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CASWELL FILE

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

SEP 16 1996

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id No.: 109702. Cypermethrin: Review of a series 82-4 subchronic inhalation toxicity study in rats and a series 83-3 developmental toxicity study in rabbits.

TOX CHEM No.: 271DD
PC No.: 109702
Barcode No.: D224639
Submission No.: S502909

FROM: John Doherty, Ph.D.
Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO[1]: Mary Clock/Paula Deschamp
RCAB
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THROUGH: Marion Copley, DVM
Section Head, Review Section IV
Toxicology Branch I
Health Effects Division 7509C

I. CONCLUSION

The series 82-4 subchronic inhalation toxicity study of 21 days duration (MRID No.: 43507101) in rats with cypermethrin was reviewed and classified as ACCEPTABLE. No additional series 82-4 study data are required at this time. A series 82-4 study of longer exposure duration may be required if additional concerns for potential inhalation risks are identified.

The series 83-3 rabbit developmental toxicity study

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(MRID No.: 43776301 and 43776302) with cypermethrin was reviewed and classified as ACCEPTABLE. No additional series 83-3 developmental studies in rabbits are required at this time.

Copies of both DERs are attached.

II. Background and Action Requested

The FMC Corporation (refer to letter from Nancy J. Hilton dated March 4, 1996) has submitted a series 82-4 subchronic inhalation toxicity study (MRID No.: 43507101) and a series 83-3b pilot and definitive rabbit developmental toxicity study (MRID No.: 43776301 for the pilot study and 43776302 for the definitive study). These studies were reviewed and copies of their DERs are attached. The studies are further identified in Part IV below.

III. Toxicology Branch Comments

A. Inhalation toxicity study.

1. TB-I classified this study as ACCEPTABLE. There were some concerns related to the duration of exposure (21-days) and the histopathological assessment.

-The series 82-4 subchronic inhalation toxicity study is normally supposed to include exposure over a period of 90 days. The requirement for 90 days exposure was, however, waived and a 21-day exposure period considered acceptable. TB-I considers that there is no immediate need for a study of longer duration unless additional inhalation concerns are identified.

-The study assessed only 5 animals/sex for histopathology. All ten animals per sex should have been assessed histologically. Since there were no indications of histopathological effects in the 5/sex assessed, TB-I is not requesting the additional readings at this time.

2. The study included a special section on analysis of cypermethrin in the brain but no cypermethrin was detected (with one possible exception). Since the limit of detection was very low (50 ng/gm of brain sample), and the rats displayed symptoms it is possible that the time of sacrifice after exposure was too long and that the cypermethrin in the brain was already removed (metabolized).

In this regard, TB-I requests that the time that the rats were sacrificed for both the 10 and 22 day satellite groups relative to the time the rats were removed from the exposure chambers be provided. This information will not impact the classification of the acute inhalation toxicity study since analysis of the brain for the test material is not required.

This information, however, is still be requested in order to help further understand the toxicity of cypermethrin.

B. Rabbit Developmental Toxicity Study.

The rabbit developmental toxicity study (MRID No.: 43776302) was reviewed and determined to be ACCEPTABLE. The study demonstrated a NOEL and LOEL of 100 and 450 mg/kg/day based on body weight effects in the does. There were no developmental effects noted in the pups.

IV. Studies Reviewed

Study Identification	Executive Summary
84-2. 21-day subchronic inhalation study, Zeneca Central Toxicology Laboratory, Study No.: CTL/P/4534 and MRO165 Technical cypermethrin, P36. RO79383 87.1% pure, approx 50% cis and 50% trans.	In a 21-day subchronic inhalation toxicity study (MRID 43507101) cypermethrin (87.1% purity, 1:1 cis:trans) was administered to 5/sex rats (Alpk:Apfsd, Wistar Derived)/sex/dose group by nose only exposure at concentrations of 0, 0.01, 0.05 or 0.25 mg/L for six hours per day, 5 days per week for a total of 15 exposures. Additional satellite groups of 5/sex were included for recovery assessment and analysis of cypermethrin in the brain. The MMAD was determined to be 2.63 to 2.86 μM. At 0.05 mg/L there was slight but consistently statistically significant (< 5% body, $p < 0.05$) body weight loss also reflected as a 16% decrease in body weight gain. All males and 4 females had occasional salivation. At 0.25 mg/L clinical signs were evident from day 10 on (particularly including decreased activity, salivation, lachrymation, tail erection, head and/or paw flicking and tip toe gait and others, see results). Changes in RBC parameters were slight and equivocal. Cypermethrin was not detected in the brain at day 10 or 22. **The LOEL is 0.05 mg/L based mainly on body weight decrease. The NOEL is 0.01 mg/L.** This study is ACCEPTABLE and satisfies the requirement for a series 84-2 inhalation toxicity study.
83-3b. Developmental Toxicity study-rabbits FMC Toxicology Laboratory, Study No.: A93-3822, October 28, 1994 Technical Cyermethrin, PL91-333, 94-96% pure, approx 50% cis and 50% trans	In a developmental toxicity study (MRID No.: 43776302) cypermethrin (94-96% pure, cis/trans ration approximately 1:1) was administered to 20 New Zealand White rabbits per dose group by gavage at dose levels of 0, 100, 450 or 700 mg/kg/day from days 7 through 19 of gestation. The does were sacrificed on day 29 of gestation. Cypermethrin was administered as a 50% w/v solution in corn oil at varying volumes and corn oil was administered to the control group. Body weight gain was decreased during dosing at 450 (25%) and 700 (30%) mg/kg/day and this was followed by compensatory increases. Exacerbation of some clinical signs such as anorexia, abdominogenital staining and decreased feces and red or pink material in the pan also resulted in the 700 mg/kg/day dose group and in a few does in the 450 mg/kg/day group. **The maternal LOEL is 450 mg/kg/day, based on body weight gain. The maternal NOEL is 100 mg/kg/day.** There were no indications of developmental toxicity. **The NOEL and LOEL for developmental toxicity is > 700 mg/kg/day.** The study is classified as ACCEPTABLE and satisfies the requirement for a series 83-3b developmental toxicity study in rabbits.

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EPA Reviewer: John Doherty, Ph.D., D.A.B.T. , Date 5/16/96
Review Section IV, Toxicology Branch I, (7509C)
EPA Secondary Reviewer:Marion Copley, DVM , Date 5/16/96
Review Section IV, Toxicology Branch I, (7509C)

DATA EVALUATION RECORD 012056

STUDY TYPE: Subchronic Inhalation Toxicity - Rat; OPPTS 870.3465 [§82-4]

DP BARCODE: D224639 SUBMISSION CODE: S502909
P.C. CODE: 109702 TOX. CHEM. NO.: 271DD

TEST MATERIAL (PURITY): Technical cypermethrin (87.1% purity), lot P36.R07983.

CITATION: Parr-Dobrzanski, R.J. (1994) "Cypermethrin: 21-day sub-acute inhalation toxicity study in the rat", Zeneca Central Toxicology Laboratory, UK., Study No.: MRO165 and Report No.: CTL/P/4534, November 23, 1994, MRID No.: 43507101. Unpublished.

SPONSOR: Zeneca, Inc. Agricultural Products

EXECUTIVE SUMMARY:

In a 21-day subchronic inhalation toxicity study (MRID 43507101) cypermethrin (87.1% purity, 1:1 cis:trans) was administered to 5/sex rats (Alpk:Apfsd, Wistar Derived)/sex/dose group by nose only exposure at concentrations of 0, 0.01, 0.05 or 0.25 mg/L for six hours per day, 5 days per week for a total of 15 exposures. Additional satellite groups of 5/sex were included for recovery assessment and analysis of cypermethrin in the brain. The MMAD was determined to be 2.63 to 2.86 uM.

At 0.05 mg/L/day there was slight but consistently statistically significant (< 5% body, $p < 0.05$) body weight loss also reflected as a 16% decrease in body weight gain. All males and 4 females had occasional salivation. At 0.25 mg/L clinical signs were evident from day 10 on (particularly including decreased activity, salivation, lachrymation, tail erection, head and/or paw flicking and tip toe gait and others, see results). Changes in RBC parameters were slight and equivocal. Cypermethrin was not detected in the brain at day 10 or 22. **The LOEL is 0.05 mg/L based mainly on body weight decrease. The NOEL is 0.01 mg/L.**

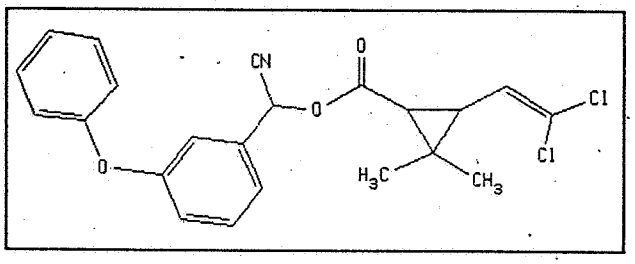
Classification: This study is classified as ACCEPTABLE. It should be noted that since the study was for 21 days only, an additional study of 90 days duration may be required if it is justified by the exposure patterns to cypermethrin. Histopathology was assessed for only 5 rats/sex and 10 rats/sex should have been assessed. Future studies should assess 10/sex/group.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Cypermethrin Technical
   Description: dark brown liquid
   Lot/Batch #: P36.R079383
   Purity: 87.1% a.i.
   Stability of compound:
   CAS #: 52315-07-8 (from REFS)



2. Vehicle and/or positive control: Not applicable.

3. Test animals:
   Species: Rat
   Strain: Alpk:Apfsd (Wistar Derived)
   Source: Alderley Park Laboratory, Cheshire, UK
   Acclimation period: 8 days
   Age: Young adult (exact age not specified but estimated to be 6-8 weeks).
   Weight: day 1: Males: approx 271 to 281 gms; females approx 229 to 237.
   Housing: 5/cage separated by sex
   Diet: CTI diet (supplied by Special Diets Services, Witham, Essex, UK. ad libitum (except during exposure).
   Water: Pottable ad libitum

B. STUDY DESIGN:

1. In life dates - start: July 19, 1994; end: August 24, 1994.

2. Animal assignment Animals were assigned by randomization (latin square) to the ten test groups as indicated in table 1.

TABLE 1: STUDY DESIGN[a,b]

Test group	Target Conc. (mg/L)	Analytical Conc.(mg/L)[1]	MMAD μm	GSA μm	Rats/sex
1 Control-Main study	0	0	--	--	5
5 Control-recovery	0	0	--	--	5
7 Control-Interim[2]	0	0	--	--	5
9 Control-Main study[3]	0	0	--	--	5
2 Low dose-Main study	0.010	0.0101±0.001	2.73±0.24	2.06±0.15	5
10 Low dose-Main[4]	0.010	0.0091±0.001			5
3 Mid dose-Main study	0.050	0.0483±.0039	2.63±0.24	1.87±0.2	5
11 Mid dose-Main[4]	0.050	0.0442±.0037			5
4 High dose-Main	0.250	0.236±0.010	2.86±0.17	1.78±0.05	5
6 High dose-Recovery	0.250	0.222±0.012			5
8 High dose-Interim[2]	0.250				5
12 High dose-Main[3]	0.250				5

[a] = Data extracted from page 16 (number of animals) and page 24 (total particulate and analyzed cypermethrin concentrations and MMAD and GSD data) of the study report. MMAD = mass median aerodynamic diameter, GSD = geometric standard deviation.
[b] The dose levels are presented as ug/L in the study report. In the DER these dose levels were converted to mg/L for conformity to the current standards for DER preparation.
[1] Two numbers are presented. The upper number is the total particulate concentrate (ug/l) and the lower number is the cypermethrin concentration resulting from analysis.
[2] These groups were sacrificed for analysis of the brain for cypermethrin after 10 days on the study.
[3] These groups were sacrificed for analysis of the brain for cypermethrin after 21 days on the study.
[4] There was no explanation for including two separate subgroups of the low and mid dose groups. Apparently only one group of 5 were assessed for clinical reactions and microscopically for selected limited tissues. The other group may have been included for brain analysis of cypermethrin but were not analyzed.

2. The test atmosphere was generated into the test chamber using a glass concentric-jet atomizer that was coupled to a Watson Marlow peristaltic pump and the resultant aerosol was fed directly into the top of the exposure chamber. Clean dry air also was supplied to the test chamber to help dilute the material emitted from the atomizer. The test chambers had variable air flow rates of 30 L/min for the control, 10 L/min for the 0.010 mg/L groups, and 20 L/min for the 0.050 and 0.250 mg/L groups.

The test chamber contained tubes to hold the animals such that the exposure was nose only. The rats were acclimatized to the restraining tubes for 3 consecutive days prior to exposure.

Exposure was for 6 hours a day for 5 days per week for a total of 15 exposures over a 21 day period.

Time to equilibrium was not provided. Although such information would be useful, it is not considered necessary for a six hour exposure.

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Analytical Chemistry.

Nominal concentration: Nominal (weight of substance used) concentrations were not determined during this study.

Particulate and chemical concentration: The test atmosphere (said to be sampled near the breathing zone, was draw at a known flow rate through a 25 mm diameter Vinyl Metricel (VM-1) filter. The weight of the filter both before and after sampling was assessed and the concentration of particulate matter determined. The filters were then stored in sealed bottles for chemical analysis. The results of the particulate and chemical analysis are presented in Table 1 above.

Particle size determination was measured daily for the first three days and once weekly thereafter by means of a Marple Cascade Impactor. The mean amount of aerosol, by weight, in each size range, was then used to calculate the aerodynamic particle size distribution of the aerosol. Using a microcomputer the data were transformed using a log/probit transform and a linear regression derived from the cumulative data to derive both the Mass Median Aerodynamic Diameter (MMAD) and the geometric standard deviation (GSD). The resulting MMAD and the GSD are in shown in Table 1 above.

3. Statistics - The following statistical methods were used to assess the parameters indicated.

Statistical Method	Parameter Investigated
Analysis of covariance	initial body weight organ weights
Analysis of variance	Heamatology Blood clinical chemistry

II. RESULTS

A. Observations Animals were inspected daily for signs of toxicity and mortality. On days 1,2,3,8,15 and prior to post mortem on day 22 the rats were weighed and given a detailed clinical examination that included the following:

condition of fur	respiration
motor activity	skin color
salivation	feces
righting reflex	condition of eyes
palpebral reflex	pinna reflex
foot withdrawal reflex	respond to sound
visual placing	splay reflex

1. Mortality - All animals survived to their scheduled sacrifice time.

2. Toxicity - Compound related clinical signs were apparent in the 0.050 and 0.250 ul/L exposure groups. Direct observation of the test animals during exposure was confounded because the rats were in cones to facilitate nose only exposure. Salivation was, however noted in some animals. Most of the symptoms noted were observed immediately after exposure. Only signs of piloerection and ungroomed appearance were noted on non-exposure days. The symptoms noted are quantitated in Table 2.

Table 2. Clinical signs in rats in the main study (5/sex/dose group) dosed with cypermethrin by the inhalation route.

Symptom		Dose (mg/L) Control	0.010	0.050	0.250	0.250[1]
Salivation (days 1-15)	M	0	0	6	26	35[3]
	F	0	0	9/4	25	31
Decreased activity (Day 1 -15)	M	0	0	0	27	26
	F	0	0	0	25	25
Lachrymation (Day 1 -15)	M	0	0	0	16	17
	F	0	0	0	19	25
Tail erection (Day 2- 15)	M	0	0	0	7	8/4[3]
	F	0	0	0	16	20
Head flicking (Day 1 - 2)	M	Not reported in males				
	F	0	0	0	2/1	2/2
Paw flicking (Day 1 - 15)	M	Not reported in males				
	F	0	0	0	15/4	18
Reduced stability (Day 2 - 15)	M	Not reported in males				
	F	0	0	0	6/2	5/3
Tip toe gait (Day 1- 15)	M	Not reported in males				
	F	0	0	0	25	25
Ungroomed (Day 22)	M	Not reported in males				
	F	0	0	0	2/2	2/2

[1] This group is the satellite 0.250 mg/L group included to verify that the high dose group developed the symptoms.
[2] The symptoms were noted from days 10 onward.
[3] The total number of times the symptom was observed. All five animals were affected unless the number is presented as a numerator (total number of times observed) and denominator (total number of animals with symptom).

Certain other signs such as "hunched", piloerection, stains around nose, wet fur and chromodacryorrhea were also reported in all dose groups. Piloerection and stains around the nose were increased in the high dose groups very probably as a result of the test material. The others are more probably related to the stress of the confinement to the test chamber and

nose only exposure.

B. Body weight and weight gain. Refer to Tables 4 attached (taken from pages 48 and 49 of the study report) and Table 3 below. Statistically significant differences in body weight were noted for the high dose group males and females at all days after day 1. Male absolute body weight was 4-6% lower and females were 3-4% lower than the respective controls. In the mid dose group, statistical significant decreases were noted on days 2 (-2.1%), 3 (-2.8%), 8 (-2.8%) and day 22 (-4.3%) in males and on days 3 (-2.7%), day 8 (-3%), day 15 (-4%) and day 22 (-5.4%). Statistical differences in absolute body weight were not noted for the group exposed to 0.010 mg/L.

Table 3[a]. Body weight gain in rats exposed to atmospheric cypermethrin for 21 days.

Sex	Dose Level (mg/L)[1]					
	Control	0.010	0.050	0.250	Control	0.250
Males	74.6 --	76.2 (+2.1%)	62.0 (16.8%)	58.7 (21.3%)	73.0 --	46.1 (36.8%)
Females	33.0 --	22.2 (33%)	16.8 (49%)	21.2 (36%)	24.2 --	17.4 (29.1%)

[a] Data were calculated from Table 4 of the study report attached.
[1] Data are grams gained between day 1 and day 22. The number in () is the percent decrease unless preceded by + which means there was a weight gain increase.

Table 3 shows that for males there is a dose adverse effect on weight gain in the 0.050 and 0.250 mg/L dose groups. This decrease in weight gain is also noted in the satellite group. In females, there was no dose response over the range from 0.010 to 0.250 mg/L. The first control group seems to have an unusually large weight gain and the 0.050 mg/L dose group has a unusually small weight gain. It can not be ascertained from these data if there was an effect on weight gain in females. Since the absolute weight for the mid and high dose females was significantly lower than the controls, TB-I concludes that there were treatment related effects on body weight in females at 0.05 and 0.250 mg/L.

C. Food consumption - The mid (up to 8% for males and 4.6% for females) and high (up to 15% for males and 12% for females at week 1) showed decreases in food consumption. The study author did not present a statistical assessment of the food consumption data.

D. Ophthalmoscopic examination - No ophthalmoscopic examinations were done.

E. Blood work Blood was collected at study group scheduled termination time, blood was obtained by cardiac puncture. EDTA was used as an anticoagulant but additional samples were collected in trisodium citrate for the blood clotting measurements. It was not stated if the rats were fasted prior to sacrifice. Hematology and clinical analysis from all surviving animals were assessed. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)
x	Platelet count*		Reticulocyte count
x	Blood clotting measurements*	x	Red Cell distribution width
X	(Thromboplastin time)		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)		

* Required for subchronic studies based on Subdivision F Guidelines

The following hematology parameters were noted to be statistically significantly different from the control for some groups.

1. Hemoglobin. The 0.050 (5%) and 0.250 (5%) mg/L dose groups in males (both $p < 0.05$) and the 0.250 mg/L (6%, $p < 0.01$) were reduced but the satellite group 0.250 mg/L (14.9 g/dl for males and 15.0 g/dl for females) group was essentially the same as its control (14.6 g/dl for males and 15.0 g/dl for females).

2. Hematocrit. The 0.010 and 0.050 mg/L dose groups were 5% ($p < 0.05$) and the 0.250 mg/L males was 7% ($p < 0.01$) less than the control in the main study while in the satellite group the 0.250 mg/L groups was 3% less than its control. In females, the 0.250 mg/L groups were 5.7% ($p < 0.5$) and 1.7% (not significant) less than the control.

3. Red blood cell count. The 0.010 mg/L groups was 5% ($p < 0.05$), 0.050 mg/L was 3% (not significant) and the 0.250 mg/L groups were 5.4% ($p < 0.05$ in the main study) not different in the satellite group in males. In females, only the 0.250 mg/L main study group was significantly decreased (5.5%, $p < 0.05$).

These differences are recognized by TB-I but TB-I concurs with the study author that they are not conclusively linked to the test material administration. There is no dose response or consistency.

The study report noted that the blood clotting parameters (kaolin-cephalin times) in females could not be assessed because of equipment failures. Since no effects in males on the kaolin-cephalin times or prothrombin times in either sex were noted. TB-I concurs with the study author and also notes that effects on the blood clotting parameters are not known to be a

characteristic of cypermethrin based on the oral toxicity studies.

b. Clinical Chemistry Blood was collected in lithium heparin anticoagulant.

X	ELECTROLYTES	X	OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*	x	Total Cholesterol
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	ENZYMES	x	Total bilirubin
x	Alkaline phosphatase (ALK)	x	Total serum protein (TP)*
	Cholinesterase (ChE)	x	Triglycerides
x	Creatine phosphokinase		Serum protein electrophores
	Lactic acid dehydrogenase (LDH)		
x	Serum alanine amino-transferase (also SGPT)*		
x	Serum aspartate amino-transferase (also SGOT)*		
x	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

The following clinical chemistry parameters were noted to be different from the control for some groups.

1. Plasma urea. Some decreases of 7% in the 50 and 11% in the 0.250 mg/L male main groups but the satellite 0.250 mg/L group was actually 9.7% higher. The standard deviation was high 15% supporting the position that the apparent differences were natural variations. No statistical significance was attained an females did not show obvious differences.

2. Creatinine. The satellite 0.250 mg/L groups was deceases (11/5%, $p < 0.05$) but the same dose level in the main study was 6% decreased and not significant. The 0.250 mg/L female main study group was actually slightly higher (2.8%).

3. Total plasma protein. Decreases were noted in the 50 (4.4%, $p < 0.05$) and 250 (5.0% $p < 0.01$) but not were not significant in the 0.250 mg/L satellite group (3.3%). The 0.250 mg/L female group was also deceased (5.4%, $p < 0.01$).

4. Plasma albumin. A decrease was noted in the 0.250 mg/L female group (6.4%, $p < 0.01$)

5. Plasma alanine transaminase. Were lower in males in the 0.050 and 0.250 mg/L groups including the satellite. All about 25%. Decreases in this enzyme are not regarded as toxicity responses.

The above differences in clinical chemistry parameters are noted but are not regarded as actual toxicity responses to the exposure to cypermethrin. They are of a small magnitude and lack consistency between the sexes, dose levels and the main study and

satellite groups.

F. Urinalysis - No urinalysis was assessed and is not required.

G. Sacrifice and pathology

1. Organ weight - The adrenals, brain, heart, kidneys, liver, lungs, spleen and testes were weighed. Statistical differences in the following organs are discussed below:

1. Brain. Absolute brain weight (4.2%, $p < 0.05$) was slightly increased in the 0.250 mg/L male main group only.

2. Kidney. The organ weight in the 0.250 mg/L groups adjusted for body weight (not organ to body weight ratio) was increased in male satellite group (15.8%, $p < 0.05$) and female main group (8.4%, $p < 0.05$) but it was decreased in the female satellite group (4.5%, $p < 0.05$).

3. Liver. A decrease in absolute liver weight was noted in the male 0.250 mg/L dose group only (18.3%, $p < 0.01$).

4. Spleen. The 0.010 (14%, $p < 0.01$), 0.050 (13.2%, $p < 0.01$) and 0.250 (9.6%, $p < 0.01$) mg/L dose were all lower than the control for the main study but no difference was noted for the satellite group.

5. Testis. Absolute organ weight was increased (9%, $p < 0.05$) in the 0.010 and 0.050 mg/L dose groups but only 8% (not significant in the 0.250 mg/L group and the satellite group was not different from its control. When expressed as organ weight adjusted for bodyweight, there was a progression of 7.8, 9.9% and 11.6% (all $p < 0.05$) for the 0.010, 0.050 and 0.250 mg/L groups. The satellite 0.250 mg/L groups was 2.3% less than its control (not significant).

These organ weight differences are noted but TB-I does not conclude that they are definitely related to treatment with cypermethrin. There is no consistency between the dose level and/or the results of the satellite group.

2. Gross pathology - A single rat in the high dose group was reported to have "red" lungs. Other conditions reported in the treated animals were pelvic dilation in the kidney and a single incident of mottled lung. These conditions were not considered by the study author to be test compound related.

3. Microscopic pathology

All animals that died and those sacrificed on schedule were said to be subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Only 5/sex from the controls and high dose groups were routinely assessed microscopically for most tissues/organs. This is a study deficiency because all 10 subjects per sex are supposed to be evaluated microscopically.

The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	x	Aorta*	x	Brain*Periph.
x	Salivary glands*	xx	Heart*		nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3
x	Stomach*	x	Lymph nodes*		levels)[T]
x	Duodenum*	xx	Spleen*	x	Sciatic nerve
x	Jejunum*	x	Thymus*	x	Pituitary*
x	Ileum*			x	Eyes (optic n.)[T]
x	Cecum*		UROGENITAL	x	Harderian gland
x	Colon*	xx	Kidneys*+		
x	Rectum*	x	Urinary bladder*		GLANDULAR
xx	Liver*+	xx	Testes*	xx	Adrenal gland*
	Gall bladder*	x	Epididymides		Lacrimal gland[T]
x	Pancreas*	x	Prostate	x	Mammary gland[T]
x	Oral cavity	x	Seminal vesicle	x	Parathyroids*++
		x	Ovaries	x	Thyroids*++
	RESPIRATORY	x	Uterus*		
x	Trachea*	x	cervix		OTHER
xx	Lung*				Bone
	Nose			x	Sternum
	Pharynx				Skeletal muscle
x	Larynx			x	Skin
x	Nasopharyngeal cavity			x	voluntary muscle
					All gross lesions and masses*

* Required for subchronic studies based on Subdivision F Guidelines.
+ Organ weight required in subchronic and chronic studies.
T = required only when toxicity or target organ.
++ Organ weight required for non-rodent studies.

The study author asserted that there were no lesions in the high dose group indicative of test material treatment. The following organs are being discussed for the reasons indicated. Table 10 of the study report (pages 71-76) indicates that only the eye, heart, kidney, lung and voluntary muscle were reported to have lesions in the males. These organs or structures and the pancreas, sciatic nerve and stomach but not voluntary muscle were reported to have lesions in females.

1. Lung. Since this is an inhalation toxicity study, the lung would be a primary target for any irritation reactions. One male rat in the high dose group was reported to have "red" lungs at necropsy.

All five of the animals for all dose groups were reported assessed. The only finding reported was "alveolitis" (minimal) and in males the control and low dose group had the highest frequency (2 incidents) and in females only a single control female had this condition. There was no specific histopathological finding that further described the condition of red lung noted at gross necropsy.

2. Kidney. Gross pathology revealed pelvic dilation in some of the animals exposed to cypermethrin

Only the control and high dose test animals were assessed. Commonly occurring lesions were noted and these did not reveal a dose dependence. It was noted that the lesions intratubular microlithiasis and tubular basophilia were present in 4 of the treated females but only three of the controls. This is not regarded as a response to treatment.

3. Sciatic nerve. Pyrethroids were at one time thought to cause a specific demyelination and or splitting of the peripheral nerves. Thus the peripheral nerve (i.e. sciatic nerve) in toxicity studies with pyrethroids are commented upon.

Only the high dose and controls were assessed microscopically. There were no reports of demyelination in the in the high dose animals. The controls females (2) were reported to have this lesion.

4. Larynx, pharynx, nasopharyngeal cavity and upper respiratory tract. Recently submitted subchronic inhalation toxicity studies with certain other chemicals, some of which are related to pyrethroids, have indicated widespread hyperplasia and/or metaplasia and other conditions in the upper respiratory tract.

There no were lesions in these structures reported. The pharynx was apparently not specifically examined.

H. Analysis of the brain for cypermethrin. The satellite groups dosed as controls and 0.250 mg/L were sacrificed after 10 or 22 days and their brains removed and analyzed for cypermethrin gas chromatographically. The method used had limit of detection of approximately 50 ng/g of brain extract.

No cypermethrin was detected in the brain samples following either the 10 or 22 day exposures except for one individual which was noted to have a possible level of 65 ng/gm following the 10 day exposure. Since none was detected following 22 days of exposure, the observation that one rat had detectable cypermethrin is not reproducible.

Thus, these data would suggest that cypermethrin did not enter the brain to a level of detection. It is known that dose levels of about 0.4 ug/gm of brain are in rats associated with definite toxicity reactions (Doherty, et al, Comp. Biochem. Physiol. 91C:371-375(1988)). The study report does not accurately define the time that the rats were sacrificed in relation to the cessation of exposure. The failure to detect cypermethrin in the brain may be related to the time that the rats were sacrificed and the brains removed relative to the time of the last exposure. Cypermethrin would very likely be removed from the brain rapidly following cessation of exposure.

III. **DISCUSSION**

A. This study is classified as ACCEPTABLE.

B. Study deficiencies/Discussion. The basic number of rats/sex/dose for a subchronic inhalation toxicity study is 10. This study utilizes a basic working unit of 5/sex/dose group for both the clinical signs and histopathology. The clinical signs aspect of the study, however, did have 10/sex/dose group because the symptoms in one of the satellite dose groups were reported. The histopathology assessments, however, are a study deficiency. The tissues from 10 rats per sex are supposed to be assessed microscopically. Only the tissues from 5 rats per sex were examined. Toxicology Branch does not consider this deficiency to be sufficient to compromise the interpretation of the study results and the study is still considered acceptable. Future studies are expected to assess all 10/sex.

The generation of a test atmosphere with a MMAD of 2.63 to 2.86 Um is currently within the acceptable range but is only slightly below the cutoff of 3 Um. The standard deviation of the MMAD was small (1.78 to 2.06 units) indicating that the amount of test material less than 1 Um would be a small percentage of the total atmosphere. The fact that the rats developed symptoms of clinical signs that resemble cypermethrin intoxication indicates that cypermethrin was systemically absorbed. The failure to detect cypermethrin in the brain of the rats exposed to the high dose group may relate to the delay in the time before the brains were assessed for cypermethrin. Thus, the failure to detect cypermethrin in the brain should not be considered a proof that cypermethrin was not systemically absorbed.

Recent subchronic inhalation studies with several compounds related to pyrethroids have indicated the presence of hyperplasia/metaplasia in the larynx, pharynx and other sections of the upper respiratory tract leading to the lung. These conditions were not noted in this study nor were there any lesions at all reported in these structures. This raises the question as to how well these structures were actually examined for the presence of hyperplasia/metaplasia or other lesions. Thus, TB-I is requesting that these structures be reassessed microscopically particularly for such lesions as hyperplasia /metaplasia or any other lesions that would indicate that the upper respiratory tract was affected in this study by atmospheric cypermethrin.

CYPERMETHRIN

Page_____ is not included in this copy.

Pages 17 through 18 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

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FMC Corporation

Agricultural Products Group
1735 Market Street
Philadelphia Pennsylvania 19103
215 299 6000

FMC

March 4, 1996

Federal Express

Ms. Veronica Dutch
Chemical Review Manager
Special Review and Reregistration Division
Office of Pesticide Programs - H7508W
US Environmental Protection Agency
Crystal Station, 3rd Floor
2800 Jefferson Davis Highway
Arlington, VA 22202

Dear Ms. Dutch:

Chemical No.: 109702 - Cypermethrin
Case No.: 2530

Enclosed please find one copy of the following three documents as you requested in our phone conversation this morning.

1. Cypermethrin Technical: Pilot Oral Teratology Study in Rabbits.
   FMC Study No. A93-3823. GRN: 83-3. MRID# 43776301

2. Cypermethrin Technical: Oral Teratology Study in Rabbits.
   FMC Study No. A93-3822. GRN: 83-3. MRID# 43776302.

3. Cypermethrin: 21 Day Sub-Acute Inhalation Toxicity Study in the Rat.
   Study No. MR0165. GRN: 82-4. MRID # 43507101

Please call if any questions.

Sincerely,

Nancy J. Hilton
Product Registrations Manager
(215)299-6753

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EPA Reviewer: John Doherty, Ph.D., D.A.B.T., Date 3/29/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley, DVM, Date 3/29/96
Review Section IV, Toxicology Branch I 7509C)

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - rabbit
OPPTS 870.3700 [§83-3 (b)]

DP BARCODE: SUBMISSION CODE:
P.C. CODE: 109702 TOX. CHEM. NO.: 271DD

TEST MATERIAL (PURITY): Cypermethrin technical, 94-96% purity, approximately 50% cis and 50% trans, lot # PL91-333.

CITATION: Freeman, C. (1994). "Cypermethrin Technical Oral Teratology Study n Rabbits", FMC Corporation Toxicology Laboratory, Study No.: A93-3822, October 28, 1994, MRID No.: 43776302. Unpublished.

Freeman, C. (1994). "Cypermethrin Technical Pilot Oral Teratology Study in Rabbits", FMC Corporation Toxicology Laboratory, Study No.: A93-3823, October 14, 1994, MRID No.: 43776301. Unpublished.

SPONSOR: FMC Corporation.

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID No.: 43776302) cypermethrin (94-96% pure, cis/trans ration approximately 1:1) was administered to 20 New Zealand White rabbits per dose group by gavage at dose levels of 0, 100, 450 or 700 mg/kg/day from days 7 through 19 of gestation. The does were sacrificed on day 29 of gestation. Cypermethrin was administered as a 50% w/v solution in corn oil at varying volumes and corn oil was administered to the control group.

Body weight gain was decreased during dosing at 450 (25%) and 700 (30%) mg/kg/day and this was followed by compensatory increases. Exacerbation of some clinical signs such as anorexia, abdominogenital staining and decreased feces and red or pink material in the pan also resulted in the 700 mg/kg/day dose group and in a few does in the 450 mg/kg/day group. **The maternal LOEL is 450 mg/kg/day, based on body weight gain. The maternal NOEL is 100 mg/kg/day.**

There were no indications of developmental toxicity. **The NOEL and LOEL for developmental toxicity is > 700 mg/kg/day.**

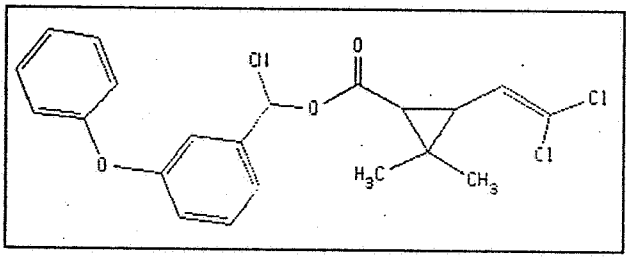
Classification: This developmental toxicity study in the rabbit is classified ACCEPTABLE and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b).

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material:
Chemical: Cypermethrin technical.
Description: Viscous amber colored liquid
Lot/Batch #: PL91-333
Purity: 94-96% a.i.
CAS #: 52645-53-1



2. Vehicle: Corn oil Lot/Batch #: Not provided.
Concentration: 50% cypermethrin in corn oil.

3. Test animals:
Species: Rabbit
Strain: New Zealand White
Source: HRP Inc. Denver, Pa.
Acclimation period: 12 days.
Age at mating: Approx 6 months.
Weight at mating: Approx. 3.11 to 3.19 kgs
Housing: Individually
Diet: Purina Rabbit Chow 5322, 150 gms rationed daily.
Water: Domestic water ad libitum
Environmental conditions:
Temperature: 62-77°F
Humidity: 20-80%
Air changes: Not stated
Photoperiod: 12 hrs dark/12 hrs light

B. PROCEDURES AND STUDY DESIGN

1. In life dates - This information was not specifically stated. Based on the Quality Assurance Inspection dates, start (mating): January 11, 1994. End (C-section): February 8, 1994.

2. Mating: Active mating with a male was used to impregnate the does. The mating was verified by the presence of sperm in a microscopic vaginal smear. The does were assigned to a dosage group after mating.

3. Animal Assignment: Animals were assigned to dose groups as indicated in Table 1. No specific randomization procedure was named for assignment of the does to the groups.

Table 1. Experimental Design for the Definitive Developmental Toxicity study in rabbits with cypermethrin.

Test Group	Number of Does[1]	Dose Level (mg/kg)	Dosing Volume
Control	20	0	1.4[2]
Low (LDT)	20	100	0.2
Mid (MDT)	20	450	0.9
High (HDT)	20	700	1.4

[1] All does assigned to each group were presumed to be pregnant.
[2] The dosing volume is in ml/kg. The control group was dosed with corn oil only.

4. Dose selection rationale: The dose selection was based on a preliminary pilot study (MRID No.: 43776301) in which groups of 8 presumed pregnant New Zealand White rabbits were dosed as control, 100, 500, 750 or 1000 mg/kg/day of cypermethrin (same lot as in definitive study) on days 7 through 19 of gestation. Cypermethrin was dosed as a 50% solution in corn oil. The high dose for this study (1000 mg/kg/day)is the limit dose for a developmental toxicity study. No effects of treatment were said to be noted at 500 mg/kg/day or below. TB-I, however, believes that weight gain was affected at 500 mg/kg/day (see weight gain discussion for the definitive study below). At 750 or 1000 mg/kg/day, the does had significant body weight decreases, abdominal spasms, anorexia, decreased feces, diarrhea, ataxia, pink or reddish brown staining of the cage litter pan, nasal discharge and unthriftyness. One doe at 750 and three does at 1000 mg/kg/day aborted. These data provide support and justification for the selection of the dose levels as 100, 450 and 700 mg/kg/day.

5. Dosage preparation and analysis Cypermethrin dosing formulations were prepared as a 50% cypermethrin in corn oil. The study author asserted that "fifty percent was chosen as the optimum concentration that would achieve target limit-dose specifications while minimizing the volume of corn oil administered to the rabbits". For example, cypermethrin was demonstrated to be some 20 times more toxic when administered to rats as a 5% solution in corn oil than when administered undiluted (FMC Corporation Study No.: A87-2292). The mortality in rats due to cypermethrin also varied when different dose levels were administered at a constant volume of corn oil (FMC Study No.: A80-436-01).

TB-I considers that the use of the minimum dilution of cypermethrin in corn oil and variation of the dose level volume administered may have resulted in less toxicity than would otherwise be realized if more dilute cypermethrin preparations were used and constant volumes were administered. The procedure used by the study author, however, although not conventional, is not sufficient to invalidate the interpretation of the objective of the study which is to determine potential adverse effects on the fetuses.

Appendix B of the study report (pages 70-140) presents the analytical chemistry aspects of the study.

- Homogeneity Analysis: Samples taken from the top, middle and bottom indicated that they were within 6.3% of each other as well as within 8.5% of target. The top, middle and bottom duplicate samples were demonstrated to be 91.5, 95.7 and 97.8% of the target concentrations for a 50% solution in corn oil.

- Stability Analysis: Cypermethrin technical was said to be demonstrated to be stable in the corn oil for a 60 day period when stored under refrigeration at 2-5°C. Actual analysis indicated that there was an increase in the concentration found at 30 days (550 mg/ml, +14.8%) and 60 days (558, +16.5%) relative to the original day 0 analysis (479 mg/ml). Other data on the stability of cypermethrin indicated that cypermethrin was stable for two years at room temperature. A sample of 95.7% purity on initial analysis was determined to be 94.6% pure after 24 months.

- Concentration Analysis: Six solutions of the dose preparations of 50% cypermethrin in corn oil were presented to the analytical laboratory and analyzed in duplicate. Corn oil was also assessed. No cypermethrin was reported in the corn oil. The results of the analysis indicated that the duplicates were from 0 to 6% different. The mean of the duplicates were from 99 to 113.5% of the stated nominal 500 mg/ml solution.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

6. Dosage administration: All doses were administered once daily by gavage on gestation days 7 through 19, in a variable volume of corn oil based on the daily body weight.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The animals were checked for mortality or clinical signs twice daily. Body weight data were said to be recorded on gestation days 0, and daily during days 7-19 and on days 24 and 29. The study report individual animal data (page 41-44, Table 3 of the study report) did not verify that daily body weights were taken during the dosing period. Food consumption was not tabulated, the does were given approximately 150 grams of feed and were said to have usually consumed all of it. Dams were sacrificed on day 29 of gestation by intravenous injection of sodium pentobarbital.

D. DATA ANALYSIS

Statistical analyses: The statistical procedures used for this study are illustrated in the following table. The "Teratostat™ System developed by Statistics Unlimited, Inc. Wellesley, Ma. was used to perform some of the statistical analysis. The Pharmaco LSR performed other tests.

Statistical Procedure	Parameters Assessed
Welch Trend Test	Maternal body weights Adjusted weight gains Gravid uterine weights
Jonkheere Trend Test	Number of implants Pre-implantation loss Litter size Percentages of: live fetuses, dead fetuses, early and late resorptions.
The Exact Permutation Trend Test	Does with complete resorptions Fetal external, soft tissue and skeletal parameters.
Analysis of Variance	Fetal weights
Test for Binomial Proportions	Sex ratio

3.Historical control data: Historical control data were provided only for caesarian sectioning data for uterine parameters.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and survival: One high dose doe was sacrificed on day 11 after displaying a variety of symptoms (swelling, scabbing, and severe ulceration of the vaginal area (this doe had a cyst-like swelling in the vaginal wall not likely attributable to the test material). The condition of this doe is thought to be unrelated to the test chemical. Another doe in the 450 mg/kg/day dose group was also sacrificed on day 26 after spontaneous abortion. This could not be conclusively related to treatment. "Misdosing" (puncture of the lung) was the cause of death in one control and one low dose doe.

Clinical Observations: No signs or symptoms were reported in the 100 mg/kg/day dose group.

Pink (1 doe, four times) or red (1 occasion for 1 doe) staining of the cage pan liner were evident in the group dosed with 450 mg/kg/day.

Some of the does dosed with 700 mg/kg/day displayed a variety of symptoms that were considered to be test compound related including:

-anorexia (16 does, 105 times vs 15 does 63 times)*
-abdominogenital staining (3 does, 16 times vs 1 doe, 2 times)
-decreased feces (13 does, 32 times vs 6 does 14 times)
-ataxia (1 doe, 5 times)
-red staining of the cage pan liner (3 does, 4 times)

*Note: The number of times and number of does for the high dose vs the control are given. If only one set, then control had zero incidents.

The does in the high dose group appeared to tolerate the test material reasonably well with a resulting exacerbation of symptoms that already occur spontaneously in control does (i.e. anorexia, abdominal staining and decreased feces). The doe that was sacrificed at day 11 did not demonstrate any unusual findings except for ulcers, scabs, and pus like material surrounding the urethra/vagina.

Overall, TB-I concurs with the study author that the NOEL for clinical signs is 450 mg/kg/day. The presence of one doe with some red or pink material in the cage pan is not considered sufficient evidence of consequential effects of dosing.

2. Body Weight - Body weight gain data are summarized in Table 2 and as follows:

TABLE 2 Maternal Body Weight Gain (g)[a]

Interval	Body Weight Gain in grams Dose in mg/kg/day (# of Dams)			
	Control (16)	100 (17)	450 (19)	700 (18)
Pretreatment: Days 0-7	170±0.01	160±0.02	190±0.01	160±0.02
Treatment: Days 7-19	280±0.03	270±0.02	210±0.03 (-25%)	180±0.04 (-36%)*
Posttreatment: Days 19-29	200±0.03	200±0.04	250±0.02 (+25%)	260±0.02 (+30%)

a Data extracted from Table 3 (page 40 of the study report that contains summary and individual animal data).
Values in () are percent different from the control.
* $p < 0.05$ for the weight gain data (not the percentage data).

The study methods section states that body weight was assessed daily during test material administration. The individual animal data as presented in Table 3 of the study report do not contain these daily weighing. Thus, TB-I could not independently assess if there was a statistical difference in weight gain for the 450 mg/kg/day dose group following the first few administrations and if there was a recovery during the later administrations (adaptation).

In conclusion, TB-I has determined that there are weight

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gain decreases in the 450 mg/kg/day dose group. This conclusion is supported by the weight gain data for days 19-29 which show 25% and 30% weight increases for the 450 and 700 mg/kg/day dose groups indicating an attempt of the doe to regain lost weight. Further support for concluding that the body weight gain is affected at 450 mg/kg/day comes from the range finding study (MRID No.: 43776301, Table 3 on page 33) which shows that day 7-19 weight gain for the groups dosed with 100, 500, 700 and 1000 mg/kg/day dose groups are +23%, -27%, -85% and -62% more or less than the control. The 27% decrease in the pilot study at 500 mg/kg/day compared very favorably with the 25% decrease in the definitive study. Thus, the decrease in weight gain near 500 mg/kg/day was seen in two studies.

The NOEL and LOEL for maternal toxicity based on body weight gain are 100 and 450 mg/kg/day.

3. Food Consumption - Data were not tabulated but based on the observation that the does consumed all the feed rationed, there were no serious effects on feed consumption.

4. Gross Pathology - Gross pathology assessment indicated that the single doe sacrificed on day 11 had a "red filled cyst like swelling in the vaginal wall". This was not attributable to the test material.

5. Cesarean Section Data - Data are as follows are summarized in Table 3.

Table 3 below demonstrates the efficiency of the study and that there were no test compound related effects on the uterine parameters of the treated dams.

TABLE 3 Cesarean Section Observations[a] (See next page for footnotes).

Observation	Dose (mg/kg/day)			
	0	LDT	MDT	HDT
# Animals Assigned (Mated)	20	20	20	20
# Animals Pregnant Pregnancy Rate (%)	17 85%	17 85%	20 100%	18 90%
# Nonpregnant	4	3	1	2
Maternal Wastage # Died # Died Pregnant # Died Nonpregnant # Aborted # Premature Delivery	 1[1] 1 0 0 --	 1[1] 0 1 0 --	 1[2] -- -- 1 --	 1[3] 0 1 0 --
Total # Corpora Lutea Corpora Lutea/Dam	138 8.63	144 8.47	172 9.05	164 9.11
Total # Implantation Implantation/Dam	133 8.31±.54	132 7.76±.43	157 8.26±.51	147 8.17±.51
Total # Litters	15	17	19	18
Total # Live Fetuses Live Fetuses/Dam	125 7.8±0.6	125 7.4±0.4	151 7.9±0.5	137 7.6±0.5
Dead Fetuses/implant/dam	0	0	0	0
Total # Resorptions Early Late Resorptions/implant/dam Early Late Litters with Total Resorptions	 6 2 0.09±0.06 0.01±0.01 1	 5 2 0.04±.02 0.01±.01 0	 4 2 0.02±.01 0.01±.01 0	 9 1 0.06±.02 0.01±.01 0
Mean Fetal Weight (g) Combined Males Females	 43.17±.95 NC[6] NC	 43.22±1.13 NC NC	 42.84±1.2 NC NC	 43.70±1.1 NC NC
Sex Ratio	0.52	0.46	0.47	0.45
Preimplantation Loss (%)[4]	3.6%	8.3%	8.7%	10.4%
Postimplantation Loss (%)[5]	6.0%	5.3%	3.8%	6.8%

[a] Data extracted from Table 5 of the study report (both summary and individual animal data). The number of corpora lutea and early and late resorptions were collated by this reviewer from the individual animal data sheets.
[1] Rabbit died from dosing accident (lung puncture)
[2] Rabbit was sacrificed on day 26 following a spontaneous abortion.
[3] Rabbit was sacrificed on day 11 for humane reasons apparently resulting from a vaginal cyst.
[4] Calculated by this reviewer by comparing the total corpora lutea to the total implantation.
[5] Calculated by this reviewer by comparing the total implantation to the total live fetuses.
[6] (NC = Not Calculated) Mean fetal weight by sex data were not provided but the individual fetal data are available for review. The mean total male and female weight is sufficient to indicate no effect of treatment.

B. DEVELOPMENTAL TOXICITY Note: All available fetuses were examined for visceral and skeletal defects by the Pharmaco LSR Laboratory (Pharmaco LSR Project Number 93-4063, report dated July 14, 1994).

1. External Examination - Assessment was made at the FMC laboratory immediately following caesarian sectioning. There were 125, 125, 151 and 137 fetuses examined from 15, 17, 19 and 18 litters for the control, 100, 450 and 700 mg/kg/day dose groups examined. All entries for these fetuses (refer to Appendix B pages 242 to 256 of the study report are "No remarkable findings". Thus, no Table 4a was prepared for this review.

2. Visceral Examination - Table 4b illustrates the results of the visceral examination conducted at the Pharmaco LSR Laboratory. Visceral or soft tissue examination was made following the method of Staples (Teratology 9 (1974).

TABLE 4b. Visceral Examinations[a]

Observations+	Dose (mg/kg/day)			
	0	LDT	MDT	HDT
#Fetuses(litters) examined	125(15)	125(17)	151(19)	137(18)
Soft Tissue Malformations #Fetuses(litters) affected[1]	1(1)	0	0	1(1)
Soft Tissue Variations #Fetuses(litters) affected	6(3)	5(4)	6(3)	5(4)
Additional left subclavian artery[2] Fetuses (litters) affected	4(2)	3(2)	5(2)	4(3)

[a] Data abstracted from Table 1 (page 234) of the study report.
[1] One fetus in the control group was reported to have distended lateral ventricles of the brain. One fetus in the 700 mg/kg/day group was reported to have three lesions described as "abnormal course of the aortic arch", "persistent truncus arteriosus" and "additional lobulation of the lung".

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[2] This lesion was the most frequently occurring variation.

In conclusion, TB-I concurs with the study author that there were no effects of cypermethrin on soft tissue parameters.

3. Skeletal Examination - Table 4c illustrates the results of the skeletal findings as assessed by the Pharmaco LSR Laboratory. The procedure of Crary (Stain Technology 37:124-125(1962)) as modified by the Pharmaco Laboratory was used to prepare the fetuses for skeletal examination.

TABLE 4c. Skeletal Examinations[a]

Observations	Dose (mg/kg/day)			
	0	LDT	MDT	HDT
#Fetuses(litters) examined	125(15)	125(17)	151(19)	137(18)
Total skeletal malformations				
#Fetuses(%) affected	6(4.8%)	2(1.6%)	14(9.3%)	10(7.3%)
#Litters(%) affected	5(33.3%)	2(11.8%)	7(36.8%)	5(27.8%)
Hyoid arch angulated:				
#Fetuses(%) affected	3(2.4%)	2(1.6%)	12(7.9%)	6(4.4%)
#Litters(%) affected	3(20%)	2(11.8%)	6(31.6%)	3(16.7%)
Total skeletal variations				
#Fetuses(%) affected	91(72.8%)	93(74.4%)	108(71.5%)	83(60.6%)
#Litters(%) affected	15(100%)	17(100%)	19(100%)	17(100%)
Hyoid body incompletely ossified[1]	5(4%)	8(6.4%)	10(6.6%)	17(12.4%)
	3(20%)	3(17.6%)	5(26.3%)	8(44.4%)
Foreleg mid phalange not ossified[1]	8(6.4%)	17(13.6%)	17(11.3%)	18(13.1%)
	5(33.3%)	8(47.1%)	8(42.1%)	6(33.3%)

[a] Data are from Table 2 (page 235-240) of the study report.
[1] These two variations showed some possibility of an increase in the mid and/or high dose test groups. Statistical significance was not reported.

In conclusion, TB-I concurs with the study author that there are no compound related effects on skeletal parameters. The appearance of some possible increases in the skeletal variations involving the hyoid arch and foreleg ossification are not considered by TB-I to be sufficient to be definite effects of the test material.

III. DISCUSSION

A. INVESTIGATOR'S CONCLUSIONS The study author concluded that the maternal NOEL and LOEL were 100 and 450 mg/kg/day and the developmental NOEL was > 700 mg/kg/day.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: The NOEL and LOEL for maternal toxicity are assigned as 100 and 450 mg/kg/day based on decreased body weight gain. This is supported by an apparent dose relationship between the decreased weight gains during dosing and the increase (compensation) following dosing that was noted in both the 450 and 700 mg/kg/day dose groups. Data from the dose range finding study also indicated that cypermethrin at 500 mg/kg caused decreased weight gain during dosing. Clinical signs (red or pink material in the cage pan) were also noted in the 450 mg/kg/day group although infrequently but could not be definitely attributed to treatment.

2. DEVELOPMENTAL TOXICITY: TB-I concurs with the study author that there were no developmental effects noted to result from dose levels as high and including 700 mg/kg/day.

C. STUDY DEFICIENCIES. No actual study deficiencies were noted that would compromise the interpretation of the study.

The selection of a 50% w/v solution of cypermethrin in corn oil is considered a procedurally questionable practice. This is because the low dilution of cypermethrin in corn oil would purposefully result in lower toxicity. Thus, if a more dilute solution of cypermethrin in corn oil was used, the maternal toxicity would be at a lower dose. TB-I recognizes this possibility but does not consider it to compromise the main objective of the study which was to demonstrate the potential for cypermethrin to cause developmental toxicity. The fact that there was decreased body weight gain indicates that cypermethrin was systemically absorbed and the study successfully established that cypermethrin does not cause developmental toxicity in rabbits at dose levels at or below dose levels causing maternal toxicity. The questionable practice of using the 50% w/v dilution of cypermethrin in corn oil was a factor in assigning the NOEL for maternal toxicity at 100 mg/kg/day instead of 450 mg/kg/day when the decrease in weight gain did not attain statistical significance. TB-I considers that cypermethrin has the potential to be more toxic than is being demonstrated by dosing rabbits in a 50% w/v corn oil solution.