations at sacrifice consisted of observations for obvious structural and pathologic changes. The uterine horns were exteriorized and the number and placement of implantations, early and late resorptions, and live and dead fetuses were noted. Other observations include sex, fetal body weight of each fetus and number of corpora lutea in each ovary.

For non-pregnant animals, each uterus was pressed between two glass plates to confirm pregnancy.

Approximately one-half of the fetuses from each litter were fixed in Bouin's solution and examined for soft tissue alterations using a variation of Wilson's sectioning technique. The remaining fetuses in each litter were eviscerated, cleared, stained with alizarin red S and examined for skeletal abnormalities.

Historical control data were not provided to allow comparison with concurrent controls, but were referenced.

Statistical analysis

Maternal body weight, feed consumption data, litter averages for percent males, fetal ossification sites, percent dead or resorbed conceptuses and percent fetal alterations were analyzed using Bartlett's Test of Homogeneity. A parametric analysis of variance (ANVOA) was performed if the Bartlett's test not significant. If the ANVOA was significant, analysis by Dunnett's test was performed. If Bartlett's test was significant, the Kruskal-Wallis test was used when less than or equal to 75% ties were present; when more than 75% ties were present, the Fisher's Exact Test was used. If the Kruskal-Wallis Test was significant, Dunn's Method of Multiple Comparisons was used to identify the significance of individual groups. Maternal body weight changes were analyzed using the Analysis of Covariance, with body weight on day 0 or day 6 of gestation. All other Caesarian-sectioning data were analyzed using Kruskal-Wallis Test.

Compliance

A signed Statement of Confidentiality Claim was provided.

A signed Statement of compliance with EPA GLP's was provided.

A signed Quality Assurance Statement was provided.

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C. **Results**

1. **Maternal Toxicity:** Toxicity was observed at 25 mg/kg/day.

Mortality: No deaths occurred during the study.

Clinical Observations: Clinical signs of toxicity were observed in the 25 and 35 mg/kg/day groups. In the 25 mg group, the symptoms were ataxia, urine-stained abdominal fur and fecal-stained perineal fur. In the HTD dose group a significant ($P \leq 0.01$) increase in the symptoms which included ataxia, hypersensitivity, urine stained abdominal fur, emaciated appearance, excess salivation, and soft or liquid feces were observed. These symptoms started about 8-10 days after initiation of the treatment and lasted through the gestation. A compound related chromorhinorrhea was observed in 0, 3, 3, 4 and 4 rats at 0, 12.5, 25, and 35 mg/kg/day dosage groups, respectively. In addition to the aforementioned clinical signs, one rat in the HTD group had tremors, red exudate on the snout, front limbs and abdomen, chromorhinorrhea, clonic convulsions, swollen snout and nasal lesion.

Body Weight:

Table I: Body Weight Gains (grams)[a]

Group:	Prior to Dosing Period G0-6	Dosing Period G6-16	Post Dosing Period G16-20	Entire Gestation Period G0-20	Corrected Body Weight Gains Dosing P.[1] G6-16	Entire[2] G0-20
Control	38.2	59.6	61.4	159.2	55.9	155.5
LDT	31.6	57.0	61.1	149.7	53.2	145.9
MDT-L[3]	34.9	55.6	63.4	153.9	51.9	150.2
MDT-H[3]	36.2	**45.9****	66.6	148.7	42.2	145.0
HDT	33.1	**29.0****	**75.7****	**137.8****	25.4	134.2

[1] = corrected body weight gain for dosing period = body weight gain for dosing period minus gravid uterus weight (mean fetal wt.).

[2] = corrected body weight gain for entire gestation period = body weight gain for entire gestation period minus gravid uterus weight (mean fetal wt.).

[3] - L= low and H= high

** = $P \leq 0.01$

a = Data extracted from the tables provided in the report.

Administration of the test material by gavage, at the 25 and 35 mg/kg/day (MDT-H and HDT, respectively) dosage, to pregnant rats significantly ($P \leq 0.01$) reduced the maternal body weight gains

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during the dosing period (23 and 51%, respectively), when compared to the controls. Within the dosing period days 6 to 9, maternal body weight gains decreased ($P \leq 0.01$) 90% in the 25 mg group and lost 80% in the 35 mg group, when compared to the controls (data not presented in table 1). During the post-dosage period, a dose- related rebound or increase in the maternal body weight gains were observed. In the 35 mg group, a significant increase (23%) of mean maternal body weight gain over the controls were observed. Despite this rebound, mean maternal weight gains for the entire gestation period decreased (13%) significantly for the 35 mg/kg group, indicating compound related toxicity. In addition, at this dose, the corrected body weight gain during the dosing and entire gestation period decreased 55 and 14%, respectively, when compared to the controls. At the 25 mg/kg group, the corrected body weight decreased 25% during the dosing period, when compared to the controls. There appears to be no change in the corrected body weight gain for the entire gestation period, at this dose, indicating that the decrease in body weight gain was temporary phenomena and rebounded to near control level. This occurrence may not be of toxicological significance. The statistical significance of corrected body weight gains was not calculated.

Food Consumption

Table 2: Food Consumption Data (grams/kg/day)[a]

Group:	Prior to Dosing Period	Dosing Period	Post-Dosing Period	Entire Gestation Period
Control	71.8	60.1	66.7	62.3
LDT	69.5	59.7	69.7	62.3
[b]MDT-L	71.6	58.3	70.1	62.3
[b]MDT-H	69.0	**54.0****	**71.3***	60.1
HDT	69.2	**45.9****	**74.4****	**57.4****

[a] = Data extracted from the tables provided in the report.
[b] - L = low, H = high
* = $P \leq 0.05$
** = $P \leq 0.01$

As can be seen in table 2 relative Food Consumption (RFC) was not affected during the pre-dosage period. At the 25 and 35 mg dosage, RFC was significantly decreased during the dosing (10 % and 24 %, respectively) and the post-dose (7 % and 12 %, respectively) period. In addition, during the entire gestation, in the 35 mg group, the RFC decreased 8%, when compared to the controls. The trend was consistent with body weight gains observed for this dose and may be compound related (see table 1).

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Gross Pathological Observations

No gross pathological changes were observed by the investigator in the maternal animals.

Cesarean Section Observations

Table 3: Cesarean Section observations[a]

Dose:	Control	LDT	[b]MDT-L	[b]MTD-H	HDT
#Animals Assigned	25	25	25	25	25
#Animals Mated	25	25	25	25	25
Pregnancy Rate (%)	100	100	84	100	92
Maternal Wastage					
#Died	0	0	0	0	0
#Pregnant	25	25	21	25	22[c]
#Non pregnant	0	0	4	0	2
#Aborted	0	0	0	0	0
#Premature Delivery	0	0	0	0	0
Total Corpora Lutea	459	460	380	450	412
Corpora Lutea/dam	18.4	18.4	18.1	18.0	17.9
Total Implantation	416	405	351	412	291
Implantations/Dam	16.6	16.2	16.7	16.5	17.0
Total Live Fetuses	390	377	329	384	347
Live Fetuses/Dam	15.6	15.1	15.7	15.4	15.8
Total Resorptions					
Early	26	28	21	28	28
Late	0	0	1	0	0
Resorptions/Dam	1.04	1.12	1.04	1.12	1.27
Total Dead Fetuses	0	0	0	0	0
Dead Fetuses/Dam	0	0	0	0	0
Mean Fetal Weight (gm)	3.75	3.77	3.75	3.67	3.65
Pre-implantation Loss(%)	9.8	12.0	7.73	8.3	5.02
Post-implantation Loss(%)	6.26	6.91	6.22	6.79	7.47
Sex Ratio (% Male)	47.5	48.6	47.1	49.4	46.4

[a] = Data extracted from tables provided in the summary.
[b] - L= low, H= high
[c] = Excludes values from dam #16263 that resorbed all conceptus due infection.

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A low conception rate was observed in the 12.5 and 35 mg/kg/day group is considered unrelated to the administration of test compound, since it is not dose-related and is within the historical control range. In addition, lower conception rate was probably due to the presumed pregnant of rats, when assigned to the study. One dam (16263) in the high dose group, with an infection from an intubation accident, resorbed its entire litter. This was considered unrelated to the treatment because its a single non-significant occurrence. The average number of corpora lutea, implantations, resorptions and fetuses were comparable to five dosage groups. Similarly, the number of dams with viable fetuses did not differ among the groups. Minor differences among the groups were neither biologically remarkable nor statistically significant.

2. **Developmental Toxicity**

No fetal deaths were reported in any of the groups. Unilateral or bilateral cervical ribs were present as the only alteration of statistical significance in four pups from two litters in the 25 mg/kg/day group. The investigator considered these variations to be unrelated to the test substance because the occurrence was not dose-dependent, and within the historical control range. Although, **no historical control data was furnished,** these variations are considered unrelated to the test substance. No other malformations or alterations of statistical significance were revealed by gross external, soft tissue or skeletal examination of the fetuses attributed to the test substance. All fetal alterations observed in this study were reported as common to this strain of rat and occurred at fetal or litter incidence rates that were not dose-dependent and/or significantly increased, as compared to the control.

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The following tables summarize the external, visceral and skeletal observations in the fetuses [(No. of incidence (% of incidence)]:

Table 4: External Observations

Observations	Control	Low Dose	Mid Dose (Low)	MID Dose (High)	High Dose
#pups(litters) examined	390(25)	377(25)	329(21)	384(25)	347(22)
Eyes:					
Bulge, Depressed					
F:	0	0	0	1(0.3)[a]	0
L:	0	0	0	1(4.0)	0
Jaw:					
Micrognathia					
F:	0	0	0	1(0.3)[a]	0
L:	0	0	0	1(4.0)	0
Body:					
Edema					
F:	0	0	0	1(0.3)	0
L:	0	0	0	1(4.0)	0

([a]) fetus also had other gross external alterations
F = Fetus affected, L = litters affected

Table 5: Visceral Observations [No. of incidence (% of incidence)]

Observations	Control	Low Dose	Mid Dose (Low)	MID Dose (High)	High Dose
#pups(litters) examined	189(25)	183(24)[a]	160(20)[b]	186(25)	167(22)
Brain: Lateral Ventricles, Moderate dilation					
F:	0	0	0	1(0.5)	0
L:	0	0	0	1(4.0)	0
Kidney: Right Pelvis, Moderate Dilation					
F:	0	1(0.5)	0	0	0
L:	0	1(4.2)	0	0	0

[a] = Excludes litter 16193 that consisted of only one fetus that was assigned for skeletal examination.
[b] = Excludes litter 16288 that consisted of only one fetus that was assigned for skeletal examination.

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Table 6: Skeletal Observations [No. of incidence (% of incidence)]

Observations		Control	Low Dose	Mid Dose (Low)	MID Dose (High)	High Dose
#pups(litters) examined		201(25)	194(25)[a]	169(21)[b]	198(25)	180(22)
Skull: Mandible-short						
	F:	0	0	0	1(0.5)[c]	0
	L:	0	0	0	1(4.0)	0
Eye Sockets-small						
	F:	0	0	0	1(0.5)[c]	0
	L:	0	0	0	1(4.0)	0
Vertebrae: Thoracic, Centrum, Bifid						
	F:	1(0.5)	0	0	2(1.0)[d]	2(1.1)
	L:	1(4.0)	0	0	2(8.0)	2(9.1)
Thoracic, Centra, Not Ossified						
	F:	0	0	0	1(0.5)[d]	0
	L	0	0	0	1(4.0)	0
Ribs: Cervical Rib at the C-7						
	F:	0	0	0	4(2.0)**	0
	L:	0	0	0	2(8.0)	0
Incompletely Ossified						
	F:	0	1(0.5)[e]	1(0.6)[f]	0	0
	L:	0	1(4.0)	1(4.8)	0	0
Wavy						
	F:	1(0.5)	5(2.6)[e]	3(1.8)[f]	0	1(0.6)
	L:	1(4.0)	1(4.0)	1(4.0)	0	1(4.5)
Sternebrae: (Incomplete and un-ossified)						
	F:	2(1.0)	2(1.0)	1(0.6)	4(2.0)	5(2.8)
	L:	2(8.0)	2(8.0)	1(4.8)	4(16.0)	2(9.1)
Fused						
	F:	0	0	0	1(0.5)[d]	0
	L:	0	0	0	1(4.0)	0
Asymmetric						
	F:	0	0	0	1(0.5)[g]	0
	L:	0	0	0	1(4.0)	0
Pelvis: Incompletely ossified pubis and ischia						
	F:	4(2.0)	1(0.5)	5(3.0)	0	5(2.8)
	L:	4(16.0)	1(4.0)	4(19.0)	0	3(13.6)
Hind Limb: Tibia & Fibula (bilateral, short)						
	F:	0	0	0	1(0.5)[d]	0
	L:	0	0	0	1(4.0)	0

a. Includes litter 16193 that consisted of only one fetus.
b. Includes litter 16228 that consisted of only one fetus.
c. Fetus 16250-1 also had other skeletal alterations.
d. Fetus 16260-9 also had other skeletal alterations.
e. Fetus 16204-15 also had other skeletal alterations.
f. Fetus 16235-1 also had other skeletal alterations.
g. Fetus 16238-2 also had other skeletal alterations.
** Significantly ($P \leq 0.01$) different from the vehicle group value.

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D. **Discussion/Conclusions**

1. **Maternal Toxicity:**

As stated earlier, maternal toxicity observed at 25 mg/kg/day dosage group and was characterized by clinical signs which included ataxia, urine-stained abdominal fur and fecal stained perineal fur. In addition, body weight gains and feed consumption decreased, non-significantly.

2. **Developmental Toxicity:**

a. Deaths/Resorptions: No fetal deaths were reported in any of the groups. The number of resorptions were not statistically significant, when treated animals were compared to the controls.

b. Altered Growth: The mean fetal weight was slightly lower but not significant, at the 25 and 35 mg/kg/day group, when compared to the controls.

c. Developmental Anomalies: Only anomaly of statistical significance was the presence of unilateral or bilateral cervical ribs in four pups from two litters in the 25 mg/kg/day group. The incidence has no dose-relationship, since it was reported only in one group of rats and is within the historical control ranges for this strain of rat. Probably, the effect has no toxicological significance. **No historical control data was furnished for confirming the findings.**

d. Malformations: No malformations or alterations of statistical significance were observed which can be attributed to the test substance. All fetal observations reported in this study were common to this strain of rat and occurred at fetal or litter incidence rate that were not dose-dependent and/or significantly increased, as compared to the controls.

D. **Study Deficiencies:** No deficiencies were reported that would alter the validity of the study.

E. **Core Classification:** Guideline

Maternal NOEL = 12.5 mg
Maternal LOEL = 25 mg
Developmental Toxicity NOEL = ≥ 35 mg

As presented, the study satisfies the requirements set forth in Subdivision F Guidelines, 83-3 for developmental toxicity.

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