4/3/91

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id # 109701-000279. Permethrin: Review of rat and rabbit developmental toxicity studies (83-3) submitted in response to FIFRA 88 toxicity data requirements.

TOX CHEM No.: 652BB
TOX PROJECT No.: 1-0782
Submission No.: S35302

FROM: John Doherty 3/19/91
Section II, Toxicology Branch I
Health Effects Division (H7509C)

TO: Jay Ellenberger
Product Manager # 50
Registration Division (H7505C)

THROUGH: Marion Copley, DVM, Section Head 3/3/91
Section II, Toxicology Branch I
Health Effects Division (H7509C)

The rat and rabbit developmental toxicity studies were reviewed and determined to be CORE MINIMUM (rabbit) and GUIDELINE (rat). Refer to DERs attached for details of the studies. No additional studies are required at this time for Toxicity Guideline study 83-3.

Action Requested

The ICI Corporation has submitted a reformatted rabbit developmental toxicity study and a new rat developmental toxicity study in response to Phase II data requirements for the pyrethroid insecticide permethrin. These studies were reviewed by Toxicology Branch I (TB-I). Refer to the DERs attached.

Reviewed by: John Doherty 3/7/91
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley, DVM 3/3/91
Section IV, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 83-3. Developmental Toxicity - rats

MRID NO.: 409436-03 TOX. CHEM. NO.: 652BB

TEST MATERIAL: Technical grade permethrin (reference # RS 78/E. The purity was stated as being 93.9% w/w. The cis/trans ratio was 38:62 (refer to letter dated July 16, 1990 from ICI to CDFA).

STUDY NUMBER(S): CTL/P/2269

SPONSOR: ICI Americas, Inc.

TESTING FACILITY: ICI Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK.

TITLE OF REPORT: "Permethrin: Teratogenicity Study in the Rat".

AUTHOR(S): M.C.E. Hodge

REPORT ISSUED: September 20, 1988

CONCLUSIONS:

NOEL (maternal toxicity) = 50 mg/kg/day. LEL = 150 mg/kg/day: tremors and head flicking and decreased body weight gain and food consumption.

NOEL (fetotoxicity): 50 mg/kg/day. LEL = 150 mg/kg/day: decreased mean fetal weight (equivocal) and increase in "short length extra ribs" (probably related to maternal stress .

Dose levels tested 0, 15, 50 and 150 mg/kg/day.

Classification: CORE-GUIDELINE. This study satisfies the Guideline requirement for a developmental toxicity study (83-3) for one species (rats).

Quality Assurance Statement: A statement signed by J.R. Bateman of the CTL Quality Assurance Unit attested that the study was inspected 8 times over the period from November 11, 1987 to September 19, 1988.

Review

TEST ANIMALS: Wistar derived rats (Alpk:APfSD strain) obtained from the ICI facilities Animal Breeding Unit, Alderley Park, Macclesfield, Cheshire UK. Breeding was conducted at the ICI Breeding Unit facilities using males of the same strain. The pregnant females were approximately 12 weeks old on arrival and weighted 222-303 gms. The rats were received over an eight day period so the pregnancy periods were staggered.

The basic design of this study consisted of dosing by gavage four groups of 24 pregnant rats with either 0, 15, 50 or 150 mg/kg/day with the permethrin test material in corn oil (10 ml/kg) on days 7-16 (inclusive) of gestation. Day 1 of the gestation period was designated as the day evidence of mating was noted, thus, the rats were dosed on days "6-16" in conformance to the current guidelines. The test material was administered by gavage in a dose of 1 ml/100 gm of body weight (10 ml/kg). On day 22 of gestation, the rats were sacrificed by an overdose of halothane BP and their uterine contents evaluated.

Analytical data were presented which indicated that the achieved dose levels were within 2% of the nominal dose levels and that the permethrin was stable on standing over the course of the 20 days of the study.

A. Maternal Toxicity

1. Mortality and clinical signs (observed daily).

There were no deaths reported. Compound related reactions were noted mostly in the high dose group only and consisted of tremors (21 of 24 rats affected between days 8-19). Other signs included "head flicking" (6 rats affected between days 8-12), piloerection (1 rat, days 13-16), and "abnormal respiratory noise (a single rat in the mid dose group on days 14-22 and 2 rats in the high dose group on days 10-22),

2. Body Weight and Food Consumption (Body weights were determined on days 1 and 4, 7-16 inclusive and on days 19 and 22 of gestation. Food consumption was evaluated over three day periods or on days 1, 4, 7, 10, 13, 16, 19 and 22.

Body weight gain was decreased during dosing for the high dose group only as indicated in the following table (Table I) adapted from Table 4B of the study report. The table shows that the high dose group had decreased weight gain (-17%) on days 4-7 just prior to dosing. There was no explanation for this decrease in weight gain at this time. During the dosing period, particularly for the interval for days 7-10, body weight gain was decreased as much as 88%. As the dosing continued, body weight gain effects lessened being only 32% and 18% decreased for the

intervals days 10-13 and 13-16 respectively. Overall body weight gain for the 7-16 day interval was 37% decreased for the high dose group relative to the control. The low and mid dose groups were equivalent to the controls.

Table I. Body weight gain.

	Dose Level (mg/kg/day)[1]			
Interval	Control	15	50	150
Number of dams[2]	22	24	24	23
"Pre-dosing"				
Days 1-7	34.5	34.6	33.8	32.8
Days 4-7	15.2	14.1	13.8	12.6*
During Dosing				
Days 7-16	47.6	49.0	46.0	30.0**
Days 7-10	9.0	10.9	10.4	1.1**
Days 10-13	17.8	16.9	16.4	12.1**
Days 13-16	20.7	21.2	19.2	16.9*
Post dosing				
Days 16-22	64.0	66.0	70.1	64.7

[1] Data are grams gained over the time interval.
[2] Two data tables were presented, one including all dams, another excluding a control dam which had an unusually low weight gain for the study. The data presented above have excluded this control dam.
* $p < 0.05$ and ** $p < 0.01$ based on the study report statistics using analysis of variance.

Statistically significant ($p < 0.05$ or 0.01) decreases (about 10%) in food consumption were evident for the high dose group during the dosing period and were associated with the body weight decreases in this group. There was also noted an increase (about 7%, $p < 0.05$) in food consumption during the later stages of the dosing period for the low dose group but this was not associated with an increase in body weight.

Necropsy findings including prominent reticular pattern in the liver (slight and believed to be related to blood) were not regarded as being related to permethrin dosing.

CONCLUSION (maternal toxicity): NOEL = 50 mg/kg/day. LEL = 150 mg/kg/day: tremors, head flicking, decreased body weight gain and food consumption.

B. Uterine Data (Embryo and Fetotoxicity).

Table II illustrates the uterine data both to demonstrate the efficiency of the pregnancies and where applicable the toxicity responses to the test material.

Table II. Uterine data.

	Dose Level (mg/kg/day)			
Parameter	Control	15	50	150
Dams Mated	24	24	24	24
Dams with fetuses at termination	23	24	24	24
Mean # corpora lutea	14.0	14.1	14.1	14.1
Pre implant loss(%)	9.0	8.9	8.0	6.8
Post implant loss(%)	6.1	4.5	2.9	3.0
Intrauterine deaths (early/late)	15/3	10/4	9/0	9/0
Mean gravid uterus wt. (g)	86.6	89.4	88.2	88.1
Total live fetuses	276	294	303	294
% males	44.9	51.0	47.9	50.7
Mean litter wt.(g)	60.0	60.9	61.7	61.8
Mean fetal wt. (g)	4.99	4.97	4.90	4.83*

* $p < 0.05$ study report statistics using analysis of variance.

The only statistically different parameter was decreased mean fetal weight. Mean fetal weight was about 3.2% lower in the high dose group when compared with the controls. It should be noted that this is a questionable toxic response because the mean litter weight was 3% higher than the control and the total number of live fetuses in the high dose group was also higher than the control (294 in the high dose group vs 276 in the control group or 6.5% higher).

Most of the data in the above table particularly the number of dams with fetuses, corpora lutea, implantation loss, intrauterine deaths, uterus weight, live fetuses and mean litter weight attest to the efficiency of mating and pregnancy.

CONCLUSION (embryo and fetal toxicity): NOEL = 50 mg/kg/day. LEL = 150 mg/kg/day: Deceased mean fetal weight (equivocal).

C. Fetal Analysis

All fetus were reportedly assessed for external abnormalities (including cleft palate) and examined internally under magnification, sexed, eviscerated and fixed in methanol. The heads was reportedly cut along the fronto-parietal suture line and the brain examined microscopically. The remaining carcass was reportedly further processed and stained with Alizarin red. Tables 8, 9, 10 and 11 of the study report present the fetal data.

Table III (adapted from Tables 8 and 9 of the study report) illustrates an overview of the structural findings in the fetuses.

Table III. Structural Findings.

	Dose level (mg/kg/day)			
Parameter	Control	15	50	150
# fetuses examined	276	294	303	294
# Fetuses with major defects[1]	3	3	1	3
# Fetuses with minor defects (%)	72(26.1)	81(27.6)	79(26.1)	89(30.3)
# Fetuses with variants (%)	260(94.2)	287(97.6)*	298(98.3)**	292(99.3)**

* $p < 0.05$ and ** $p < 0.01$, study report statistics, Fisher's exact test.
[1] The text (9 major defects) and table 9 (10 major defects) differ in regard to the number of fetuses with major defects. Table 9 data are presented. Note structural findings/litter were not tabulated in the study report. This information can be extracted from Appendix 6 of the report.

Two different fetuses were affected with major defects in the high dose group. One fetus (#80A) had both a cardiac abnormality and an "extremely wide anterior and posterior

fontanelle". Another fetus (77C) had brain lateral ventricles extremely dilated. There was no common pattern of major defects.

All dose levels had a slight but statistically significant increase in "variants" but the frequency of "variants" was said to be within historical control range (92.3 - 99.7%). The high dose group also had an apparent increase in "minor defects" (compare 30.3% vs 26.1% for the control) although statistical significance was not attained. The "defects" and "variants" data are presented in a Table (Table 10 of the study report) 13 pages long. The following table (Table IV) illustrates the structures showing "defects" together with historical control data when available.

Table IV. "Defects" and 'variants" data.

	Dose Level (mg/kg/day) Percent Fetuses/Percent Litters Affected			
Condition	Control	15	50	150
Dilated ureter (slight)	12/44	10/38	12/67	19*/78*
	[Historical control range for fetuses about 18-38%.]			
Transverse process part ossified 7th unilateral	21/70	31**/23*	34**/96*	32**/96*
	[Historical control range for fetuses about 17-34%.]			
Transverse process part ossified 4 unilateral	59/100	66*/100	67*/100	58/100
	[Historical control range for fetuses about 45-65%.]			
Extra Ribs 14th unilateral short length	11/57	7/54	13/71	31**/87*
	[Historical control range for fetuses about 5-13%.]			
Odontoid not ossified	26/69	22/71	28/79	34*/78
Centrum not ossified	32/87	37/96	37/88	45**/91
Calcaneum not ossified	41/83	40/88	47/83	52**/96
Thickened mid-point 10th rib	0/0	0/0	0/0	2*/17

* $p < 0.05$ and ** $p < 0.01$. Fisher's Exact Test, study report.

Of these several "defects" and "variants" the report

author regards "short length extra ribs" as response to permethrin administration. All of the other conditions listed above are regarded by the study author to be within historical control range or sufficiently close to it or do not show a dose response.

The skeletons were assessed for the degree of ossification. The individual bones of the manus and pes were assessed and the result converted to a four point scale. Manus and pes skeletal ossification scores are illustrated in Table V (adapted from Table 11 of the study report):

Table V. Manus and pes scores.

	Structure[1]		
Dose Level	N[2]	Manus	Pes
Control	23/276	2.22	2.78
15 mg/kg/day	24/294	2.17	2.83
50 mg/kg/day	24/303	2.37*	2.89*
150 mg/kg/day	23/294	2.34*	2.91*
(Historical control range		2.10-2.40	2.77-2.96)

[1] Data are mean score for degree of ossification with the higher score being less ossified.
[2] N = number of litters examined/number of fetuses examined.
* $p < 0.05$ study report statistics by analysis of variance.

The mid and high dose groups were demonstrated to have a statistically significant lesser degree of ossification than the control. The pes scores for the low dose group are also slightly higher than the control. The study report author, however, contends that all mean scores are within historical control range for this strain of rat and the apparent increase is not toxicologically significant. TB-I considers this condition as possibly being related to maternal stress rather than as a direct developmental toxicity response.

CONCLUSION (Developmental toxicity): NOEL = 50 mg/kg/day. LEL = 150 mg/kg/day: decreased mean fetal weight (equivocal) and increase in "short length extra ribs" (probably related to maternal stress).

DISCUSSION.

The study report author concluded that permethrin was

not teratogenic to the rat in this study. A NOEL of 50 mg/kg/day was set for both maternal toxicity (decreased body weight gain and tremors) and fetotoxicity (increase in "short length extra ribs" and decrease in mean fetal weight).

TB-I concurs with the study authors assessment. It is noted, however, that TB-I considers the decrease in mean fetal weight to be an equivocal response to permethrin and the increase in extra ribs to be a minimal response and probably related to stress on the dams.

STUDY CONCLUSION. This study is CORE GUIDELINE. The following "one liner" applies:

NOEL (maternal toxicity) = 50 mg/kg/day. LEL = 150 mg/kg/day: tremors and head flicking and decreased body weight gain and food consumption.

NOEL (fetotoxicity): 50 mg/kg/day. LEL = 150 mg/kg/day: decreased mean fetal weight (equivocal) and increase in "short length extra ribs" (probably related to maternal stress).

Dose levels tested 0, 15, 50 and 150 mg/kg/day.

Permethrin
ICI Labs # CTL/P/2269
Sept. 20, 1989

008344

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 20 litters/dose group for mice, rats or hamsters are available. At least 12 litters /dose group for rabbits are available (three test groups and control group).
3. ✓ At the high dose, maternal effects are reported as significant (or a limit dose is given, 1,000 mg/kg).
4. * ✓ At the low dose, no developmental toxicity is reported.
5. ✓ Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6. * ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
7. ✓ Individual daily observations.
8. ✓ Individual body weights.
9. ✓ Individual food consumption.
10. ✓ Necropsy on all animals
11. ✓ Individual uterine examination including number of fetal deaths, early and late resorptions and numbers of viable fetuses per sex.
12. ✓ All ovaries examined to determine number of corpora lutea.
13. ✓ Individual litter weights and/or individual fetal weights per sex/litter.
14. ✓ Individual fetus external examination.
15. ✓ Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all rabbits.
16. ✓ Individual fetus soft tissue examination.

Criteria marked with a * are supplemental and may not be required for every study.

Reviewed by: John Doherty John Doherty 3/19/91
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley. DVM Marion P. Copley 4/3/91
Section IV, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 83-3. Developmental Toxicity - rabbits

MRID NO.: 92142-091 TOX. CHEM. NO.: 652BB

TEST MATERIAL: Technical grade permethrin. Batch # D108136E. Stated as being 92.5% pure with a cis/trans ratio of 32.3/60.2 (nominal 40/60).

STUDY NUMBER(S): RB0138 and Report No.: CTL/P/523.

SPONSOR: ICI Corporation

TESTING FACILITY: Central Toxicology Laboratory Alderley Park, Macclesfield, Cheshire (England).

TITLE OF REPORT: "Permethrin: Teratogenicity Study in the Rabbit".

AUTHOR(S): D. Richards, P.B. Banham and M. Kilmartin. The study was reformatted by E. M. Guttmann.

REPORT ISSUED: The in-life phase of the study was conducted between July 9, 1979 and September 4, 1979. The date of the original report is August 1980.

The date of the reformatted report is April 20, 1990.

CONCLUSIONS: Maternal toxicity:

NOEL < 600 mg/kg/day: LEL ≤ 600 mg/kg/day: Decreased body weight gain (equivocal). At 1800 mg/kg/day: tremors.

Embryo/fetal toxicity:

NOEL = 600 mg/kg/day. LEL = 1200 mg/kg/day: post implantation loss and resorptions; hind and forelimb poor ossification (equivocal). At 1800 mg/kg/day: decreased fetal weight (not statistically significant, thus equivocal).

Dose levels tested: 0, 600, 1200 and 1800 mg/kg/day.

Classification: CORE-MINIMUM (Protocol designed prior to 1984 guidelines). This study satisfies the data requirement for a developmental toxicity study (83-3) for one species.

Quality Assurance Statement: A Quality Assurance Statement (signature intelligible) indicated that the study (protocol, in-life phase, draft report and final report) was inspected.

REVIEW

TEST ANIMALS: Female Dutch rabbits obtained from Ranch Rabbits, Crawley Down, Sussex, England. They were 1.84 to 3.30 kg at the start of the study (ages not specified). Six proven male Dutch rabbits from the same supplier were used for mating. The rabbits were randomly placed into four groups following mating but in a manner to distribute the females mated with any given male evenly among the four groups.

The basic design for this study consisted of dosing by gavage on days 6 to 18 inclusive of pregnancy four groups of female rabbits with either 0, 600, 1200 or 1800 mg/kg/day of the permethrin test material as a suspension in 0.5% aqueous Tween 80 at a rate of 5 ml/kg. There were 19, 21, 20, and 23 does mated for the control, low, mid and high dose test groups.

The procedure used to impregnate the does is described as follows. Six bucks were used to impregnate all does. The bucks were mated with three females per test group for six days over a six week period. Each doe was examined for signs of coitus and fertility of the male by examining a vaginal smear for the presence of sperm. Two matings per doe were made. Within 1.5 hours after the time the second mating was noted, the does were injected intravenously with 25 iu of chorionic gonadotrophin in order to "stabilize" ovulation. The day of mating was designated as day 0 of pregnancy.

Data on the analysis of permethrin (Table 2, page 22) in the dosing solution indicated that 95% or greater (i.e. within ± 10%) of the theoretical dose level was achieved. Additional data indicated there was no decomposition of permethrin over the 6 week storage period.

Results

I. Maternal Effects. The does were observed daily for reactions and general condition.

A. Clinical reactions and mortalities. The study report maintains that there were no statistically significant increases (as determined by Fisher's Exact Test) for any behavioral response or deaths.

Body tremors, an expected sign of permethrin intoxication, were evident in 5 of the high dose group does but

not in any of the other does. Four of the five does had tremors on only a single day (day 16, 17 or 19). The fifth doe had tremors on day 12, 20 and 21).

The control group displayed very few unusual clinical observations with the only condition reported being little or no feces or urine produced and only 2/19 (11%) does had this condition. This condition had an apparent dose related increase with there being 4/21 (19%), 6/20 (30%) and 8/23 (35%) having this condition on at least one occasion. Other conditions which were noted in the low, mid or high dose group (no more than two animals per group responding) which may possibly have been related to the test material were "abdominal griping" (2 high dose does), "hindlimbs held high, backwards or forwards" (2 mid and 2 high dose group does), and salivation one low and one mid dose group doe and 2 high dose group does).

There were 5 deaths due to "accidents" (one each in the low and mid dose group and three in the high dose group). There were 0, 5, 5 and 4 does (all pregnant) found dead or were sacrificed moribund for the control, low, mid and high dose test groups. Although there were none in the control group, there was no dose response over the broad range of permethrim dosing (600 to 1800 mg/kg). Some of the does which died also had little or no feces or urine, were hypothermic and salivating and had an unusual amount of fur in their stomachs. In addition, 2 (40%), 4 (80%) and 1 (25%) of the does which died had aborted their litters. The excess fur in the stomachs was stated in the report as being related to abortions and was also said to be related to the cause of death in some animals. The mortality reported in this study is disturbing, but there is insufficient basis to more definitely relate these deaths to test article administration, primarily because there was no dose response over the broad range of doses tested.

B. Body Weight and Body Weight Gain. Individual body weights were recorded on days 0, 6-18 inclusive, 24 and 29 of gestation. Food consumption data were not monitored.

Inspection of Table 5 (Intergroup Comparison of Mean Maternal Bodyweight, p. 25) indicates that the high dose group was always about 3% or so within the control group for body weight. No statistical differences were noted (ANOVA, study report analysis). It is noted, however, that at day zero the high dose group was slightly higher (2.6%, mean 2.40 ± 0.52 kg) than the control (mean 2.34 ± 0.41 kg) but at the end of the gestation period it was slightly lower (-3.5%, mean 2.62 ± 0.53 kg) than the control (mean 2.61 ± 0.38 kg).

The body weight data for this study is replotted and shown in the attached figure. This replot indicates that after day 6 there is a sharp drop in weight for the low, mid and high

dose groups but there is only a slight drop for the control that is noticeable after day 12. Body weight for the dosed groups stays lower but rebounds starting at or after day 15 (while the rabbits are still being dosed with permethrin). This plot strongly suggests that weight gain is reduced for all dose groups soon after initiation of dosing. A clear dose response, however, is not evident.

[Note: the data entry for the high dose test group is incorrectly written as "0.38" rather than the apparent correct value of "2.38".]

Body weight gain (Table 6, p.26) was decreased as indicated in the following table.

Body Weight Gain (mg/kg/day)

Interval	Dose Group: Control	600	1200	1800
Pregnant does	15	13	14	12
0 - 18	0.157	0.033*	0.079	0.014*
	(0.15	0.03	0.08	0.04)
(6-18	0.10	0.01	0.01	-0.01)
0 - 29	0.308	0.248	0.251	0.136*
	(0.27	0.21	0.22	0.12)
(18-29	0.12	0.18	0.14	0.08)

* $p < 0.05$. t-test, one sided, from the study report.
Data in ( ) was calculated by J. Doherty from Appendix 2. The calculated values did not always agree with the data in Table 6.

There is an apparent decrease in body weight gain in the low, mid and high dose groups for days 0-18 with only the low and high dose groups but not the mid dose group being statistically significant. For the 0-29 day and 18-29 day intervals the weight gain data indicate that the low and mid dose groups may have regained any weight they might have lost earlier. The high dose group, based on both consistency and magnitude better indicate that weight gain was affected (decreased) at this dose level.

It should be noted that standard deviations for the body weight data were of the order of 20% (sometimes more) and for the body weight gain data the standard deviations ranged from 54% to 139% of the means.

C. Macroscopic Findings. On day 29 of gestation, the does were sacrificed by air embolism. An autopsy was said to be performed and all animals (except those dying or sacrificed moribund prior to day 9) were examined macroscopically.

There were 2/19(11%), 4/20(20%), 8/19(42%) and 7/20(35%) does with more than normal or an excessive amount of fur in their stomachs for the control, low, mid and high dose groups respectively.

CONCLUSION (maternal toxicity): NOEL < 600 mg/kg/day. LEL ≤ 600 mg/kg/day: At this level there is an apparent body weight gain decrease (equivocal). At 1800 mg/kg/day: tremors.

Note: TB concurs with the study report that body weight gain is affected at the lowest dose level tested. Deaths, decreased urine and fecal excretion and increased fur in stomach were not considered definitely related to dosing.

D. Uterine Data. The following table illustrates the uterine data.

Parameter	Dose Level (mg/kg/day) Control	600	1200	1800
Mated	19	21	20	23
Not Pregnant	4	2	0	2
Pregnant dams at day 29[1]	15	13	14	13
Mean gravid uterus weight (gms)	345	294 (-15%)	247* (-28%)	266 (-23%)
Resorptions-early -late	2(1.8) 2(1.8)	5(5.7) 2(2.3)	14(16.1) 4(4.6)	18(18.8) 6(6.3)
Transformed (proportion of pre-implantation loss)	0.68	0.90 (+32%)	1.05* (+54%)	0.82 (+21%)
Transformed (proportion of post-implantation loss)	0.29	0.45 (+55%)	0.74* (+155%)	1.01* (+248%)
Live fetuses	110	80	69	72
Mean litter size (live)	7.33	6.15	4.95	5.53
% Males	46.4	51.3	49.3	48.6
Total litter weight (gm)	234	196	155*	188
Mean fetal weight (gm)	34	35	34	31

* $p < 0.05$, ** $p < 0.01$, t-test, one sided, study report statistics.
[1] See also page 3 of this review for accidental deaths and moribund sacrifices.

The above table indicates that there were higher incidents of post-implantation loss for the mid and high dose groups in an apparent dose related manner (+55%, +155% and +248%). Pre-implantation loss was also higher in the mid dose group (+54%) but not statistically significantly higher in the low (+32%) and high (+21%) dose groups. It should be noted that the small numbers involved result in large percentage increases that may exaggerate the appearance of an effect. The increase in post-implantation loss is considered by TB-I to be possibly

related to permethrin administration.

Early and late resorptions were also higher but statistical significance was not reported.

The number of live fetuses and mean litter size was decreased relative to the control group for all dose groups but no dose response was evident or statistical significance noted.

Mean gravid uterus weight and total litter weight in all treated groups were lower than the controls but dose responses were not evident. The mean fetal weight (-9%) was lower for the high dose group but statistical significance was not reported. These weight decreases are concurrent with the apparent weight decreases noted in the does.

CONCLUSION (uterine data including both maternal and embryo/fetal toxicity): NOEL = 600 mg/kg/day. LEL = 1200 mg/kg/day: post implantation loss and resorptions. At 1800 mg/kg/day: decreased mean fetal weight (not statistically significant, thus equivocal).

Note: other conditions listed above lack dose responses and/or statistical differences.

II. Fetal Data

Methods. Fetuses from all litters were examined externally for variations and malformations. Approximately one half of the fetuses were processed for skeletal malformations following fixation in 70% methanol. After 24 hours they were eviscerated and returned to methanol after which they were stained with Alizarin red using the method of Staples and Schnell. The other half of the fetuses were preserved and decalcified in Bouins fixative at least eight weeks prior to examination. Sections were made following the techniques of Wilson through the head. Other sections were reported as being made through the thorax, heart, abdomen, lungs, liver and kidneys.

A. External Examination

Isolated incidents of abnormalities were noted in the dosed groups only. The only apparently dose related condition was reduced viability with there being 0/110, 1/80 (1.25%), 1/69 (1.5%) and 3/72 (4.2%) in the control, low mid and high dose test groups.

Other conditions such as vestigial tail (single incident in the low dose group and two incidents in the mid dose

group, "gross abnormality" (single incident, not further described), both forefeet flexed and hind limb broken (single incidents in the mid dose group) were also present.

B. Visceral Examination

There were 53, 40, 34 and 37 fetuses examined for the control, low, mid and high dose test groups. Only singular incidents of abnormal conditions were reported in the groups dosed with permethrin. In the control group, two incidents were reported for three abnormal conditions related to "slight" dilations of kidneys or brain. No effect of permethrin was evident.

C. Skeletal Examination

There were 57, 40, 35 and 35 fetuses examined for the control, low, mid and high dose test groups. No statistically significant differences in incidents were reported. There was some (not statistically significant) indication of poorer ossification in the fore and hind limbs in the mid and high dose groups as indicated in the following table:

	Score[1]			
Structure	Control	600	1200	1800
Forelimb	1.92	1.99	2.00	2.25
Hindlimb	1.65	1.56	1.89	1.90

1. The score was determined by assigning the degree of ossification as 1, 2, 3 or 4 with 1 being good and 4 being poor. The means were determined. Therefore the higher the score, the poorer the degree of ossification.

CONCLUSION (Fetal Effects): NOEL = 600 mg/kg/day. LEL = 1200 mg/kg/day: Poor ossification of fore and hindlimds (equivocal).

Note: TB accepts the study report conclusions that the poor ossification was related to the test material although statistical significance was not attained but since the ossification score for hindlimbs was so close together (i.e 1.89 and 1.90) for the mid and high dose, TB assigned the dose level of 1200 mg/kg/day as a LEL rather than 1800 mg/kg/day as assigned by the study report.

DISCUSSION (Study report conclusions)

The study report concluded that "despite some evidence for maternal toxicity at 600 mg/kg/day and above no teratogenic effects were seen, There were indications of embroyotoxicity at 1200 and 1800 mg/kg/day".

CONCLUSION (Study as determined by TB): Classification CORE MINIMUM. This study was conducted and designed prior to the 1984 Guidelines. For rabbit studies, all of the fetuses are supposed to examined for skeletal effects. Since there were two dose groups over the limit dose of 1000 mg/kg/day, TB considers that there were a sufficient number of fetuses examined to conclude that no malformations result at dose levels up to and including 1800 mg/kg/day, The following one liner is supported.

Maternal toxicity:

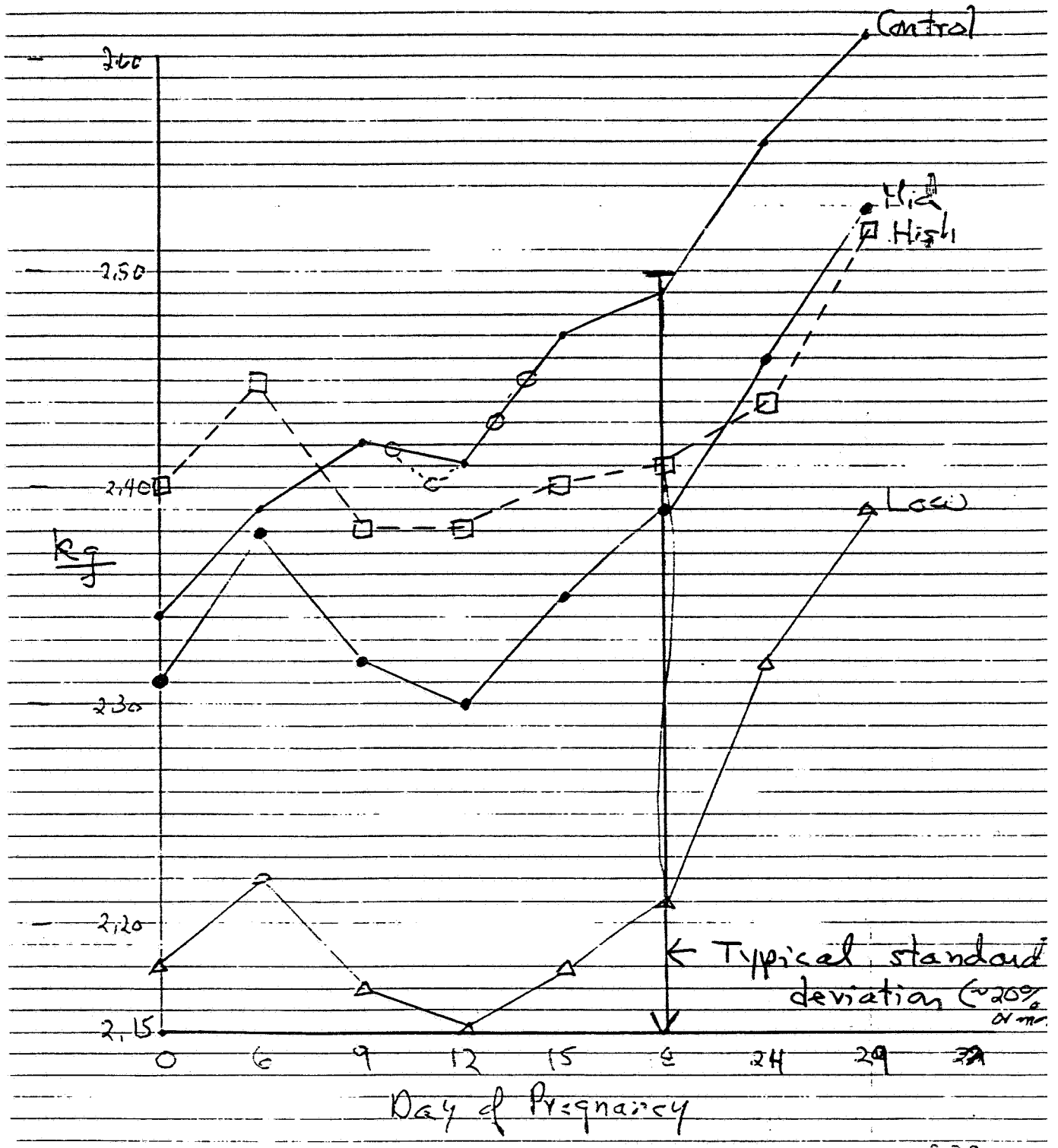
NOEL < 600 mg/kg/day, LEL ≤ 600 mg/kg/day based on decreased body weight gain (equivocal).
LEL = 1800 mg/kg/day: tremors.

Embryo/fetal toxicity:

NOEL = 600 mg/kg/day. LEL = 1200 mg/kg/day: post implantation loss and resorptions; hind and forelimb poor ossification (equivocal). At 1800 mg/kg/day: decreased fetal weight (not statistically significant, thus equivocal).

Dose levels tested: 0, 600, 1200 and 1800 mg/kg/day.

Replot of Body Weight Data



Permethrin
ICI Labs # CTL/P/523
Original date August, 1980
Reformatted date April 20, 1990
MRID # 92142-091

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 20 litters/dose group for mice, rats or hamsters are available. At least 12 litters /dose group for rabbits are available (three test groups and control group).
3. ✓ At the high dose, maternal effects are reported as significant (or a limit dose is given, 1,000 mg/kg).
4. * ✓ At the low dose, no developmental toxicity is reported.
5. ✓ Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6. * ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
7. ✓ Individual daily observations.
8. ✓ Individual body weights.
9. NO Individual food consumption.
10. ✓ Necropsy on all animals
11. ✓ Individual uterine examination including number of fetal deaths, early and late resorptions and numbers of viable fetuses per sex.
12. ✓ All ovaries examined to determine number of corpora lutea.
13. ✓ Individual litter weights and/or individual fetal weights per sex/litter.
14. ✓ Individual fetus external examination.
15. * Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all rabbits.
16. ✓ Individual fetus soft tissue examination.

* Not all rabbit fetuses given skeletal exam

Criteria marked with a * are supplemental and may not be required for every study.