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

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DEC 2 1991

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 11/15/91
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:

o 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] had decreases in RBC, WBC, HGB and HCT and increases in BUN. Females in the 900 ppm group (65.2 mg/kg/day)[a] 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.)

o 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

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Results - Only the 0 and 250 ppm diets were analyzed for homogeneity. The homogeneity of the 250 ppm diet ranged from 194 to 217 ppm (active ingredient). Thirty-, 40-, and 60-day stability tests were conducted only on the 0 and 250 ppm diets. At 30 days the dietary concentration of the 250 ppm diet ranged from 192 to 202 ppm. The dietary concentration was 206 ppm at 40 days. The range varied from 183 to 195 ppm at the 60-day analysis. The concentration of the 10 ppm diet ranged from 5.9 to 9.0 ppm during the 11-week analysis period. The 50 ppm group varied from 38.9 to 49.1 ppm. The 150 ppm group varied from 108 to 131 ppm. The 250 ppm group varied from 201 to 213 ppm. The 500 ppm group varied from 395 to 430 ppm. The 900 ppm group varied from 686 to 768 ppm.

3. Statistics - Data that were determined to be normal by the Proc Univariate test were analyzed by an Analysis of Variance test. If differences existed between treatment groups and there was no unusual variance (Bartlett's Test), treatment group means were compared to the control group using Dunnett's test. If Bartlett's test indicated that the variance was not homogeneous, then a T-test for differences between the control and treated groups was conducted. If the data were not normally distributed according to the Proc Univariates, the data were analyzed with the procedures used above using log transformed data. If the data were still not normal, then non-parametric methods were used. The Kruskal-Wallis Non-Parametric ANOVA was used to determine if significant differences existed between groups. Dunn's Test for Multiple Rank Comparisons was used to identify groups different from the control. The percent decrease in body weight gain compared to controls was tested using a T-test. Female body weight gain by week were also analyzed using repeated measures of analysis. All statistical analyses were performed using the Statistical Analysis System (SAS) except for Dunn's Test for Multiple Rank Comparisons which was run by FMC Statistical Services.

4. Quality Assurance - A Quality Assurance Statement was included, signed by William D. Barta dated April 19, 1990.

C. METHODS AND RESULTS:

1. Observations - The animals were observed once daily for mortality and clinical signs of toxicity.

Reviewed By: William B. Greear, M.P.H. William B. Greear 11/26/91
Review Section IV, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. Marion Copley 11/26/91
Review Section IV, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

Study Type: Guideline Series 82-1
90-Day Feeding - Rats

PC No.: 109702
TOX Chem. No.: 268AA
MRID No.: 417761-01

Test Material: FMC 56701 Technical (88.2% ai)

Synonyms: Cypermethrin-S

Study Number: A89-2880

Sponsor: FMC Corporation
Philadelphia, PA 19103

Testing Facility: FMC Corporation Toxicology Laboratory
Princeton, NJ 08543

Title of Report: FMC 56701 Technical: Ninety-Day Feeding Study in Rats

Author: Jane D. McCarty

Report Issued: April 20, 1990

Conclusions:

NOEL = 250 ppm (M = 13.8 mg/kg/day; F =16.3 mg/kg/day)*
LEL = 500 ppm (M = 28.2 mg/kg/day; F = 32.2 mg/kg/day)*
(decreased body wt and body wt gain, decreased food consumption, interference with the estrous cycle in females and decreased glucose in females)

In addition, males in the 900 ppm (55.7 mg/kg/day)* group had decreased RBC, WBC, HGB, and HCT and increase in BUN. Mortality was observed in both sexes.

Classification: Core-Minimum

Study Acceptability:

The study satisfies the requirements for a Guideline Series 82-1 90-Day Feeding Study.

* in terms of a.i.

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

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A. MATERIALS:

1. Test Compound - FMC 56701 Technical; Description: brown liquid; Ref. No.: E6278-103; Purity: 88.2%; Contaminants: not reported.

2. Test Animals - Rat; Strain: Fisher 344(CDF); Age: not reported; Weight: males 101 to 123 g; females 91 to 105 g; Source: Charles River Laboratories, Kingston, NY.

B. STUDY DESIGN:

1. Animal Assignments - Animals were randomly assigned to the following test groups:

90-Day Oral Toxicity Study

Test Group	Dose in Diet (ppm)	Number of Animals Males	Females
Control(1)	0	10	10
2	10	10	10
3	50	10	10
4	150	10	10
5	250	10	10
6	500	10	10
7	900	10	10

On receipt of the animals, the animals were acclimated to laboratory conditions for a period of 17 days during which time the rats were examined to determine their health status. In addition, the rats were examined once daily for clinical signs. The rats were individually housed in stainless steel cages with wire bottoms in an animal room which contained no other species or strain of test animal, and no other test materials. The room was maintained at temperature of 68 to 77 °F, relative humidity of 29 to 90 percent and a 12-hour on/12-hour off light cycle. Purina Certified Rodent Chow 5001 and municipal drinking water were provided ad libitum.

2. Diet Preparation - Each dietary concentration of the test material was weighed, mixed into 50 mL corn oil and added to 50 g of diet to form a premix. The premix was mixed by hand, then added to the appropriate amount of diet and mixed in a blender for 10 min. The treated rations were placed in plastic bags in a closed container and stored at room temperature. Prior to use, samples of each batch were analyzed for concentration at Weeks 1, 2, 3, 5, 6, 7, 8, and 11. Duplicate samples were used to analyze homogeneity, stability, and dietary concentration.

Results - The following table provides information on mortality that occurred during the study:

Table 1: Mortality at 90-Days

Group	Dose Level (ppm)	Number Dead/Number at Initiation and Percent Mortality (%)	
		Male	Female
Control (1)	0	0/10	0/10
2	10	0/10	0/10
3	50	0/10	0/10
4	150	0/10	0/10
5	250	0/10	0/10
6	500	0/10	0/10
7	900	7/10 (70)	10/10 (100)

The females died between days 18 and 52 and males died between days 54 and 96. Males and females in the 900 ppm group exhibited abdominal-genital staining, ataxia, clonic convulsions, chromodacryorrhea, chromorhinorrhea, decreased feces, decreased locomotion, dehydration, hypersensitivity to touch and sound, splayed hindlimbs, and unthriftiness. Females in the 900 ppm group also exhibited abdominal recumbency and walking on toes.

2. Body Weight - Individual body weights were determined initially and weekly thereafter for 13 weeks.

Results- Males in the 900 ppm group exhibited significant decreases (≈38%) in body weight from Week 1 to 13 and a significant decrease (≈63%) in body weight gain for the 13-week period when compared to controls. At 500 ppm, males exhibited significant decreases in body weight (≈12%) compared to controls from Week 1 to 8 and significant decreases (≈15%) in body weight gain. Females in the 900 ppm group had significant decreases (≈35%) in body weights throughout the study until death occurred. Females in the 500 ppm group had significant decreases (≈9%) in body weight from Week 1 to 13 and significant decrease (≈21%) in body weight gain. Females in the 250 ppm group had significant decreases (≈9%) in body weight gain over the 13-week period. The decrease in body weight gain in females in the 250 ppm group appears to be equivocal. Females in the 150 ppm group had significant decreases (≈71%) in body weight from Weeks 8 to 13 and a significant decrease (≈15%) in body weight gain (see Table 2). The decrease does not appear to be related to treatment given the absence of a dose-response relationship.

Table 2: Body Weight (g) in Grams and Percent (%) Decrease Compared to Controls

Dose Level (ppm)	Week 3		Week 6		Week 10		Week 13		Total Weight Change	
Males										
0	186		231		270		287		175	
10	181	(2.7)	225	(2.6)	266	(1.5)	283	(1.4)	172	(1.7)
50	182	(2.2)	224	(3.0)	263	(2.6)	278	(3.1)	167	(4.6)
150	184	(1.1)	222	(3.9)	260	(3.7)	276	(3.8)	163	(6.9)
250	187	(+)	231	(0)	268	(0.7)	284	(1.0)	172	(1.7)
500	164	(11.8)**	204	(11.7)**	246	(8.9)**	261	(9.1)DD	143	(14.9)**
900	119	(36.0)**	137	(40.7)**	166	(38.5)**	181	(36.9)DD	65	(62.9)**
Females										
0	138		157		173		182		85	
10	136	(1.4)	156	(0.6)	172	(0.6)	180	(1.1)	82	(3.5)
50	137	(0.7)	156	(0.6)	174	(+)	181	(0.5)L	82	(3.5)
150	136	(1.4)	149	(5.1)	163	(5.8)**	169	(7.1)L	72	(15.3)**
250	135	(2.2)	154	(1.9)TT	168	(2.9)**	174	(4.4)	77	(9.4)*
500	125	(9.3)TT	143	(8.9)TT	160	(7.5)**	164	(9.9)**L	67	(21.2)**
900	92	(33.3)TT	100	(36.3)T	-		-		11	(N/A)

* $p < 0.05$, ** $p < 0.01$ as determined by ANOVA and Dunnett's Test
DD $p < 0.01$ as determined by Kruskel-Wallis followed by Dunn's Test for Multiple Rank Comparisons.
L Log transformed data.
T $p < 0.05$, TT $p < 0.01$ as determined by a T-test.
N/A not applicable.

3. Food Consumption, Food Efficiency and Compound Intake - Individual animal food consumption was measured weekly for 13 weeks. Compound intake was calculated using food consumption, target concentration and body weight data.

Results - Food consumption was significantly decreased, approximately 11 and 27 percent in males in the 500 ppm and 900 ppm, respectively during the 13-week period. Food consumption was significantly decreased approximately 11 and 29 percent in females in the 500 ppm and 900 ppm groups, respectively, during the study (see Table 3). Food efficiency was significantly decreased in males (47.6%) and females (64.9%) in the 900 ppm group (see Table 4). Mean compound intake is presented in Table 5.

Table 3: Food Consumption in g/Animal/Week and Percent (%) Decrease Compared to Controls

Dose Level (ppm)	Week 3		6		10		13	
Males								
0	107		105		107		110	
10	104	(2 3)	102	(2.9)	106	(0.9)	108	(1.8)
50	101	(5.6)	99	(5.7)	100	(6.5)	106	(3.6)
150	106	(0.9)	104	(1.0)	101	(5.6)	105	(4.5)
250	107	(0)	104	(1.0)	103	(3.7)	108	(1.8)*
500	93	(13.1)**	94	(11.5)**	98	(8.4)**	98	(11.9)**
900	65	(39.3)**	72	(31.4)**	87	(18.7)**	88	(20.0)**
Females								
0	91		82		78		86	
10	89	(2.2)	83	(+)	79	(+)	86	(-)
50	88	(3.3)	81	(1.2)	80	(+)	87	(+)
150	89	(2.2)	77	(6.1)	76	(2.6)	82	(4.7)
250	89	(2.2)	82	(0)	77	(1.3)	81	(5.8)**
500	78	(14.3)**	74	(9.8)**	73	(6.3)	76	(11.6)**
900	60	(34.1)**	63	(23.2)**	-		-	

*Significantly different from the controls $p < 0.05$
**Significantly different from the controls $p < 0.01$

Table 4. Food Efficiency and Percent (%) Decrease Compared to Controls

Sex	Dose Level (ppm) 0	10	50	150	250	500	900
Males	0.126	0.119 (5.6)	0.128 (+)	0.123 (2.4)	0.127 (+)	0.122 (3.2)	0.066 (47.6)
Females	0.077	0.075 (2.6)	0.075 (2.6)	0.068 (11.7)	0.072 (6.5)	0.068 (11.7)	0.026 (64.9)

Table 5: Mean Compound Intake (mg/kg/day)[1]

	Dose Level (ppm)					
	10	50	150	250	500	900
Males	0.7 (0.6)[2]	3.3 (2.7)	10.2 (8.37)	16.7 (13.8)	33.7 (28.2)	68.0 (55.7)
Females	0.8 (0.6)	4.0 (3.3)	11.7 (9.61)	19.7 (16.3)	38.4 (32.2)	79.5 (65.2)

[1] Intake was based on the "target" concentrations of the technical containing 88.2% a.i.

[2] Actual intake of the a.i. based on the mean actual concentration of the active ingredient in the diet.

4. Ophthalmological Examinations were performed initially and at termination on all animals. Eyes were examined by focal illumination and indirect ophthalmoscopy after producing mydriasis with 1 percent atropine.

   Results - Treated animals were comparable to controls. It was noted that all rats that were examined had bilateral central corneal dystrophy.

5. Blood samples were taken via puncture of the orbital sinus plexus from all surviving rats on day 95. All rats were fasted overnight prior to bleeding. The CHECKED (X) parameters were determined.

   a. Hematology

X	Hematocrit (HCT)
X	Hemoglobin (HGB)
X	Leukocyte count
X	Erythrocyte count
	Platelet count

X	Total plasma protein (TP)
X	Leukocyte differential count
X	Mean corpuscular HGB (MCH)
X	Mean corpuscular HGB conc. (MCHC)
X	Mean corpuscular volume (MCV)

   Results - The mean erythrocyte and leukocyte counts were decreased by approximately 37 and 15 percent, respectively, in males in the 900 ppm group when compared to controls. Hemoglobin and the hematocrit were decreased approximately 14 and 13 percent, respectively, when compared to controls. The

decreases observed were primarily due to two males (#AC 1216 and #AC 1219) of the four surviving males (see Table 6) and are believed to be treatment related. Similar changes were not observed in females.

Table 6: Selected Hematology Parameters and Percent Decrease (%) Compared to Controls in Males

Dose Level (ppm)

Parameter	0	10	50	150	250	500	900
Erythrocyte count	8.7	8.2 (5.7)	7.7 (11.5)	8.1 (6.9)	7.6 (12.6)	7.5 (13.8)	5.5 (36.8)**
Leukocyte count	8.00	8.19 (+)	7.78 (5.0)	8.20 (+)	7.87 (1.6)	7.88 (1.5)	6.75 (15.3)*
Hemoglobin	16.0	16.6 (+)	15.4 (3.8)	16.2 (+)	15.5 (3.1)	15.8 (1.3)	13.7 (14.4)*
Hematocrit	46.8	48.5 (+)	45.7 (2.4)	48.1 (+)	45.4 (3.0)	46.4 (0.9)	40.9 (12.6)*

*Significantly different from controls at $p < 0.05$
**Significantly different from controls at $p < 0.01$

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorus		Cholesterol
X	Potassium		Globulins
X	Sodium	X	Glucose
	Enzymes	X	Total bilirubin
	Alkaline phosphatase	X	Total protein
	Cholinesterase		Triglycerides
	Creatinine phosphokinase		Thyroxine (T4)
	Lactic acid dehydrogenase (LDH)		Triiodothyronine (T3)
		X	Albumium/Globulin ratio
X	Serum alanine aminotransferase (SGPT)		
X	Serum aspartate aminotransferase (SGOT)		
	Gamma glutamyltransferase		

Three of the four surviving males had decreases in glucose ranging from 9-21% when compared to control mean values.

Results - Glucose was significantly decreased (≈16%) in females in the 500 ppm group when compared to controls. The decrease was attributed to decreased food consumption (see Table 7). Blood urea nitrogen was significantly increased (50%) in males in the 900 ppm group when compared to controls. Clinical chemistries were not performed for females in the 900 ppm group because of their failure to survive the 90-day period.

Table 7: Selected Clinical Chemistry Parameters and the Increase/Decrease in Percent (%) Compared to Controls

	Dose Level (ppm)						
	0	10	50	150	250	500	900
Male							
Glucose (mg/dl)	87	90 (3.4)	96 (10.3)	102 (17.2)	99 (13.8)	83 (-4.6)	81 (-6.9)
BUN (mg/dl)	18	19 (5.6)	20 (11.1)	19 (5.6)	20 (11.5)	19 (5.6)	27 (50.0)*
Female							
Glucose (mg/dl)	86	90 (4.7)	84 (2.3)	76 (-11.6)	85 (-1.2)	72 (-16.3)*	-
BUN (mg/dl)	19	18 (-5.3)	17 (-10.5)	18 (-5.3)	18 (-5.3)	19 (0)	-

*Significantly different from controls at $p < 0.05$
**Significantly different from controls at $p < 0.01$

6. Urinalysis - not conducted.

7. Sacrifice and Pathology - All animals that died and that pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	X	Aorta	XX	Brain
	Salivary glands	XX	Heart	X	Periph. nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes		
X	Duodenum	X	Spleen	X	Pituitary
X	Jejunum	X	Thymus	X	Eyes (optic nerve)
X	Ileum		Urogenital		
X	Cecum	XX	Kidneys		Glandular
X	Colon	X	Urinary bladder	XX	Adrenals
X	Rectum	XX	Testes	X	Lacrimal gland
XX	Liver	X	Epididymides	X	Mammary gland
	Gallbladder	X	Prostate	X	Parathyroids
X	Pancreas		Seminal vesicle	X	Thyroids
	Respiratory	XX	Ovaries		Other
X	Trachea	X	Uterus	X	Bone
X	Lung	X	Vagina		Skeletal muscle
					Skin
					All gross lesions and masses

Results

a. Organ Weight - There were significant decreases in the absolute weights of the heart (≈23%), liver (≈38%), and kidneys (≈21%) in males in the 900 ppm group. There was a significant decrease (≈23%) in the heart/body weight ratio of males in the 900 ppm group. There were significant decreases in the heart and kidney/brain weight ratios of ≈21 and ≈19 percent in males in the 900 ppm group, respectively, and a large (≈36%) non-significant decrease in the liver/brain weight ratio that paralleled the absolute organ weight changes. The heart, liver, and kidney/body weight ratios, however, were increased or unchanged. These changes probably reflect decreases in body weight gain that were observed in the study.

Table 8: Selected Organ Weight and Percent (%) Increase/Decrease in Males When Compared to Controls

Organs/Wt	Dose Level (ppm)						
	0	10	50	150	250	500	900
Heart Wt (g)	0.87	0.87 (0)	0.87 (0)	0.86 (1.1)	0.87 (0)	0.82 (-5.7)	0.67* (-23.0)
Heart/ Body Wt	0.319	0.322 (0.9)	0.328 (2.2)	0.328 (2.2)	0.320 (0.3)	0.332 (4.1)	0.391* (22.6)
Heart/ Brain Wt	49.11	48.43 (-1.4)	48.80 (-0.6)	48.82 (-0.6)	49.02 (-0.2)	45.61 (-7.1)	38.79* (-21.0)
Liver Wt (g)	9.26	8.94 (-3.5)	8.76 (-5.4)	8.80 (-5.0)	9.41 (1.6)	8.84 (-4.5)	5.79* (-37.5)
Liver/ Body Wt	3.36	3.28 (-2.4)	3.29 (-2.1)	3.34 (0.6)	3.46 (3.0)	3.55 (5.7)	3.36 (0)
Liver/Brain Wt	520.6	496.1 (-4.7)	491.9 (-5.5)	500.1 (-3.9)	530.9 (2.0)	490.1 (-5.9)	333.7 (-35.9)
Kidney Wt (g)	1.85	1.83 (-1.1)	1.78 (-3.8)	1.83 (-1.1)	1.84 (-0.5)	1.80 (-2.7)	1.46* (-21.1)
Kidney/ Body Wt	0.674	0.674 (0)	0.670 (-0.6)	0.700 (3.9)	0.676 (0.3)	0.724 (7.4)	0.344 (25.2)
Kidney/Brain Wt	103.9	101.4 (-2.4)	99.8 (-3.9)	104.2 (0.3)	103.6 (-0.3)	99.7 (-4.0)	84.2* (-19.0)

*Significantly different from controls at $p < 0.01$

b. Gross Pathology - Unremarkable.

c. Microscopic Pathology - Deaths in 7 of 10 males and all females in the 900 ppm group were attributed to "inanition." Tissue findings included hepatocellular atrophy, thymic involution, depletion of lymphoid tissues (lymph nodes and spleen), depression of extramedullary hematopoiesis in the spleen,

degranulation of acinar cells of the pancreas, decreased follicular colloid in the thyroid gland, cessation of the estrous cycle and ovulation with atrophy of the uterus, ovary, and vagina in females, prostatic atrophy in males, and loss of subcutaneous fat. These changes were observed to varying degrees in all animals that died and were believed to be due to inanition. It was reported that interference of the estrous cycle occurred in females in the 500 ppm group. This was believed to be associated with decreased food intake and was, therefore, nutritionally related.

D. DISCUSSION:

Mortality rates of 70 and 100 percent were observed in males and females in the 900 ppm group. Males and females in the 900 ppm group exhibited abdominal-genital staining, ataxia, clonic convulsions, chromodacryorrhea, chromorhinorrhea, decreased feces, decreased locomotion, dehydration, hypersensitivity to touch and sound, splayed hindlimbs, and unthriftiness. Females also exhibited abdominal recumbency and walking on toes. Males and females in the 500 and 900 ppm groups had significantly decreased weights at several intervals and body weight gain when compared to controls. Food consumption was significantly decreased in males and females in the 500 and 900 ppm groups at several intervals during the test period. Males in the 900 ppm group had significant decreases in the erythrocyte count and leukocyte count when compared to controls. Hemoglobin and the hematocrit were also decreased in males in the 900 ppm group and are believed to be treatment related. Males in the 900 ppm group had significant increases in the BUN and females in the 500 ppm group had significantly decreased glucose levels.

GUIDELINE: 83-3

Primary Reviewer: Guruva B. Reddy, DVM, PHD
Section IV , Tox.Branch I (H7509C)
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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/kg the maternal LEL = 25 mg/kg based on ataxia, urine-stained abdominal fur, fecal-stained perineal fur, decreased food consumption and decreased weight gain. The developmental NOEL = ≥ 35 mg/kg

Core Classification: Guideline

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

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.

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.

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	81.4	159.2	55.9	155.5
LDT	31.6	57.0	81.1	149.7	53.2	145.9
[3]MDT-L	34.9	55.6	83.4	153.9	51.9	150.2
[3]MDT-H	36.2	**45.9****	86.6	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

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).

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.

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.

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.

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≤0.01) different from the vehicle group value.

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.