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WASHINGTON, D.C. 20460

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JUL 13 1993

010385

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID # 109701. Permethrin: Review of a Series 82-2,  
21-Day Dermal Toxicity, Study.

Tox Chem No.: 652BB  
PC No.: 109701  
Barcode No.: D188200 and D189440  
Submission No.: S435415 and S437411

FROM: John Doherty *John Doherty 7/12/93*  
Section IV, Toxicology Branch-I  
Health Effects Division (H7509C)

TO: Linda DeLouise/Jay Ellenberger  
Product Manager #50  
Special Review and Reregistration Division (H7508W)

THRU: Marion Copley, DVM, Section Head *Marion Copley 7/9/93*  
Section IV, Toxicology Branch I  
Health Effects Division (H7509C)

I. CONCLUSION

The series 82-2, 21-day dermal toxicity, study (ICI Laboratory, Study No.: CTL/P/2445 May 11, 1989) was reviewed and determined to be Core-Minimum. The data support a NOEL and LEL of 150 and 500 mg/kg/day for systemic effects. Signs of local site of application irritation were present at all dose levels. No additional series 82-2 dermal toxicity data are required at this time.

II. Action Requested

The ICI Americas Corporation has submitted a series 82-2, 21-day dermal toxicity, study with rats as a part of the reregistration requirements for permethrin. The study was reviewed and the DER is attached.

*JSD*



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III. Studies Reviewed.

Study Identification	Material	MRID No.	Results	Classification
<p>82-2.</p> <p>21-day dermal toxicity rats. ICI Laboratory, Study No.: CTL/P/2445. May 15, 1989</p>	<p>Technical Permethrin lot RS/38 /F and #Y00040/085/001</p> <p>Purity 95.6% (38.6% CIS and 61.4% trans)</p>	<p>411438-01 426533-00 and-01</p>	<p>NOEL and LEL (systemic effects) = 150 and 500 mg/kg/day. At 500 mg/kg/day: increased liver weight in females. Signs of local site of application dermal irritation at all dose levels.</p> <p>Rat strain: Wistar derived Alp:Apfd SPF. Dose levels tested: 0, 50, 150 or 500 mg/kg/day applied undiluted.</p>	<p><i>Core-minimum</i></p> <p><b>010385</b></p>

[82-2. Permethrin/1989]

010385

Reviewed by: John Doherty, Ph.D.  
Toxicology Branch-I, HED (H7509C)  
Secondary Reviewer: Marion Copley, DVM  
Toxicology Branch-I, HED (H7509C)

*John Doherty* 7/9/93

DATA EVALUATION RECORD

MRID NO.: 411438-01 and 426533-01 TOX CHEM No.: 652BB  
PC No.: 109701

STUDY TYPE: 82-2. 21-day Dermal toxicity-rats.

SPONSOR: ICI Americans, Inc.

TESTING FACILITY: ICI Central Toxicology Laboratory

TITLE OF REPORT: "Permethrin: 21-day Dermal Study in Rats"

AUTHOR(S): G. M. Milburn

STUDY NUMBER: CTL/P/2445 and LR0533

DATE ISSUED: May 11, 1989

CONCLUSIONS: NOEL and LEL (systemic effects): 150 and 500 mg/kg/day. At 500 mg/kg/day: Increased liver weight in females. Signs of local site of application dermal irritation at all dose levels.

Rat strain: Wistar derived Alpk:Apfsd SPF. Dose levels tested: 0, 50, 150 or 500 mg/kg/day applied undiluted.

CLASSIFICATION: ~~Core-Minimum~~ . No additional series 82-2 21-day dermal toxicity study data are required at this time.

Quality Assurance Statement: Provided  
Good Laboratory Practice Statement: Provided

REVIEW

[Note: The ACCEPTANCE CRITERIA check sheet is attached as Appendix I.]

A. Experimental Constants:

1. Test Material:

Chemical: Permethrin  
Source: ICI Agrochemicals  
Batch: Reference Number Z00040/85/, reference # RS/38F  
Purity: 95.6% cis and 61.4% trans isomer ratio)  
Vehicle: None (applied undiluted).

## 2. Test System:

Species: Rat - Wistar derived Alpk:Apfsc SPF  
Supplier: ICI Animal Breeding Unit  
Age: 42-49 days on arrival  
Weight: Males 213-268 gms, females 144-193 gms.  
Feed: "ctl diet"

## 3. STUDY DESIGN:

Four groups of 5 male and 5 female rats were dosed with either 0, 50, 150 or 500 mg/kg/day of undiluted technical permethrin daily for 21 days. These dose levels were selected on the basis of a preliminary study in which a dose level of 1000 mg/kg/day resulted in significant dermal reactions at the site of application. No other reactions (including systemic) were reported in the preliminary test. At the end of 21 days the rats in the main study were sacrificed, samples of blood taken, necropsied and selected tissues were assessed histologically.

In the main study, prior to application of the test material (16-24 hours), a section (10 x 5 cm) of the dorsal-lumbar region was prepared by clipping. Undiluted test material was applied and kept in contact with the skin for "approximately" 6 hours using occlusive dressings which consisted of a gauze patch to cover the treated area which was further covered with a plastic film held in place using adhesive tape. This was secured by a piece of PVC tape wrapped around the rat. At the end of the contact period, the dressing was removed and the area washed with adsorbent "cotton wool" and water. TB-I notes that a plastic film was used. This would be expected to promote hydration of the area and possibly affect absorption by the rat. This practice is not recommended by Guidelines but does not require that the study be declared unacceptable.

4. Analytical Chemistry: No Analytical chemistry data were provided except for a certificate of analysis of the test material as provided.

Permethrin was used neat and TB-I has other study data on the stability of permethrin. Thus, the absence of additional data for analytical chemistry are not considered significant.

5. Statistics:

Test	Parameter Investigated
ANOVA	Body weight gain, final body weight, weekly food consumption, biochemical and hematological data.
ANOVA and analysis of covariance (All analyses allowed for the replicate structure of the study design.)	Final body weight.
Student's t-test based on the error mean square in the analysis.	Group means compared with the control.

**RESULTS**1. Observations and survival (Observations twice daily).

No compound related deaths were noted. A single low dose male rat was sacrificed in extremis apparently due to having its lower jaw trapped in the bandage.

No clinical signs indicative of systemic toxicity were noted. All treated rats had signs of dermal irritation at the site of application that included desquamation, erythema and oedema.

2. Body weight and food consumption (Body weight determined daily and food consumption determined weekly).

The initial mean body weights for the control were 242 and 175.4 gms and that for the high dose group were 228.6 and 166.0 gms for male and females, respectively. This indicated that the randomization process resulted in both the males (-5.8%, not significant) and females (-5.1% not significant) having a lower body weight at initiation in the high dose. Both males and females in the high dose group had initial (first few days, ) depressions in body weight (refer to Figures 1 and 2, photocopied from the study report attached). Final body weights for the high dose group males was also lower (-5.5%,  $p < 0.05$ ) but females were essentially the same. The testing laboratory recognizes the weight differences but does not ascribe them to a toxic response to the test material.

Food consumption was essentially similar in all dose groups for males. The females generally had higher rates (up to 22.5%) of consumption in the treated groups for the later weeks of the study. This did not correspond to an increase in body weight and the apparent increase in feed consumption was not dose related.

CONCLUSION (Body weight): LEL  $\geq$  500 mg/kg/day.

Note: The initial transient body weight in both sexes in the high dose group may be considered a toxicity response to permethrin in contrast to the study report conclusion. Body weight decrease is a typical response to permethrin in oral studies and the increase in liver weight in the high dose group females is consistent with the premise that the initial bodyweight effect is related to permethrin. The weight difference, however, is too small (only about 2-3% and lasting for 1-3 days) to make a more definite conclusion.

For sections 3 and 4 below, blood samples were taken by cardiac puncture at termination and collected in tubes containing sodium citrate or EDTA.

### 3. Hematology.

<input checked="" type="checkbox"/> Erythrocyte count.	<input checked="" type="checkbox"/> Leucocyte count
<input checked="" type="checkbox"/> Hemoglobin	<input checked="" type="checkbox"/> Differential count
<input checked="" type="checkbox"/> Hematocrit	<input checked="" type="checkbox"/> Platelet count

Others: MCV, MC:H, MCHC prothrombin time, K-C time (clotting measures)

No compound related differences were noted.

### 4. Clinical Chemistry

<input checked="" type="checkbox"/> Alkaline phosphatase	<input checked="" type="checkbox"/> Total Protein
<input checked="" type="checkbox"/> Aspartate aminotrans	<input checked="" type="checkbox"/> Albumin
<input checked="" type="checkbox"/> Creatinine kinase	<input checked="" type="checkbox"/> Urea
<input type="checkbox"/> Lactic dehydrogenase	<input checked="" type="checkbox"/> Inorganic phosphate
<input checked="" type="checkbox"/> Glucose	<input checked="" type="checkbox"/> Calcium
<input checked="" type="checkbox"/> Bilirubin	<input checked="" type="checkbox"/> Potassium
<input checked="" type="checkbox"/> Cholesterol	<input checked="" type="checkbox"/> Sodium
<input checked="" type="checkbox"/> Creatinine	<input checked="" type="checkbox"/> Chloride

glutamyl transferase, alanine transaminase, triglyceride

No compound related differences were noted.

5. Urinalysis: No urinalysis was conducted. Based on the results of the rat and dog oral 90-day and chronic feeding studies, there were no indications of adverse effects of permethrin on urinary parameters. Thus, the exclusion of urinalysis from this study is justified.

### 6. Organ Weights:

<input checked="" type="checkbox"/> adrenals	<input type="checkbox"/> lung
<input checked="" type="checkbox"/> brain	<input checked="" type="checkbox"/> ovaries
<input type="checkbox"/> heart	<input type="checkbox"/> spleen
<input type="checkbox"/> liver	<input checked="" type="checkbox"/> testis
<input checked="" type="checkbox"/> kidneys	

The data summary tables included the means for absolute weights and weight "adjusted for body weight" in grams. The data were not accompanied by the standard deviations but the approximate 95% confidence interval for the data sets were presented. The individual animal data gave the absolute weight

only. No method for calculating the "adjusted for body weight" was given.

Liver weight was increased in females as indicated in Table 1.

Table 1. Absolute and relative liver weights for females

Liver Weight

Dose Group	Absolute Weight (gm)	Relative weight <sup>1</sup>
Control	10.897 ± 0.450	.047 ± .003
50 mg/kg	10.894 ± 0.619	.049 ± .004
150 mg/kg	11.888 ± 0.240 (+9.9%)	.047 ± .001
500 mg/kg	12.023 ± 1.134 (+10.3%)*	.052 ± .003 (10.6%)*

1. Calculated by J. Doherty.

\* p < 0.05, study report statistics.

Liver weight gain is a typical response to permethrin based on the oral feeding studies. Male liver weight was essentially similar for all treatment groups.

CONCLUSION (body weight): NOEL and LEL = 150 and 500 mg/kg/day. Liver weight increases in females.

7. Necropsy. No compound related findings were noted except for at the local site of application.

8. Histopathology:

The rats were sacrificed at termination with halothane and exsanguination (cardiac puncture). Based on the histopathology report, the adrenal gland, brain, kidney, liver, lung, ovary, sciatic nerve, skin (treated) and spinal cord and testis (epididymis) were examined histologically for the control and high dose groups. The gross lesions were not always followed up microscopically but this was not considered detrimental to the interpretation of the study since they were rather self-evident and there was no evidence of their being compound related.

No evidence of compound related histopathological lesions were noted. The liver weight increase in females was not accompanied by associated pathological changes.

CONCLUSION: This study is ~~Core-minimum~~. The following "one liner" is supported.

NOEL and LEL (systemic effects): 150 and 500 mg/kg/day. At 500 mg/kg/day: Increased liver weight in females. Signs of local site of application dermal irritation at all dose levels.

Rat strain: Wistar derived Alpk:Apfsd SPF. Dose levels tested: 0, 50, 150 or 500 mg/kg/day.



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PERMETHRIN

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82-2 Repeated Dose Dermal Toxicity (21-day) **C10385**

Chemical: Permethrin Classification: ACCEPTABLE  
Laboratory: ICI Central Toxicology Laboratory  
Study No.: CTL/P/2445  
Date: May 11, 1989  
MRID No.: 411438-01 and 426533-01

- 1.  Technical form of the active ingredient tested.
- 2.  At least 5 animals/sex/dose group (3 groups and control)
- 3.  Dosing duration at least 6 hours/day for 21 days or 5 days/week for 3 weeks.
- 4.  ? Application site at least 10% of body surface area.
- 5.  No Doses tested include signs of toxicity at high dose, no or minimal dermal irritation, minimal lethality or a limit dose (1000 mg/kg) if nontoxic.
- 6\*.  Doses tested include a NOEL.
- 7.  Individual daily observations.
- 8.  Individual body weights.
- 9.  Individual or cage food consumption.
- 10.  Clinical pathology data of 11 and 12 below at termination.

- 11.  Hematology:
 

<input checked="" type="checkbox"/> Erythrocyte count.	<input checked="" type="checkbox"/> Leucocyte count
<input checked="" type="checkbox"/> Hemoglobin	* <input checked="" type="checkbox"/> Differential count
<input checked="" type="checkbox"/> Hematocrit	<input checked="" type="checkbox"/> Platelet count
	- (clotting measure)

(others: MCV, MCH, MCHC, prothrombin time, K-C time (clotting measures)).

- 12.  Clinical chemistry:
 

<input checked="" type="checkbox"/> Alkaline phosphatase	<input checked="" type="checkbox"/> Total Protein
<input checked="" type="checkbox"/> Aspartate aminotrans	<input checked="" type="checkbox"/> Albumin
* <input checked="" type="checkbox"/> Creatinine kinase	<input checked="" type="checkbox"/> Urea
<input checked="" type="checkbox"/> Lactic dehydrogenase	<input checked="" type="checkbox"/> Inorganic phosphate
<input checked="" type="checkbox"/> Glucose	<input checked="" type="checkbox"/> Calcium
<input checked="" type="checkbox"/> Bilirubin	* <input checked="" type="checkbox"/> Potassium
<input checked="" type="checkbox"/> Cholesterol	<input checked="" type="checkbox"/> Sodium
* <input checked="" type="checkbox"/> Creatinine	* <input checked="" type="checkbox"/> Chloride

13.\*  No Urinalysis (only when indicated by expected of observed activity), Justified.

14.  Individual necropsy of all animals.

- 15.  Organ weights.
 

<input checked="" type="checkbox"/> adrenals	<input type="checkbox"/> lung
<input checked="" type="checkbox"/> brain	<input checked="" type="checkbox"/> ovaries
<input type="checkbox"/> heart	<input type="checkbox"/> spleen
<input checked="" type="checkbox"/> liver	<input checked="" type="checkbox"/> testis
<input checked="" type="checkbox"/> kidneys	

- 15.  Histopathology on all control and high dose animals,
- No All animals that died or were killed on study
- No All gross lesions on all animals
- N/A Target organs on all animals
- No Skin lungs, liver and kidneys of all animals.

\* Supplemental and may not be required for every study.