



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

MEMORANDUM

001570

DATE:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Permethrin: Studies Conducted by the U. S. Army Environmental Hygiene Agency.

TOX Chem. No. 652BB

FROM: John Doherty *John Doherty* 3/8/82 *Added 3/8/82*
Toxicology Branch/HEH (TS-769)

TO: F. D. R. Gee, PM #17
Registration Division (TS-767)

Toxicology Branch has received the following list of studies with the test chemical Permethrin. The studies were conducted by the U. S. Army Environmental Hygiene Agency. The sample of Permethrin used in these studies was obtained from the S. B. Penick Company and was from lot RAX-6, and stated as being of 92.66% purity and 60/40 cis/trans ratio. (See letter attached confirming that preparation was 40/60 cis/trans.)

Of the several studies included, a 21 day irritation study (rabbits), a 21 day wear test (rabbits) and a 90 day inhalation study with rats, guinea pigs and dogs may be especially useful for supporting the various nonfood uses of Permethrin.

STUDY	RESULTS	CLASSIFICATION
Acute Oral LD50, rat (#75-51-0831-76) no date, technical grade	Long Evans rats 4892 (2853-8386) mg/kg for males. 2712 (1232-5968) mg/kg for females.	Supplementary
	Sprague-Dawley rats 3801 (3295-4385) mg/kg for females - undiluted. 563 (475-667) mg/kg for males - diluted with corn oil. 414 (347-493) mg/kg for females - diluted with corn oil.	Supplementary
Acute Dermal LD50, rabbit (#75-51-0831-76) no date	> 10,000 mg/kg	Supplementary
Photochemical Sensitization, guinea (#75-51-0831-76) Pigs	Not a photosensitizer	Supplementary

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cont.

Primary Skin Irritation, rabbit (4 studies) (#75-51-0831-76)	Highest Draize Score was 1.6, other 3 studies were < 1.0.	Supplementary
Primary Eye Irritation, rabbit (#75-51-0831-76)	No corneal involvement transient irritation.	Supplementary
Teratology, rat (#75-51-0831-79) (no date)	Study report concludes: Not teratogenic at 83 mg/kg/day (HDT)	(Not reviewed in detail, report is hand written.)
Dermal Irritation Study 21-Day, rabbit (#51-0831-77) (no date)	NOEL = 1.0 gm/kg/day (HDT)	Minimum
Dermal Irritation Study 21-Day Cloth Impregnated, rabbit (wear test) (#75-51-0831-79) (no date)	NOEL = 1.25 ^{mg/cm²} gm/kg/day (HDT)	Minimum
14-Day Feeding, rat (#75-51-0831-76) (no date)	Study report concludes: NOEL = 216 mg/kg/day LEL = 432 mg/kg/day (tremors, increase liver to body weight effects)	(Not reviewed in detail, report is largely hand written.)
90-Day Feeding, rat (#75-51-0831-79)	Study report concludes: NOEL = 85 mg/kg/day LEL = 270 mg/kg/day (increases in liver to body weight ratios)	(Not reviewed in detail, report is largely hand written.)
90-Day Subchronic Inhalation, rat, dogs, guinea pigs (#75-51-0026-80) (May-December, 1978)	NOEL = 250 ug/l for rats LEL = 500 ug/l, tremors and convulsions for rats increases in liver microsomal enzyme activity. NOEL = 500 ug/l for guinea pigs and dogs (HDT)	Minimum
Mutagenic, Ames Test Litton Bionetics #2575, Dec., 1975	Not mutagenic in any testor strain (Lab Conclusion). 5 strains of Salmonella and 1 strain of Saccharomyces.	N/A
Sensitization, guinea pigs, #75-51-0831-76	Not a sensitizer (Lab conclusion)	Minimum
Inhalation LC50 (#51-0831-79)	Study conclusion: LC50 = 1.672 mg/l for males and females	(Not reviewed in detail)

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Subchronic Inhalation Toxicity of 3-(phenoxyphenyl) methyl (+)-cis,
trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
(Permethrin)

U. S. Army Environmental Hygiene Agency, Study No. 75-51-0026-80,
May-December, 1978.

Four groups of rats, dogs and guinea pigs were exposed to atmospheric concentrations of 0, 125, 250 or 500 mg/l³ (ug/l) of permethrin (obtained from the S. B. Penick Corporation). The cis and trans ratio was stated as being 60/40* and the product was designated as SBP-1513, NRDC 143, FMC 33297 and A13-29158 and was from lot #RAX-6. The test animals were housed during exposure in 1000 or 2000 liter dynamic flow chambers and the test material was introduced into the chambers using Collison nebulizers. The atmospheric concentrations were monitored by sampling at 1, 3 and 5 hours. The sampling results indicated that the particle size was 1 μ or less for 85% of the total number of particles.

The test animals were exposed to the aerosols containing permethrin for 6 hours/day, 5 days/week for 13 weeks. Following exposure all animals were evaluated by gross necropsy and histopathology. Each species was also evaluated by special procedures as outlined below. There were 20 rats, 10 guinea pigs and 2 dogs of each sex used for each dosage group.

Results:

1. No compound related deaths were noted in any of the three species. Signs of convulsions and tremors (severe) were noted in the rats (male and female) exposed to 500 μ g/l of permethrin. These symptoms were reported as disappearing by the second week of exposure.
2. Body weight and organ-to-body weight ratios - There were no consistent compound related effects on body or organ weight parameters in any animal tested.
3. Sensitization reaction - guinea pig only. Following the 13 week exposure period the guinea pigs were assayed to determine if exposure sensitized them to permethrin. Fourteen days after the last exposure the guinea pigs were treated with intradermal injections of 0.05 ml of 3.0% permethrin in propylene glycol.

No signs of sensitization reactions were noted at 24 or 48 hours following the challenge intradermal injection.

See letter attached confirming that preparation was 40/60 cis/trans.

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4. Recovery, 10 male and 10 female rats were sacrificed after the last exposure and 10 more of each sex from each exposure group were sacrificed 13 weeks after the last exposure. No significant differences were noted in the animals allowed 13 weeks for recovery.
5. Clinical chemistry and hematology (dogs only) - Blood samples were drawn weekly from the beagle dogs and the following chemistry parameters were determined: Ca^{++} , Na^+ , K^+ , SGOT, SGPT, GGTP, alkaline phosphatase, BUN, cholesterol, triglycerides, LDH, glucose, total protein and bilirubin. The following hematological values were also determined: RBC, mean cell volume, hematocrit, WBC and hemoglobin. No test chemical related effects were noted in these parameters.
6. Pulmonary function test (dogs only). The following parameters were determined: tidal volume, minute volume, transpulmonary pressure, compliance and resistance. No effects of the test chemical were reported. The dogs showed wide variations in these parameters but all values were considered to be within acceptable limits. This aspect of the study was complicated by the incidence and severity of pneumonia in the test animals.
7. Oxygen consumption (rats only) 5 male rats from each exposure group were monitored for oxygen consumption as a means of determining their overall metabolic state during exposure to permethrin. The technique used employed a Collins small animal environmental chamber into which the rats were placed for 15 minutes both prior to and immediately following exposure. No effects on oxygen consumption were noted.
8. Urine metabolites (rats only). Chemical structures of the urinary metabolites were not identified. However, analysis of the urine revealed the presence of a metabolite which rapidly tailed off when exposure was curtailed.
9. Enzyme induction studies (rats only). Ten male rats were injected with hexobarbital just after exposure to permethrin and after 30 days from their last exposure and the sleeping times determined. The group exposed to 500 $\mu\text{g}/\text{l}$ of permethrin slept 44 ± 14 minutes and the control group slept 77 ± 19 minutes. The animals assayed 30 days after the last exposure did not show statistical differences in their sleeping times. These data indicate that the liver microsomal metabolizing enzymes are induced but that this induction by exposure to permethrin is reversed following removal of permethrin.

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10. Necropsy and histopathology. The report states that a complete necropsy was performed on each animal. The brain, lungs, heart, liver, kidneys, spleen, eyes, bone marrow, trachea, nasal turbinates, thymus, stomach, small intestine, large intestine, pancreas, adrenal glands, urinary bladder, testes, skin, skeletal muscle and bone were fixed in 10% neutral buffered formalin. In addition the sciatic nerves from selected animals were stained with Luxol Fast Blue myelin stain to assess myelin sheath integrity.

No consistent compound related lesions were noted or reported.

Conclusion:

This series of test is assigned a Core Minimum classification. A NOEL of ~~of~~ 250 $\mu\text{g}/\text{l}$ for rats is assigned. A NOEL of 500 $\mu\text{g}/\text{l}$ for guinea pigs and dogs is assigned. Note that the data are in summary form only and individual animal test data were not presented. Note also that the highest test dose level was 500 $\mu\text{g}/\text{l}$ and that some indoor uses of permethrin may approach this concentration which showed effects on the rat liver enzyme systems.

21 Day Wear Test With Cloth Impregnated With Permethrin (A13-29158):

U.S. Army Environmental Hygiene Agency, Study No. 75-51-0831-79, (no date).

Four groups of 10 male New Zealand White rabbits were treated as follows: first group: Impregnated cloth treated with 1.25 mg/cm^2 of permethrin; second group plain cloth, third group: impregnated cloth with artificial sweat; and fourth group: plain cloth - no solvent w/artificial sweat. The rabbits were shaved and the test cloths were applied each Monday and Thursday until a total of six applications were made. The cloths were in contact with the skin for a total of 21 days. On each Wednesday blood samples were withdrawn and analyzed.

Results:

No skin irritation was observed. No changes in the weights of liver, lung, kidney, testes and spleen were noted.

(NOTE: SGOT, SGPT, LDH, Alk. Phosphatase, total protein, GGTP, total bilirubin, glucose, BUN, Na^+ , K^+ , were determined and no effects noted.)

This study is Core Minimum.

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21-Day Dermal Irritation Study With Permethrin

U. S. Army Environmental Hygiene Agency, Study No. 51-0831-77. (no date).

Four groups of 8 male rabbits were prepared (4 from each group were abraded) and dosed with 0, 0.10, 0.32, and 1.0 gm/kg of Permethrin. The test chemical was applied by inunction over an area which approximated 10% of the total body area. A new dose was applied each day for 21 days. The test animals were sacrificed 16 days after application of the last dose.

Results:

No significant changes were noted in body weight gain over the test or recovery period. There were no changes in organ to body weight ratios. There were no changes in SGOT, SGPT, TLDH, alkaline phosphatase, GGTP, glucose, BUN, bilirubin, total protein, Na⁺ or K⁺.

In the later days of the experiment (after 18 days) a mild irritation developed in some animals.

This study is Core Minimum.



DEPARTMENT OF THE ARMY
U.S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

001570

REPLY TO
ATTENTION OF

HSE-LT

19 MAR 1982

Dr. John Doherty
Toxicology Branch
Hazard Evaluation Division
United States Environmental Protection Agency
Washington, DC 20460

Dear Dr. Doherty:

The assumption in your inquiry of 2 March 1982 concerning the cis/trans ratio of the permethrin used in Report No. 75-51-0026-80 is correct.

The stated cis/trans ratio of 60/40 was, in fact, transposed from a data sheet supplied by the S.B. Penick Company. If further confirmation is required, you may contact Ms. Emily Hedel, S.B. Penick Company, 215 Watchung Avenue, Orange, NJ 07050, telephone no. 201-673-1325. The company records indicate that Lot #RAX-6 was a 40/60 cis/trans mix. An errata sheet is in preparation and will be sent to all addressees on the original distribution list.

A sample of the original material has been retained in our Toxicology Division and is available for analysis if required.

Sincerely,

JOHN F. MAZUR
LTC, MSC
Director, Laboratory Services

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