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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id. No.: 109702-019182. Cypermethrin: Review of the rat metabolism studies with ^{14}C label in the aryl or cyclopropyl positions. Executive Summaries and updated DERs for 10 older toxicity studies.

TOX CHEM No.: 268AA
PC No.: 109702
Barcode No.: D180777
Submission No.: S422096

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I. CONCLUSION

The rat metabolism studies with labelled cypermethrin (MRID Nos: 41551102, 41551103 and 41551104) were reviewed and determined to be SUPPLEMENTARY. These studies however, confirm the results of other metabolism studies already reviewed. The series 85-1 metabolism data requirement for cypermethrin is considered satisfied based on the results of these studies and other studies (refer to discussion under comments below). No additional rat metabolism data are required at this time.

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Executive summaries and other revisions to update previously written DERs for 10 older toxicity studies were prepared as listed in Part IVb below. These documents are attached.

II. Action Requested and Additional Inclusions

Three additional rat metabolism studies have been submitted to Health Effects Division for review as a part of the reregistration case for cypermethrin. DERs for these studies were prepared and the following comments apply. These studies are listed in Part IVa below.

TB-I prepared cypermethrin toxicity data base for re-review by the RfD Committee and for review by the Toxicology Endpoint Selection (TES) Committee as well as prepared the Toxicology Chapter for the cypermethrin RED document. In the process of completing these activities, many older DERs were updated by the preparation of Executive Summaries and inclusion of additional tables to clarify the responses to treatment. The studies reevaluated are listed in Part IVb and the revised DERs are attached.

III. Toxicology Branch Comments

1. All of the metabolism studies were individually classified as SUPPLEMENTARY. The data however, can be taken together with other metabolism studies to help to satisfy the series 85-1 metabolism study in rats. Data on the metabolism of cypermethrin in rats can be found in MRID Nos.: 00056806, 00056807, 00056809, 00056810, 00056812, 00089002, 00089003 and 00089004. In addition to the above studies, several other studies are available that demonstrate the metabolism and pharmacokinetics in mice (MRID Nos.: 00089007, 00089008 and 00089009) and dogs (00089010, 00089011, 00089012 and 00089013).

2. Metabolism studies in rats, dogs and mice with cypermethrin were reviewed previously (refer to HED Document Nos.: 002391 and 004825). Overall the series 85-1 metabolism requirement is considered satisfied and no additional series 85-1 metabolism study data are required at this time.

In summary, in rats cypermethrin has been demonstrated to be absorbed from the gastrointestinal tract and readily excreted with the majority of the radiolabel being in the urine. Very little was retained in the tissues. Metabolism consisted of elimination of the cyano moiety and cleavage at the esteratic linkage site. The resulting divinyl chloro acid and phenoxybenzyl alcohol were detected in the urine as conjugates with glucuronides and other ligands.

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IVa. Studies Reviewed.

Study Identification	Executive Summary
85-1. Metabolism - rats Shell Research Study # CTL/C/1154 or TLGR.0183.78, November 1978 ^{14}C- cyclopropyl ring labelled cypermethrin	In a series of nine different studies, labelled cypermethrin (< 1 mg/kg) in corn oil or separated cis or trans cypermethrin isomers were given by gavage to single or groups of two or three Wistar strain rats. Their urine and in some cases fecal matter were collected at various intervals such as 18 hours to 3 days. In another set of experiments, labelled cypermethrin was administered to rats that were fitted with bile duct cannalulas and their bile collected for 4-5 hours while the rat was under anesthesia. MRID NO.: 41551104. cis and trans ^{14}C-cyclopropyl labelled cypermethrin was demonstrated to form glucuronide conjugations of cis and trans acids and hydroxyacids. Only 1.6% or less of the total dose is excreted in the bile. Most of the label in the feces was unchanged cypermethrin. The glucuronide conjugates in the urine were found to be unstable and subject to hydrolysis. This study is classified as CORE-SUPPLEMENTARY. The study when combined with other metabolism studies satisfies the requirement for the series 85-1 study.
85-1. Metabolism - rats Shell Research Study # CTL/C/1147 or TGLR.0004.77, January 1977 ^{14}C-cyclopropyl ring labelled cypermethrin	One group of three/sex Wistar strain rats was dosed with a single oral dose (approximately 1.3 mg/kg) of ^{14}C-cyclopropyl labelled cypermethrin in corn oil (0.8 ml). The rats were then placed in glass metabolism cages and their urine and feces were collected. Special metabolism cages for trapping any radioactivity expired through their respiratory system were used for one male and female rat. The rats were sacrificed after three days and their blood and selected tissues were assessed for radioactivity. MRID NO.: 41551103. 85.5% for males and 97.2% for females of initial ^{14}C dose was excreted in 72 hours. The urine (55.8% for males and 69.4% for females) was the major route of excretion with the feces containing the balance. The air contained only 0.1% or less. Tissue retention was highest in the skin (1.2%) and liver (0.74% for males but only 0.18% for females) and fat (0.57 to 0.66%). This study is classified as CORE-SUPPLEMENTARY. The study when combined with other metabolism studies satisfies the requirement for the series 85-1 study.

85-1. Metabolism - rats Shell Research Study No.: CTL/C/1146 or TLGR.0131.77, December, 1977. ^{14}C-aryl labelled cypermethrin	Wistar strain rats were dosed at 0.61 mg/kg of aryl ^{14}C labeled cypermethrin in corn oil and their urine and feces assessed for radioactivity. About 70% of <u>cis</u> and 80% of <u>trans</u> cypermethrin was excreted in 24 hours. Essentially all was excreted in 8 days. Most of the label was excreted in the urine (>53%) with less in the feces (<20%) and < 1% in the air). A sex difference with respect to excretion in the urine from the <u>cis</u> isomer was noted since about equal amounts (35%) were found in both the urine and feces. Several urinary and fecal metabolites were tentatively characterized. This study is classified as CORE-SUPPLEMENTARY. The study when combined with other metabolism studies satisfies the requirement for the series 85-1 study.

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IVb. Studies for which new DERs and Executive Summaries were prepared.

Study Identification	Executive Summary
82-1. Subchronic feeding study - rats: ICI Study No.: CTL/P/327, January 8, 1980. Technical Cypermethrin 92% purity.	In a subchronic toxicity study (MRID 00056802 and 92027034 cypermethrin (92% purity) was administered to four groups of 20 SPF Alderley Park strain rats/sex at dose levels of 0, 75, 150 or 1500 ppm (corresponding to 0, 3.75, 7.5 or 75 mg/kg/day) for 90 days. Groups of 4/sex/dose were allowed 28 days for recovery. The male rats dosed with 7.5 mg/kg/day had increases (260%) in hepatic aminopyrine demethylase. This was increased to 539% in the 75 mg/kg/day dose group. Females (466%) were increased in the 75 mg/kg/day dose group only. Recovery was evident after 28 days. Body weight was decreased in the 75 mg/kg/day dose groups for both males (i.e. 17% at week 9) and females (i.e. 8% at wee 9). **The LOEL is 1500 ppm (75 mg/kg/day) based on body weight. The NOEL is 150 ppm (7.5 mg/kg/day).** The increase in hepatic aminopyrine demethylase is considered a physiological rather than toxicological response but its presence is indicated. This study is classified as SUPPLEMENTARY. The series 82-1 subchronic study in rats is considered fulfilled by other data.
82-2B. Subchronic feeding-dog. Shell Laboratory, Study No.: 1112, November 1977. Technical Cypermethrin, 98% purity.	In a subchronic toxicity study (MRID No.: 00112929) cypermethrin (98% purity) was administered to four groups of 4 beagle dogs/sex at dose levels of 0, 5, 50, 500 or 1500 ppm (corresponding to 0, 0.125, 1.25, 12.5 and 37.5 mg/kg/day) for 13 weeks. Responses to treatment were noted at 37.5 mg/kg/day in both sexes and consisted of whole body tremors, exaggerated gait, ataxia, incoordination, hyperaesthesia, licking and chewing of paws as well as diarrhea and anorexia and decreased body weight, **The LOEL is 1500 ppm (37.5 mg/kg/day) based on clinical signs indicating neurotoxicity. The NOEL is 500 ppm (12.5 mg/kg/day).** The study is classified as SUPPLEMENTARY. The series 82-1b subchronic study in dogs is considered fulfilled by the chronic dosing study with dogs.

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Study Identification	Executive Summary
82-2. 21-day dermal toxicity-rabbit ICI Laboratory, Study No.: LB 0019, Feb.4, 1981. Technical Cypermethrin.	In a 21-day dermal toxicity study (MRID No.: 00090035) with rabbits, 10/sex/dose group, cypermethrin was applied at dose levels of control, 2, 20 or 200 mg/kg/day applied in 20% (w/w) PEG 300 with daily applications for three weeks for a total of 15 applications. 5/sex/group were abraded prior to application of the test material. At 200 mg/kg/day, liver necrosis was noted in 4 of 5 females and 3 of 5 males with abraded skin. Two of 5 females but no males with unabraded skin were also affected. There was also a possibility of an effect on the testis since there was a decrease in absolute (19%, $p < 0.05$) and relative (15%, not significant) weight that was not accompanied by pathological changes. 200 mg/kg/day was considered a threshold level for clinical signs (i.e. flaccid body, salivation). There was local site of application irritation noted in all dose groups. **The LOEL is 200 mg/kg/day based on liver effects. The NOEL is 20 mg/kg/day.** This study is considered ACCEPTABLE and to satisfy the requirement for a series 82-3 dermal toxicity study in rabbits.
83-1b. Chronic (capsule) dosing study in dogs. ICI Laboratory. Study No.: PDO398, July 6, 1982 Technical Cypermethrin, 90.6% purity	In a chronic toxicity study (MRID 00112909, 42068503, 92027037 cypermethrin (90.6%) dissolved in corn oil was administered to 4 groups of 6/sex beagle dogs in gelatin capsules at dose levels of 0, 1, 5 or 15 mg/kg/day for 52 weeks. The males (4.75 fold) and females (10 fold) dosed with 5 mg/kg/day had increased passage of liquid stools evident in the first week and this condition increased to 31 fold at the 15 mg/kg/day dose level. At 15 mg/kg/day, body tremors, gait abnormalities, uncoordination, disorientation and hypersensitivity to noise were evident in addition to body weight decrease. **The LOEL is 5 mg/kg/day based on gastrointestinal effects. The NOEL is 1 mg/kg/day.** This study is considered ACCEPTABLE and to satisfy the requirement for a series 83-1b chronic toxicity study in a non-rodent species.

Study Identification	Executive Summary
83-2. Carcinogenicity-mice. ICI Laboratory, Study No.: CTL/P/687, June 1982. Technical Cypermethrin 9105-94.2% purity.	In a carcinogenicity study (MRID 00112911 and 92027038) cypermethrin (53-54% cis and 46-47% trans) was administered to groups of 70/sex Swiss derived Alderley Park strain SPF mice at dose levels of control-1, control-2, 100, 400 and 1600 ppm (corresponding to 0, 0, 14, 57 or 229 mg/kg/day) for 97 weeks for males and 101 weeks for females. Liver weight was increased at 57 mg/kg/day (20% absolute weight) and above in males and for females at the high dose only (15% for relative weight) at the interim sacrifice but not at the terminal. Other systemic effects were noted at 229 mg/kg/day included reduction in RBC parameters (hemoglobin, hematocrit and RBC count in males, mean cell volume and hemoglobin) and platelet counts (for males at interim but not terminal sacrifice) and neutrophils and body weight gain (i.e. about 9% at week 6 for males and 12% for females at week 11). **The LOEL is 400 ppm (mg/kg/day) based on liver weight. The NOEL is 100 ppm (14 mg/kg/day).** This study was determined to be **positive for induction of benign alveologenic neoplasms.** Adequacy of dosing for carcinogenicity is based upon typically 9% decreases in males and 12% in females in the first months of the study. This study is classified as ACCEPTABLE and to satisfy the requirement for a series 83-2 carcinogenicity in mice.
83-3a. Developmental Toxicity-rats Life Sciences Research Study No.: 78/SHL/364, October 4, 1978. Technical Cypermethrin 98.2% purity.	In a developmental toxicity study (MRID 00056804, 92027039 or 92027061, cypermethrin (98.2% purity) in corn oil was administer-ed by gavage to four groups of 25 mated CD strain Charles River rats at dose levels of 0, 17.5, 35, or 70 mg/kg/day on days 6-15 of gestation. The rats were sacrificed at day 21 of gestation. Dose levels of 35 (12%) and 70 (28%) mg/kg/day resulted in decreased body weight gain. The dams dosed with 70 mg/kg/day displayed neurological signs such as splayed limbs, spasms, and hypersensitivity to noise and convulsions. **The maternal LOEL is 35 mg/kg/day, based on body weight. The maternal NOEL is 17.5 mg/kg/day.** No effects on either skeletal or visceral structures were reported. **The developmental LOEL is > 70 mg/kg/day. The developmental NOEL is > 70 mg/kg/day.** This study is classified as ACCEPTABLE and to satisfy the requirement for a series 83-3a developmental toxicity study in rats.

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Study Identification	Executive Summary
83-3b. Developmental Toxicity-rabbits Shell Toxicology Laboratory, Study No.: 1103, January 1978. Technical Cypermethrin 98.5% purity	In a developmental toxicity study (MRID 00056805), cypermethrin (98.5% purity) in corn oil was administered to banded Dutch rabbits by gelatin capsule at dose levels of 0 (empty capsule), 0 (capsule plus corn oil), 3, 10 or 30 mg/kg/day on days 6 to 18 inclusive of gestation. There were no effects on the does of any kind reported. **The maternal LOEL is > 30 mg/kg/day. The maternal NOEL is > 30 mg/kg/day.** There were no treatment related effects on either the skeletal or visceral structures reported. **The developmental LOEL is > 30 mg/kg/day. The developmental NOEL is > 30 mg/kg/day.** This study is classified as ACCEPTABLE and to satisfy the requirement for a series 83-3b study in rabbits.
83-4. Multi-generation reproduction-rats ICI Laboratory, Study No.: RR0143, July 9, 1982 Technical Cypermehrin 90.6 to 93.1% purity.	In a 3 generation reproduction study (MRID 00112912, 42068504, 92027040) cypermethrin (90.6 to 93.1%) was administered to four groups of 15 male and 30 female Wistar derived SPF strain rats at dose levels of 0, 50, 150 or 1000/750 ppm (reduced to 750 ppm after 12 weeks because of severe neurological symptoms). These dose levels correspond to 2.5, 7.5 or 50/37.5 mg/kg/day. Three successive generations were produced, each consisting of 2 separate breedings to produce six sets of litters. At 150 ppm (7.5 mg/kg/day), parental weight gain was decreased in males (i.e. about 7% for F_2 at week 5) and females (i.e. about 4.5% for F_0 at week 8 and about 10% for F_2 week 8). At 1000/750 ppm (50/37.5 mg/kg/day) parental body weight gain was typically 10% decreased for both males and females and there was decreased mean litter weight gain during lactation (i.e. 12% to 21% for F_1B and 12 to 17% for F_1B females for days 10 to 28). At 1000 ppm (50 mg/kg/day) there were obvious clinical signs of neurotoxicity (i.e. ataxia etc). **The LOEL is 150 ppm (7.5 mg/kg/day) based on consistent decreased body weight gain in both sexes. The NOEL is 50 ppm (2.5 mg/kg/day).** This study is classified as ACCEPTABLE and satisfies the requirement for a series 83-4 multi generation reproduction study in rats.

Study Identification	Executive Summary
83-4. Multi-generation reproduction-rats Shell Laboratory, Study No.: TLGR.0188.78, February, 1979 Technical Cypermethrin 98% purity	In a 3 generation reproduction study (MRID 00090040) cypermethrin (98% purity) was administered to four groups of 30/sex Wistar SPF strain rats/sex/dose group in their diets at dose levels of 0, 10, 100 or 500 ppm [0, 0.5, 5, or 25] mg/kg/day. The first parental group produced two litters (F1A and F1B), the F1B litter was culled to produce the F2A and F2B litters and the F2B litter was culled to produce the F3A and F3B litters. At 25 mg/kg/day there was decreased parental weight gain (i.e. about 3% for males and 7 % for females for the F1 generation and pup weight at day 21 of lactation (about 4% but $p < 0.01$). **The LOEL is 500 ppm (25 mg/kg/day based on decreased weight gain. The NOEL is 100 ppm (5 mg/kg/day).** This study is classified as SUPPLEMENTARY and the requirement for a series 83-4 multi generation reproduction study is fulfilled by another study.
83-5. Chronic feeding/ carcinogenicity-rats ICI, Study No.:CTL/P669, June 1982. Technical Cypermethrin, 88-93% purity.	In a chronic toxicity/carcinogenicity study (MRID 00112910) cypermethrin (88-93% purity, 55% cis and 45% trans) was administered to 5 groups of 52/sex Wistar derived Alderley Park SPF strain rats at dose levels of control-1, control-2, 20, 150 or 1500 ppm (corresponding to 0, 0, 1, 7.5 or 75 mg/kg/day) for 2 years. Satellite groups of 12/sex were sacrificed after one year of dosing. Definite signs of toxicity were evident at 75 mg/kg/day and these consisted of body weight gain decrease throughout the study (i.e. about 10% for males and 13% for females at week 13), *slight* effects on several hematological parameters (both red and white cells), *slight* effects on clinical chemistry parameters (decreased cholesterol and triglycerides and glucose and increased urea. Decreases in urine volume, pH and an increase in specific gravity were noted. Liver weight was increased in females. **The LOEL is 1500 ppm (75 mg/kg/day) based on body weight. The NOEL is 150 ppm (7.5 mg/kg/day).** Cypermethrin was not considered to be oncogenic in this study. A possible association with increased testicular interstitial tumors was not considered definite. This study is classified as ACCEPTABLE and to satisfy the requirement for a series 83-5 chronic feeding/oncogenicity study in rats.

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Section IV, Toxicology Branch I 7509C Marion Copley 9/16/96

DATA EVALUATION REPORT

STUDY TYPE: 85-1. Metabolism - rats

DP Barcode: D180777
PC No.: 109702
Submission No.: S422096
TOX. CHEM. NO.: 271DD

TEST MATERIAL: ^{14}C-cyclopropyl labelled cypermethrin.

SPONSOR: ICI Corporation

CITATION: M.J. Crawford and D.H. Hudson (1978) "Cypermethrin: The metabolic fate of the cis and trans isomers of cypermethrin in the rat. Metabolites derived from the ^{14}C-labelled cyclopropyl ring". Shell Research Sittingbourne, Kent UK, STUDY NUMBER(S): CTL/C/1154 or TLGR.0183.78. November, 1977. MRID NO.: 41551104. Unpublished.

Executive Summary:

In a series of nine different studies, labelled cypermethrin (1 mg/kg or less) in corn oil or separated cis or trans cypermethrin isomers were given by gavage to single or groups of two or three Wistar strain rats. Their urine and in some cases fecal matter were collected at various intervals such as 18 hours to 3 days. In another set of experiments, labelled cypermethrin was administered to rats that were fitted with bile duct cannalulas and their bile collected for 4-5 hours while the rat was under anesthesia. MRID NO.: 41551104.

cis and trans ^{14}C-cyclopropyl labelled cypermethrin was demonstrated to form glucuronide conjugations of cis and trans acids and hydroxyacids. Only 1.6% or less of the total dose is excreted in the bile. Most of the label in the feces was unmetabolized cypermethrin. The glucuronide conjugates in the urine were found to be unstable and subject to hydrolysis.

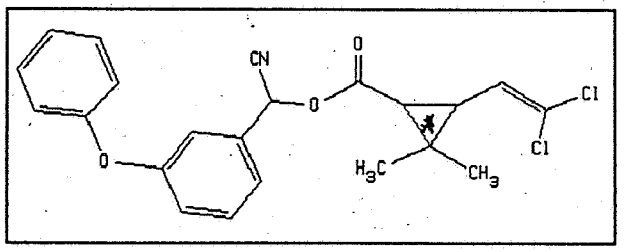
Classification: CORE-SUPPLEMENTARY. This study itself cannot satisfy the requirement for a series 85-1 general metabolism study. These data may be taken together with other metabolism data to help to satisfy the requirement for the series 85-1 metabolism study. See cover memo for lists of MRID Nos..

Quality Assurance Statement: None. Study is circa 1978.
Good Laboratory Practice Statement: None. Study is circa 1978.

REVIEW

Experimental Constants:

Test Chemical: The test material was ^{14}C cyclopropyl labelled cypermethrin that was synthesized in the Shell Bioscience Laboratory. The specific activity was stated as being 9.6 Uci/mg and 11.1 Uci/mg and based on TLC had a radiochemical purity of >99%. cis and trans isomers were reportedly obtained from this source by chromatographic separation. The test material was administered by gavage in corn oil.



Test System: Wistar strain rats. No information on their source was provided.

Basic Experimental Designs

Several different dosing levels of administration of labelled cypermethrin or separated cis or trans cypermethrin were given by gavage to single rats or groups of two or three rats. Their urine and in some cases fecal matter were collected at various intervals such as 18 hours to 3 days. In another set of experiments, labelled cypermethrin was administered to rats that were fitted with bile duct cannalulas and their bile collected for 4-5 hours while the rat was under anesthesia.

Experiment 1. Three male and three female rats were administered single oral doses of ^{14}C-cypermethrin (0.32 mg/animal) in corn oil (0.8 ml) and their urine and feces collected for 3 days and saved for identification of metabolites.

Experiment 2. Individual male rats were separately dosed with labelled cis- cypermethrin (0.58 mg/animal in 0.35 ml of corn oil or labelled trans-cypermethrin (0.55 mg/animal in 0.35 ml of corn oil and their urine and feces were collected for 3 days.

Experiment 3. A male rat was dosed with 0.89 mg of labelled cypermethrin in 0.5 ml of corn oil and its urine collected for 18 hours.

Experiment 4. Two males rats were dosed with 0.68 mg of labelled cypermethrin in 0.8 ml of corn oil and their urine was collected for 24 hours.

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Experiment 5. One male was dosed with 0.5 to 0.6 mg of labelled cypermethrin (vehicle and volume ?) and its urine collected for 20 hours.

Experiment 6. The bile duct of a male rat (weight: 230 gm) was cannalulated and the rat was then dosed with 0.52 mg of labelled cypermethrin in 0.8 ml of corn oil. Bile (estimated 7 ml) was collected for 4.5 hours while the rat was maintained under anesthesia (thiopentone).

Experiment 7. A male rat was first dosed orally with 0.52 mg of labelled cypermethrin in 0.8 ml of olive oil. The bile duct was then cannalulated and 3.7 ml of bile was collected during a 4 hour interval while the rat was under anesthesia.

Experiment 8. Similar to experiment 7 but only 0.26 mg of labelled cypermethrin was administered and the urine (0.4 ml) and bile (3.2 ml) was collected for 5 hours while the rat was under anesthesia.

Experiment 9. The purpose of this aspect of the study was to obtain "accurate quantitative data for the various metabolites i.e. using conditions avoiding the formation of artifacts".

Two female rats were dosed with 1.075 mg of labelled cis-cypermethrin in 0.5 ml of corn oil and the urine and feces were collected daily for three days and composite samples (for 0-2 days) of the urinary and fecal samples from both rats were prepared. Two other female rats were dosed with 0.87 mg of trans-cypermethrin in 0.45 ml of corn oil and their urine and fecal samples were similarly collected.

For the above experiments, when necessary, the urine, fecal and bile samples were stored frozen at -20° C prior to and/or after analysis.

The biliary, fecal and urinary samples were subjected to analysis by either TLC (Merck Silica gel F_{254} plates using one or more of 8 different solvent systems), gas-liquid chromatography (glrc) fitted with electron capture and radioactivity detectors, gas-liquid chromatography-mass spectrometry (gcms) or high pressure liquid radiochromatography (hplrc).

Results

1. Biliary excretion and identification of biliary metabolites.

Only 0.95 to 1.6% of the administered dose of labelled cypermethrin (mixture of isomers) was recovered in the bile in the 4-5 hour sampling intervals. Only conjugated metabolites (polar) were found in the bile as indicated by TLC. Beta-glucuronidase hydrolysis was reported to yield 81% ether extractables and further TLC indicated that the cis and trans

acids were present in a ratio of 5:3.

2. Urinary metabolites.

Male and female urine samples (0-24 hours, estimated 44% of the dose frozen and thawed) resulted in similar TLC profiles in TEA solvent (toluene:ethyl acetate:acetic acid, 75:25:1, v/v) and these were combined from both sexes for further experimental identification of the metabolites. TLC analysis in TEA revealed a polar fraction (Rf 0, 50% of the applied material). Spots corresponding to trans acid (Rf 0.29, 26%), cis acid (Rf 0.37, 15%) and a smaller peak (9%, Rf 0.1). Beta-glucuronidase treatment overnight was said to increase the proportions of the trans and cis acids to 29% and 23% respectively. Meaning only a slight increase in the trans acid and a nearly 54% increase in the cis acid.

A sample of the urine was treated by adjusting to pH 2 and extracting with ether. The ether extract was further treated by methylating with diazomethane and analyzed by TLC with DCM solvent (dichloromethane). The major peak (Rf 0.88) on the TLC plate was further characterized by GLRC and shown to be cis and trans acid (hydrolysis products of cypermethrin). The trans acid exceeded the cis approximately 2:1. The identity of these metabolites was reported confirmed by GCMS.

The experiments in which rats were dosed with the separated cis and trans isomers of labelled cypermethrin (Experiment 2), 48% and 55% of the total radioactive dose resulted in the urine respectively from the cis and trans treated animals respectively in 2 days. TLC analysis of the urine in CA solvent (chloroform:acetic acid, 95:5), revealed 42 or 43% polar metabolites (Rf 0) and 34 and 42% free cis or trans acids. The cis isomer had 15% hydroxy acids (Rf 0.25) a much larger proportion than the trans isomer. TLC separation and methylation and GCMS were reported to establish the structures of the metabolites as hydroxy acids.

Conjugated metabolites. The urine from experiment 1, stored frozen for 4 months, was used. 42% and 43% of the urinary metabolites from the cis-isomer and trans-isomer respectively were polar and presumed to be conjugates. Preliminary experiments using TLC and EFW solvent (ethyl acetate:formic acid:water, 70:4:4) indicated that there were no taurine conjugates in the urine by comparison with "authentic samples" of the taurine conjugates.

Beta-glucuronidase treatment of this urine resulted in only partial hydrolysis of the conjugated fraction. Additional hydrolysis of the glucuronides with acid (pH 1, 100° C, 2 hours or pH 9, NH_4OH, 80° C, 5 hours) was also carried out. These treatments resulted in the identification of cis and trans acids as indicated by HPLRC cochromatography with standards.

Reverse phase HPLRC was also employed to try to isolate the conjugate fraction. The separation consisted of basically using a 10 x 1 cm Spherisorb ODS column using s linear gradient from water ().25% acetic acid) with concentrations of acetonitrile (in 0.25% acetic acid) from 0 to 80%. Both UV and radioactivity detectors were used to monitor the effluent. This treatment resulted in three major radioactivity peaks with the following characteristics.

Fraction A. A mixture of conjugates emerging at about 50% acetonitrile and prior to the UV absorbing materials. TLC separated fraction A into at least two components with Rfs of 0.51 (A1) and 0.59 (A2). Beta-glucuronidase hydrolyzed fraction A1 to a mixture of cis and trans acids but fraction A2 was resistent to this enzymatic hydrolysis.

Urines that were not stored (resulting from experiment 2) were more susceptible to hydrolysis by beta-glucuronidase. For the cis isomer, enzymatic treatment resulted in 88% free acids and only 15 conjugates. For the trans isomer, enzymatic treatment resulted in 4% conjugates and 93% free acids. Urine derived from experiments 3 and 4 both resulted in single peaks with Rf expected for conjugates. Freezing the urine from both experiments 3 and 4 resulting in a diminishing of the single peak for conjugates and an increase in a peak for free acids. This diminishing of the conjugates on storage was attributed to the pH of the stored sample being 9. This demonstrates that the glucuronides of cyclopropane carboxylic acid are hydrolyzed at pH values of 7 to 9 even in frozen solutions. The glucuronides are believed to be altered to metabolites of similar polarity at pH 9 but not necessarily at pH 7.

Fraction B. Containing (supposedly) hydroxy acids and emerging at about 58% acetonitrile. TLC analysis of this fraction indicated products that cochromatographed with cis and trans hydroxyacids with the cis product predominating.

Fraction C. Containing (supposedly) free acids and emerging at 62-64% acetonitrile. This fraction was methylated with diazomethane and the esters purified by TLC. Most of the radioactivity was reportedly lost during the evaporation procedure. GCMS analysis of this fraction, however, revealed the presence of both cis and trans acid methyl esters with a recovery form the preparative process of only 50%. Much of the content of the evaporate was found to be also cis and trans acids.

Biliary metabolites. Only 1-1.6% of the oral dose was believed to be excreted by the biliary route. These were hydrolyzed by beta glucuronidase and determined to be cis and trans acids.

Fecal metabolites. Unchanged cypermethrin was the major component from both cis and trans cypermethrin being 33% and 34% respectively. 4'-hydroxy-cypermethrin (3% and 4% respectively

for the cis and trans) was also detected.

CONCLUSION. This study is SUPPLEMENTARY. These data represent a series of experiments that address individual refinements in developing methods to finally isolate and identify the urinary and fecal metabolites of cis and trans cypermethrin. These data when considered with other data to help to satisfy the data requirement for a series 85-1 metabolism study. See cover memo for MRID Nos. for other studies.

Addendum.

Table 8 (Study Report, page 26) "Analysis of the urinary metabolites of the separately-dosed cis- and trans- isomers of cypermethrin"

Figure 1. "Structures of cypermethrin isomers and related compounds" Photocopied from the study report.

I and II are cis and trans cypermethrin
III is an hydroxylated (on the methyl groups on the cyclopropane ring) metabolite.
IV-IX are various forms of the acid moiety following cleavage at the esteratic site.
X-XII are conjugated metabolites forms of the acid moiety following cleavage at the esteratic site.

CYPERMETHRIN

Page_____ is not included in this copy.

Pages 16 through 17 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.

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____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

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Reviewed by: John Doherty 7/30/96
Section IV, Toxicology Branch I 7509C
Secondary reviewer: Marion Copley, DVM 9/16/96
Section IV, Toxicology Branch I 7509C

DATA EVALUATION REPORT

STUDY TYPE: 85-1. Metabolism (partial) - rats

DP Barcode: D180777 **Submission No.:** S422096
PC No.: 109702 **TOX. CHEM. NO.:** 271DD

TEST MATERIAL: ^{14}C-cyclopropyl labelled cypermethrin

SPONSOR: ICI Corporation

TITLE OF REPORT: M.J. Crawford (1977) "Cypermethrin: The metabolism of WL 43467 in Mammals. The fate of a single oral dose of [^{14}C-cyclopropyl] WL 43467 in the rat." Shell Research, Settingbourne, Kent, England. Study numbers: CTL/C/1147 or TLGR.0004.77. January 1977. MRID NO.: 41551103. Unpublished.

Executive Summary

One group of three/sex Wistar strain rats was dosed with a single oral dose (approximately 1.3 mg/kg) of ^{14}C-cyclopropyl labelled cypermethrin in corn oil (0.8 ml). The rats were then placed in glass metabolism cages and their urine and feces were collected. Special metabolism cages for trapping any radioactivity expired through their respiratory system were used for one male and female rat. The rats were sacrificed after three days and their blood and selected tissues were assessed for radioactivity. MRID NO.: 41551103.

85.5% for males and 97.2% for females of initial ^{14}C dose was excreted in 72 hours. The urine (55.8% for males and 69.4% for females) was the major route of excretion with the feces containing the balance. The air contained only 0.1% or less. Tissue retention was highest in the skin (1.2%) and liver (0.74% for males but only 0.18% for females) and fat (0.57 to 0.66%).

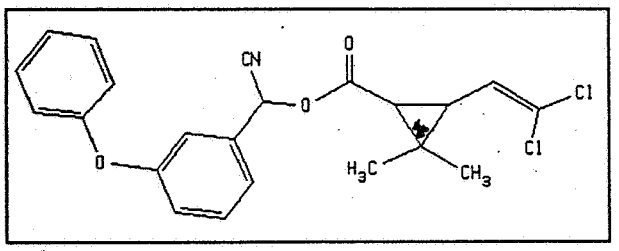
Classification: CORE-SUPPLEMENTARY. This study by itself does not satisfy the series 85-1 general metabolism data requirement but these data can be combined with other studies to help meet the requirement. See cover memo for list of MRID Nos.

Quality Assurance Statement: Not provided. Study is circa 1977.
Good Laboratory Practice Statement: Not provided.

REVIEW

Experimental Constants:

Test Chemical: ^{14}C-cypermethrin radiolabelled in the cyclopropane ring. The specific activity was stated as being 9.6 uCi/mg with a radiochemical purity of greater than 99% when analyzed by thin layer chromatography.



Test System: Wistar strain male (430 gms) and female (240 gms) rats. The source of the rats was not provided. Their age was not given but based on their bodyweight mature adults.

Basic Experimental Design:

One group of three male and three female rats was dosed with a single oral dose (0.52 gms) of the labelled cypermethrin in corn oil (0.8 ml). The rats were then placed in glass metabolism cages and their urine and feces were collected while they were given free access to feed and water. Special metabolism cages for trapping any radioactivity expired through their respiratory system were used for one male and female rat. The rats were sacrificed (Nembutal, cardiac puncture) after three days and their blood and selected tissues were assessed for radioactivity.

Results

1. Excretion as indicated by urine, feces and expired air.

[Urine was assessed for radioactivity by diluting to a specified volume and sampled and counted. Feces and tissue radioactivity was assessed by combustion. Aliquot of the sodium hydroxide trapping solution were counted for radioactivity.]

Excretion was rapid with most of the material excreted in the urine as indicated by Table 1 below.

Table 1. Accountability of radioactivity from ^{14}C-cyclopropyl labelled cypermethrin 72 hours after administration to male and female rats.

Location	% of Administered Dose	
	Males	Females
Urine	55.8 ± 1.3	69.4 ± 3.2
Feces	28.7 ± 3.0	27.0 ± 3.2
Air	0.098	0.090
Tissues	13.3 ± 3.6	5.8 ± 1.9
Total	97.9	102.3

In addition another 6.3% for males and 4,4% for females was collected from the cage washing.

Thus total recovery was within acceptable limits.

b. Tissue retention.

Table 4a (photocopied from the study report) illustrates the tissue distribution of radioactivity found in the tissues after 72 hours. The intestine retained the highest percentage of radioactivity (males 8.5% and females 2.8% mean values). This however, was likely in the feces because the rats were noted to have a low production of fecal matter during the experiment. The skin, liver and body fat were the next highest retainers of radioactivity.

CONCLUSION. This study is SUPPLEMENTARY. The protocol for this study is very limited and provides for only a segment of the requirements for a metabolism study.

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Table 4a - Radioactivity remaining in rats 3 days after receiving an oral dose of [^{14}C-cyclopropyl]W1. 43467

Mat No.	Sex	% of dosed radioactivity remaining in rats 3 days after administration of W1. 43467 (0.5 mg P.O.)									
		Liver	Kidney	Fat*	Muscle*	Brain	Blood*	Intes-tines	Skin	Remain. Carcass	Total
1	Male	0.67	0.055	0.40	0.008	0.004	0.13	10.7	1.7	3.2	16.9
2	Male	0.68	0.039	0.64	0.020	0.003	0.058	5.7	0.6	2.0	9.7
3	Male	0.86	0.044	0.93	0.025	0.003	0.058	8.9	1.2	1.4	13.4
Mean		0.74	0.046	0.66	0.018	0.003	0.082	8.5	1.2	2.2	13.3
1	Female	0.19	0.025	0.33	0.006	0.002	0.048	1.9	0.8	1.1	4.4
2	Female	0.16	0.017	0.91	0.009	0.003	0.053	1.9	1.0	1.0	5.1
3	Female	0.19	0.016	0.47	0.006	0.002	0.038	4.7	1.5	1.1	8.0
Mean		0.18	0.019	0.57	0.007	0.002	0.046	2.8	1.1	1.1	5.8

* The figures given here represent the % dose found in the sub-samples taken. Thus the radioactivity in the remaining carcass includes that from the fat, muscle and blood not sub-sampled for separate radioanalysis.

This page contains information which must not be sent to the USA.
CTL/C/1147:PHASE 3 REFORMAT - 12

Reviewed by: John Doherty 7/3-/92
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley, DVM 2/16/94
Section IV, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 85-1. Metabolism - rats

DP Barcode: D108777 **Submission No.:** S422096
PC No.: 109702 **TOX. CHEM. NO.:** 271DD

TEST MATERIAL: ^{14}C-aryl labelled cypermethrin

SPONSOR: ICI Corporation

CITATION: M.J. Crawford and D.H. Hutson (1977) "Cypermethrin: The metabolic fate of the cis and trans isomers of WL 43467 (Cypermethrin). Metabolism and elimination of ^{14}C-aryl labelled cis and trans isomers in rats". Shell Sittingbourne Laboratory, United Kingdom, STUDY NUMBER(S): CTL/C/1146 or TLGR.C131.77. December, 1977. MRID NO.: 41551102. Unpublished.

EXECUTIVE SUMMARY:

First group. Six/sex rats Wistar strain rats were dosed with a single dose 0.61 mg/animal of labelled cis-cypermethrin isomers in 0.5 ml of corn oil. The rats were individually housed in metabolism cages and their urine and fecal matter collected daily until sacrifice. Two rats of each sex were sacrificed after 24 and 72 hours and after eight days. Samples of the blood and selected tissues were assessed for radioactivity content. Second group. Three/sex rats were dosed with 0.615 mg/animal of labelled trans cypermethrin in 0.8 ml of corn oil. In addition to the urine and fecal collections, expired air was also collected from one male and one female. MRID NO.: 41551102.

Total recovery was from 97.2 to 100.5%. About 70% of cis and 80% of trans cypermethrin was excreted in 24 hours. Essentially all was excreted in 8 days. Most of the label was excreted in the urine (>53%) with less in the feces and (< 20%) for the trans (males and females) and cis (males only) groups and and < 1% in the air for all groups. A sex difference with respect to excretion in the urine from the cis isomer was noted for females since about equal amounts (35%) were found in both the urine and feces. Several urinary and fecal metabolites were tentatively characterized.

Classification: CORE-SUPPLEMENTARY. This study by itself does not satisfy the requirement for a series 85-1 general metabolism study. Data will be considered together with other studies to help meet the series 85-1 requirement.

Quality Assurance Statement: None provided. Study is circa 1977.

Good Laboratory Practice Statement: Study is circa 1977.

REVIEW

Experimental Constants:

Test Chemical: ^{14}C labelled cis-cypermethrin (alpha-cyano-3-phenoxy [^{14}C] benzyl 2-(2,2-dichlorovinyl)-3,3-dimethylcyclopropane-carboxylate] synthesized at the Shell Bioscience Laboratory. The specific activity was reported as 35 uCi/mg and reportedly demonstrated to be > 99.5% pure by TLC analysis in toluene.

A single isomeric preparation of labelled trans cypermethrin was also synthesized at the Shell Biosciences Laboratory and had a reported specific radioactivity of 35 Uci/mg and also to be of > 99.5% purity.

Test System: Six male (appro. 350 gms) and six female (approx. 250 gms) Wistar strain rats reportedly 12 weeks of age were used in this study.

Basic Experimental Design

First group. Six male and six female rats were dosed with a single dose 0.61 mg/animal of labelled cis-cypermethrin isomers in 0.5 ml of corn oil. The rats were individually housed in metabolism cages, given free access to feed and water and their urine and fecal matter collected daily until sacrifice. Two rats of each sex were sacrificed after 24 and 72 hours and after eight days. Sacrifice was by anesthetizing with Nembutal followed by cardiac puncture. Samples of the blood and selected tissues were assessed for radioactivity content.

Second group. Three rats of each sex were dosed with 0.615 mg/animal of labelled trans cypermethrin in 0.8 ml of corn oil. In addition to the urine and fecal collections, expired air was also collected from one male and one female by collecting in a 3 N sodium hydroxide trap.

Results

1. Total recovery of administered label.

Table 1 illustrates the excretion of labelled cis or trans cypermethrin in the urine and feces at 24 hours and the total recovery after 8 (cis) or 3 (trans) days.

For cis cypermethrin, there was noted a marked difference between males and females in the 0-24 hour recovery. Males excrete more via the urinary route, while females excrete more via the fecal route. This difference was not noted for the trans isomer which eliminated the labelled material similar to the way the male eliminated the cis labelled material.

Table 1. Excretion of labelled cis or trans cypermethrin in the urine and feces following an oral administration in corn oil to Wistar rats.

Interval	cis-cypermethrin Males	cis-cypermethrin Females	trans-cypermethrin Males	trans-cypermethrin Females
24 hours				
Urine	53	35	59.2	62.0
Feces	19	35	18.9	15.8
Total Recovery	100.5	97.3	99.7	97.2
Urine	59.9	41.7	71.4	74.4
Feces	28.0	46.1	28.3	22.7

Data extracted from Tables 3, 4 and 5, page 20, 21 and 22 of the study report.

2. Excretion into the expired air.

Only 0.02% for the male and 0.015% for the female of the total radioactivity was excreted in the expired air meaning that the labelled ring structure was not metabolized by the rat during the three day interval.

3. Radioactivity in the tissues.

Samples of rat tissues (liver, kidney, fat, muscle, brain and blood) were assessed for radioactivity from rats dosed with the cis isomer on day 1, 3 and 8. Rats dosed with the trans isomer were assessed on day 3 only.

Cis-isomer data. The fat retained the most radiolabelled material (0.83 to 1.46 ug/gm tissue). There was little reduction of the radiolabel from the tissue between day 1 and day 8 meaning the material stays in the fat. The females had the higher amount at day one but afterwards the sexes were about equal. The liver had the second highest concentration (0.41 to 0.98) with only a possibility of the females being higher. The liver content of radioactivity fell to about one tenth of that amount by day 8. The remaining organs had lower amounts which decreased to < 0.05 ug/gm by day 8.

trans-isomer data. A similar pattern was noted with the fat having the highest levels (0.83 to 1.04 for both sexes at day 8).

4. Identification of urinary metabolites.

The pooled 0-24 hour urine samples from each sex and each isomer were chromatographed using two solvent systems. In some cases methylation was used to assist in characterizing the derivatives. Several compounds were tentatively identified based

on cochromatography. These are described in Table 7 (attached) photocopied from the study report.

Metabolite U1: Methyl 3-phenoxybenzoate and methyl-(4-methoxyphenoxy)benzoate. Obtained from urine derived from females treated with cis isomer.

Metabolite U2: 3-(4-hydroxyphenoxy)benzoic acid)

Metabolite U3: 3-phenoxybenzoylglycine. Maximum in the urine from rats dosed with trans-cypermethrin.

Metabolite U4: sulfate conjugate of 3-(4-hydroxyphenoxybenzoic acid)

Metabolite U5: Other probable sulfate metabolites.

5. Identification of fecal metabolites.

90% (for males) and 95% (for females) of the radioactivity in the feces was reported to be unchanged cypermethrin from rats dosed with cis isomer. Nine different compounds comprised the remaining radioactivity. Two compounds were thought to be tentatively identified, these were 3-phenoxybenzoic acid and 3-(4-hydroxyphenoxy)benzoic acid. Less tentative identification of other compounds was also made but since these were minor components of the fecal matter their identities were not confirmed.

Similar results were obtained for the fecal matter obtained from the rats dosed with trans isomer.

CONCLUSION. These data when taken alone are SUPPLEMENTARY. They will be considered together with other studies to meet the metabolism data requirement for cypermethrin.

CYPERMETHRIN

Page 26 is not included in this copy.

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7-15-96

[Cypermethrin/1980] Subchronic Oral Study (82-1(a))

EPA Reviewer: John Doherty 7/15/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley, DVM
Review Section IV, Toxicology Branch I (7509C) 7/15/96

SUPPLEMENTARY DATA EVALUATION RECORD
Original DER in HED Document No.: 004825
(attached with supporting tables)

STUDY TYPE: Subchronic Oral Toxicity feeding study - rats. OPPTS 870.3100 (rodent) [§82-1 (a).

DP BARCODE: D180777 SUBMISSION CODE: S422096
P.C. CODE: 109702 TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): Cypermethrin, 92% purity, 44% cis and 56% trans. Batch B1947/182/?W (lot number barely legible).

SYNONYMS:

CITATION: J.B. Glaister (4 other authors). 1980 "PP383: 90 day feeding study in rats". ICI Central Toxicology Laboratory, Study No.: CTL/P/327. January 8, 1980. MRID No.: 00056802 and 92027034. Unpublished.

SPONSOR: Not specified.

EXECUTIVE SUMMARY:

In a subchronic toxicity study (MRID 00056802 and 92027034 cypermethrin (92% purity) was administered to four groups of 20 SPF Alderley Park strain rats/sex at dose levels of 0, 75, 150 or 1500 ppm (corresponding to 0, 3.75, 7.5 or 75 mg/kg/day) for 90 days. Groups of 4/sex/dose were allowed 28 days for recovery.

The male rats dosed with 7.5 mg/kg/day had increases (260%) in hepatic aminopyrine demethylase. This was increased to 539% in the 75 mg/kg/day dose group. Females (466%) were increased in the 75 mg/kg/day dose group only. Recovery was evident after 28 days. Body weight was decreased in the 75 mg/kg/day dose groups for both males (i.e. 17% at week 9) and females (i.e. 8% at wee 9). **The LOEL is 1500 ppm (75 mg/kg/day) based on body weight. The NOEL is 150 ppm (7.5 mg/kg/day).** The increase in hepatic aminopyrine demethylase is considered a physiological rather than toxicological response but its presence is indicated.

This subchronic toxicity study is classified SUPPLEMENTARY and does not satisfy the guideline requirement for a subchronic oral study (82-1) in rats. The study does not require upgrading because an acceptable chronic feeding study with rats is available.

COMPLIANCE: The study is circa 1980 and only a signed and dated Quality Assurance statement was provided.

A copy of the original DER from HED Document No.: 004825 dated October 28, 1981 is attached. In addition to the DER the following tables are included to support the NOEL and LOEL and to illustrate the results of the hepatic aminopyrine demethylase results.

Table 3 (males) and Table 4 (females) Intergroup comparison of body weights.

These tables are not readable in many places but are included because they still clearly show which weeks the high dose group was statistically significantly greater than the controls.

It should be noted that body weight gain was also said to be decreased in the early weeks of the study but no table of body weight gain was included in the report. This generalization was made from Tables 3 and 4 but can't be verified with the available copy.

Table 5a (males) and Table 6a (females) Intergroup comparison of bodyweight (recovery groups).

These tables are for the recovery group but photocopied better than Tables 3 and 4. The percent difference can be calculated such that it can be shown that there is a 17% decrease in male weight at week 9 for males and a 8% decrease for females at this interval.

Table 17. Hepatic aminopyrine demethylase.

Table included to illustrate the increase and its reversibility. Increases in this enzymes activity are considered to be a response to a xenobiotic and involved in detoxification.

004825

Challenge - Fourteen days after the last induction dose the animals were given a challenge application of 0.3 ml of a 5% (w/v) solution of cypermethrin in maize oil/animal. The challenge application was evaluated 24 and 48 hours after the removal of the dressings.

Results: No guinea pig showed signs of sensitization. Some signs of irritation developed during the induction period only. Core Guidelines.

PP383: 90-Day Feeding Study in Rats

Central Toxicology Laboratory, issued January 8, 1980, Report No. CTL/P/327.

Four groups of 20 male and 20 female SPF Alderley Park rats were dosed (fed) with 0, 75, 150, or 1500 ppm of cypermethrin (92% pure, 44% cis, 56% trans) for a period of 90 days. After 90 days, 16 from each group were sacrificed and 4 were placed on a control diet for 28 additional "recovery" days.

Results:

1. Clinical Observations:
No deaths occured during the experiment. The animals developed conjunctivitis and all experimental groups were affected. No evidence of neuro-muscular impairment was noted by testing the animals in the rotating wheels (test were made weekly). No abnormal eye lesions developed as noted by ophthalmology. Body weight gain was adversely affected in the high dose test group only.

2. Haematology:
Eight animals per group per sex were examined preexperimentally and at 28 days, after sampling by tail vein. At 90 days samples from the same animals were taken by cardiac puncture. Hemoglobin concentration, PCV, total white cell count and plalelet count and bone marrow smears were evaluated. At 90 days prothrombin time and kaolin-cephalin times were determined.

No effects other than an increase in myeloid/erythroid ratio in bone marrow in the mid dose group ("slightly increased") and in the high dose female groups ("increased"). This was not noticed in the recovered animals. Thus, this effect is reversible if it was due to the test chemical.

3. Clinical Biochemistry:
Sampling frequency was same as haematology, except four animals only per group per sex were tested, blood urea, glucose, plasma alanine transaminase and aspartate transaminase were determined.

No effects were noted.

-75
-150
-1500

9

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4. Hepatic aminopyrene demethylase was assayed for liver samples after 90 days and with the animals allowed to recover.

   At 90 days, liver tissue showed elevations for the activity of this enzyme in males in the mid (260%) and high dose (539%) level groups. Only the high dose female (466%) group was elevated.

   After the recovery period, the males were still slightly elevated (146% and 158%).

   This increase in enzyme activity was considered by the testing laboratory to be a physiological response rather than a toxicological response. A physiological NOEL of 75 ppm is supported.

5. Urinalysis: No effects noted.

6. Pathology - Organ Weights:
   No consistent absolute and/or relative changes in organ weight were noted to indicate a true dose response adverse effect.

7. Pathology:
   (Gross pathology was conducted on all animals, histopathology on only the control and high dose groups). Macroscopic and microscopic findings did not indicate adverse effects due to the presence of cypermethrin.

   The central and peripheral nervous systems were specially stained. Electron microscopy revealed that 7 of 16 males in the 1500 ppm group demonstrated variable degrees of splitting and/or vacuolation. Only 2 of 12 control males were reported as having this type of lesion.

   Electron microscopy also revealed increased amounts of smooth endoplasmic reticulum in livers in males and females in the high dose group. The mid dose male group was also affected while the mid dose female group was reported as being minimally affected. This increase in smooth endoplasmic reticulum is thought to be associated with the adaptation of the test animals to the xenobiotic.

   This test is Core Minimum. The individual animal pathology information was not submitted, the data are in summary tables only. A NOEL of 75 ppm for pharmacological effets is supported. The effects noted at 150 ppm are considered to be related to the metabolism of cypermethrin.

   The toxicological NOEL for this study is 150 ppm.

CYPERMETHRIN

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EPA Reviewer: John Doherty
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley, DVM
Review Section IV, Toxicology Branch I (7509C)

7/15/96

SUPPLEMENTARY DATA EVALUATION RECORD
Original DER in HED Document No.: 004825
(attached with supporting tables)

STUDY TYPE: Subchronic Oral Toxicity-feeding - dogs
OPPTS 870.3151 (nonrodent) [§82-1 (b)

DP BARCODE: D180777 SUBMISSION CODE: S422096
P.C. CODE: 109702 TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): WL 43467, technical cypermethrin, 50% cis and 50% trans, 98% purity.

SYNONYMS:

CITATION: A.C. Buckwell and S. Butterworth, 1977 "Toxicity studies on the pyrethroid WL43467: A 13 week feeding study in dogs. Shell Toxicology Laboratory Tunstall, Study No.: 1112, November 1977. MRID No.: 00112929. Unpublished.

SPONSOR: Not provided.

EXECUTIVE SUMMARY:

In a subchronic toxicity study (MRID 00112929) cypermethrin (98% purity) was administered to four groups of 4 beagle dogs/sex at dose levels of 0, 5, 50, 500 or 1500 ppm (corresponding to 0..125, 1.25, 12.5 and 37.5 mg/kg/day) for 13 weeks.

Responses to treatment were noted at 37.5 mg/kg/day in both sexes and consisted of whole body tremors, exaggerated gait, ataxia, incoordination, hyperaesthesia, licking and chewing of paws as well as diarrhea and anorexia and decreased body weight. **The LOEL is 1500 ppm (37.5 mg/kg/day, based on clinical signs indicating neurotoxicity. The NOEL is 500 ppm (12.5 mg/kg/day).**

This subchronic toxicity study is classified SUPPLEMENTARY and does not satisfy the guideline requirement for a subchronic oral study (82-1) in dogs. The limiting factors include no data tables for clinical signs to determine their onset and duration, there is no discussion of the body weight effect at 1500 ppm and the copy available is unreadable in most places.

COMPLIANCE: The study is circa 1977 and signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were not provided.

A copy of the original DER from HED Document No.: 004825 dated October 28, 1977 is attached.

Comments: The study was retrieved from the OPP Document Center but the paper copy made available to HED from the fiche was in most places unreadable. It will be impossible to verify the findings without obtaining an original copy of this study report.

The LOEL is based on clinical signs but the study report does not present a data table which identifies which dogs were affected with which signs and their onset and duration. Only a summary of the effects is presented in the Results and Discussion section of the report (an attempt to photocopy this page is attached). Some indications of the effects can be scrounged from this photocopy.

This study can be used for regulatory purposes depending upon ones acceptance of the original DER which was prepared using a readable copy of the study report and the photocopies as attached to support the NOEL and LOEL.

Table 1. "Mean bodyweight of dogs fed WL 43467 for 13 weeks" is as photocopied from the study report is attached.

This table, although barely readable, clearly shows that both the male and female high dose groups were statistically significantly lower in bodyweight at week 1 and remained lower throughout the 13 weeks. This is consistent with the reports of this dose group having diarrhea and anorexia.

The indication of reduced body weight was not included in the orignal review probably because the toxicity in the nervous system was so severe (i.e. ataxia and tremors etc) that a LOEL was already identified. The effect on body weight should be identified. The study report mentions this effect only in the the study summary but does not discuss it in the results section of the report.

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004825

Toxicity Studies on the Pyrethroid Insecticide WL43467: A 13-Week Feeding Study in Dogs

Shell Toxicology Laboratory (Tunstall), November, 1977, Exp. No. 1112.

Twenty male and twenty female beagle dogs (8 + 3 months of age) were grouped 4/sex/dose level into five groups and dosed with 0, 5, 50, 500 or 1500 ppm of WL43467 (50% cis, 50% trans cypermethrin) for a period of 13 weeks.

Results:

Clinical Observations: Signs of intoxication were reported in the high dose male and female dogs only. These signs included diarrhea, anorexia, licking and chewing of the paws, whole body tremors, exaggerated gait, ataxia, inco-ordination and hyperaesthesia. Two male and two female dogs in the high dose group had to be sacrificed prior to scheduled termination. Symptoms of intoxication were not reported as being present in dogs in the other test groups.

Opthalmoscopic examination (prior to administration of test chemical and prior to sacrifice) no compound related effects noted. No histopathology was associated with the eyes.

Haematology (pretest, weeks 1, 4, 8, and 13 with venous blood) haemoglobin content, packed cell volume, erythrocyte count, leucocyte count, prothrombin time and kaolin-cephalin clotting time (KCCT). Differential leucocycte counts in control and top dose groups only. No consistent dose related adverse effects were noted.

Clinical Chemistry (pretest, weeks 1, 4, 8 and 13) total plasma protein, urea, sodium, chloride and potassium ion concentrations and the activities of plasma alkaline phosphatase, glutamic-pyruvic transaminase, glutamic -oxaloacetic transaminase and blood glucose.

No consistent dose related adverse effects were noted.

Organ Weights (brain, heart, liver, thyroid, adrenal, kidneys, testes). No consistent effects for animals receiving 500 ppm or less. Organ weights were probably affected in the high dose group but there were not enough survivors in this group to compute reliable differences.

Pathological Findings: (at least 26 organs or tissues per dog were examined) Signs of "non-specific pathological" changes were noted in the high dose group dogs only. These changes, including focal bronchopneumonia, were said to be expected in cases of severe intoxication.

Conclusion: This test is Core Minimum. Only 4 dogs/sex/dose group were used. A NOEL of 500 ppm is supported.

11

0, 5, 50, 500, 1500

1.25 1.25 12.5

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CYPERMETHRIN

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Pages 39 through 40 are not included.

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____ Identity of product inert ingredients.

____ Identity of product impurities.

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____ The product confidential statement of formula.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

EPA Reviewer: John Doherty 7/30/91
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley, DVM
Review Section IV, Toxicology Branch I (7509C)

SUPPLEMENTARY DATA EVALUATION RECORD
Original DER in HED Document No.: 002391
(attached with supporting tables)

STUDY TYPE: Subchronic Dermal Toxicity- Rabbits
OPPTS 870.3200, 82-2

DP BARCODE: D180777 SUBMISSION CODE: S422096
P.C. CODE: 109702 TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): Technical cypermethrin (53:47 cis:trans, 91.5% purity, sample p19).

CITATION: C. Henderson and G.R. Parkinson, 1981, "Cypermethrin Technical: Subacute Dermal Toxicity in Rabbits". ICI Laboratory. Study No.: LB0019, Reference YO0334/017/002. February 4, 1981.

SPONSOR: ICI

EXECUTIVE SUMMARY:

In a 21-day dermal toxicity study (MRID No.: 00090035) with rabbits, 10/sex/dose group, cypermethrin was applied at dose levels of control, 2, 20 or 200 mg/kg/day applied in 20% (w/w) PEG 300 with daily applications for three weeks for a total of 15 applications. 5/sex/group were abraded prior to application of the test material.

At 200 mg/kg/day, liver necrosis was noted in 4 of 5 females and 3 of 5 males with abraded skin. Two of 5 females but no males with unabraded skin were also affected. There was also a possibility of an effect on the testis since there was a decrease in absolute (19%, $p < 0.05$) and relative (15%, not significant) weight that was not accompanied by pathological changes. 200 mg/kg/day was considered a threshold level for clinical signs (i.e. flaccid body, salivation). There was local site of application irritation noted in all dose groups. **The LOEL is 200 mg/kg/day based on liver effects. The NOEL is 20 mg/kg/day.**

This subchronic dermal toxicity study is classified ACCEPTABLE and satisfies the guideline requirement for a subchronic dermal study (82-2) in rabbit.

COMPLIANCE: A signed and dated Quality Assurance statement was provided.

A copy of the original DER from HED Document No.: 002391 dated 12/28/82 is attached. In addition to the DER the following

support the NOEL and LOEL and to clarify the liver pathology response and body weight effect.

-Table 34. Cypermethrin Technical: Subacute Dermal Group Mean Organ Weights (g) for male rabbits.

This Table indicates that at 200 mg/kg/day, the absolute weight of the testis is 19% less ($p < 0.05$) than the control and other groups and that relative weight is also less (15%) than the control but does not reach statistical significance.

-Table 67. Summary of Pathological Findings. Separate pages for the liver and testis are provided.

The liver shows more incidents of focal necrosis in the high dose groups for males and females in the abraded animals but only in females for the unabraded animals.

The testis data indicate that there was no dose related pathology in this organ that accompanied the 19% decrease in organ weight at 200 mg/kg/day.

-The following table was prepared to illustrate the clinical reactions.

Symptom	Males (mg/kg/day)				Females (mg/kg/day)			
	Control	2	20	200	Control	2	20	200
Subdued behavior (usually slight)	-	-	-	1	1	2	0	3
Fecal incontinence	-	3	-	-	2	3	2	3
Flaccid	-	-	-	-	-	-	-	2
Salivation	-	-	-	-	-	-	-	1
Urinary incontinence	-	-	-	1	-	-	-	1
Sore limbs	2	2	-	1	-	2	1*	1
Limbs swollen	1	-	1	2	1	1	4	1
Eye red/discharge	-	1	-	1	-	-	-	-

*One rabbit had a broken leg.
Based on 10 rabbits/sex/group.

In general, there are no pronounced effects on clinical signs. The increase in salivation and flaccid appearance suggest a effect on clinical signs at the highest test dose since these signs might be expected to result from pyrethroid intoxication. The subdued behavior and fecal incontinence also might suggest an effect but these symptoms were noted at lower doses and there is no dose response. In conclusion, the 200 mg/kg/day dose group is considered a threshold level for clinical signs (i.e. flaccid body and salivation).

Interstitial Cell Adenomas

Dose Group	52 weeks to termination	Termination	Total
Control - 1	2/25	5/27	7/52*
Control - 2	0/22	8/28	8/50
20 ppm	0/26	7/26	7/52
150 ppm	2/28	5/21	7/49
1500 ppm	6/24^{xx}	7/27	13/51^{NS1}

* incidences/number examined (does not include rats dying in first year).

^{xx} P=.007) Fisher's one-tailed P
^{NS1} P=.098) statistic by TB computer.

Only the rats which died prior to termination of the study showed a statistically significant increase in this tumor type (at the high dose level only).

Nonneoplastic pathology of the testis was unremarkable in that only non-dose-related lesions were present. The report indicated that there were slight increases in incidences of tubular atrophy and calcification of the testes. Testes weight changes did not show statistically significant increases. An 18% apparent increase in relative weight is reduced to 7% when one extreme value is eliminated from the high dose test group.

TB notes that at least one other synthetic pyrethroid has been demonstrated to induce testicular interstitial neoplasms in rats. However, due to the failure of the data with cypermethrin in the above table to reach consistent statistical significance, TB cannot conclude from these data that the testis is a neoplastic target organ for cypermethrin.

3. Pathology of the nervous system. At least some synthetic pyrethroids have given indications that a particular type of axonal lesion results from exposure to high doses. The sciatic nerves were routinely fixed in formol saline and examined in this study. In addition, some special examination of the sciatic and posterior tibial nerves was conducted by fixing the tissues in formol glutaraldehyde and embedding in glycol methacrylate. The nerves were cut and stained in H&E and in addition were stained by Palmgrins silver impregnation techniques for axons and the solochrome cyanin technique for myelin. Histological findings did not reveal a test chemical effect in the structure or integrity of

the nerves from rats dosed with cypermethrin. The overall incidence of l- ions in nerve tissue is shown in the following table.

Sciatic Nerve-Neuropathy

	Males				Females			
	Combined Control	20 ppm	150 ppm	1500 ppm	Combined Control	20 ppm	150 ppm	150 ppm
Number examined	102	49	47	51	102	48	50	51
minimal/slight	31	13	14	13	40	18	26	21
moderate/marked	64	32	27	33	55	23	23	28
severe	5	1	3	3	0	2	1	1

4. Examination of the pituitary revealed frequent occurrences of adenomas and occasional carcinomas but there was no evidence of a dose response. There were 66 incidences of adenomas among the male groups and 213 incidences among the females. These were distributed as 22/61, 12/64, 15/55, 10/59 and 7/57 among the males and 46/62, 46/63, 38/59, 42/62 and 41/61 among the females for the controls, low, mid and high dose test groups.

There were 2 incidences of carcinomas in the pituitary for the males (a control and low dose group) and 13 incidences among the females. There were 4, 2, 1, 2 and 4 in the control groups, low, mid and high dose groups respectively (see above for denominators.)

There was no indication that the pituitary neoplasms developed earlier in the rats dosed with cypermethrin.

Other Oncogenic Aspects

The following table indicates the total number of neoplasms in each group (not including testicular interstitial adenomas, pituitary adenomas or generalized lymphosarcomas):

	Incidences of Neoplasms*	
	Males	Females
Control-group #1	35	32
Control-group #2	30	47
20 ppm	34	28
150 ppm	27	32
1500 ppm	35	37

* Total of 64 rats in each group.

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The various neoplastic types which developed did not show evidence of being related to increasing the dose of cypermethrin in the diet.

Conclusion: This study is CORE GUIDELINES. A NOEL of 150 ppm is assigned. Some minor developments (slight weight loss, increased SER and blood effects) are not considered sufficient to determine that 150 ppm is a LEL. The LEL is 1500 ppm, at this level there is weight loss, general changes in blood elements and cholesterol levels and evidence of liver weight increases.

No evidence that cypermethrin induced an oncogenic response at up to and including 1500 ppm was presented.

Cypermethrin Technical: Subacute Dermal Toxicity Study in Rabbits. 0025

Central Toxicology Laboratory, ICI, Study No. LB0019, Feb. 4, 1981, EPA Acc. No. 070564[redacted], TAB # 17C

Four groups of 10 male and 10 female New Zealand White rabbits which were 77-119 days of age at the start of the experiment were prepared by clipping and half from each group were further abraded. Additional clippings and abrasions were made during the experiment. The rabbits were dosed with 0, 2, 20 and 200 mg/kg/day of cypermethrin (91.5% purity, 53/47 cis/trans) dissolved in polyethylene glycol. The dose was administered at 1 ml/kg and kept in contact for six hours by means of occlusive dressings. A total of 15 applications were made during the 21 day exposure period (a series of three 5 consecutive applications were made).

Results:

1. Clinical observations - Fecal incontinence and subdued behavior were noted but the data do not indicate clearly if the test animals were more adversely affected than the controls. The rabbits showed signs of local dermal irritation which was most severe in the high dose test group. The low dose group was slightly affected.

2. Body weight - The female high dose test group was shown to be adversely affected (less body weight gain). The abraded females were affected to a greater degree and only this group attained statistical significance.

3. Organ weights (the liver, kidney, adrenals, heart, gonads, thyroid and pituitary were weighed). Of these organs, only the high dose male group testes were apparently affected. For example, the absolute weight was 19% lower and the relative weight was 15% lower.

4. Biochemical analyses - Samples were taken from the central ear artery before the first application and 18 hours after the final application. Plasma urea, glucose and triglycerides, aspartate transaminase, alanine transaminase, and alkaline phosphatase, Ca++, Mg++, phosphorous, total protein, albumin, cholesterol, Na+, and K+ were determined using laboratory test kits.

   No consistent adverse effects on these parameters were noted.

5. Hematology - Samples were taken from the ear artery before the first application and 18 hours after the final application. Hemoglobin, hematocrit, total white cell count, red cell count, mean cell volume, mean cell hemoglobin and mean cell hemoglobin concentrate were measured by a Coulter counter. Platelet count was determined by an "auto counter."

   With the exception of apparent decreases in total white blood cell counts in the high dose groups (in females) and, in particular, decreases in lymphocytes at all dose levels (-30% maximum) in females, there were no other apparent effects of cypermethrin on the blood.

6. Gross Pathology - (No table summarizes the results, they are presented in the individual animal pathology sheets). No increases in gross necropsy observations noted, except for possible increases in miscellaneous changes in the liver in the mid and high dose group rabbits.

7. Histopathology - Lesions of various kinds were reported in the adrenals, brain, heart, skin, uterus, subcutaneous tissue, fallopian tube, kidneys, liver, lungs, thyroid, and thymus.

Of these tissues, the liver was reported as having increased incidences of necrosis in the high dose groups only and abraded rabbits were more frequently affected than the nonabraded. The heart may also have been affected with higher incidences of myocardial fibrosis. There were an insufficient number of test rabbits at each dose level to conclude formally that these organs were adversely affected by these commonly occurring lesions.

Conclusion - This study is CORE MINIMUM.

A NOEL of 20 mg/kg/day is assigned.

The effects at 200 mg/kg include liver necrosis and some loss in weight gain and possible decreases in testes weight without associated pathology. The dermal irritation effects are not included in the NOEL but their presence is indicated. The differences noted in decreases in white blood cell counts are not considered by this reviewer to be a response to the test chemical, chiefly because there is no dose response and this type of reaction is not characteristic of pyrethroids.

CYPERMETHRIN

Page_____ is not included in this copy.

Pages 45 through 47 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.

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[Cypermethrin/1982] Chronic Oral Study-dog (83-1(b))

EPA Reviewer: John Doherty
Review Section I, Toxicology Branch IV (7509C)
EPA Secondary Reviewer: Marion Copley, DVM
Review Section I, Toxicology Branch IV (7509C)

6/28/96

6/28/96

SUPPLEMENTARY DATA EVALUATION RECORD
Original DER in HED Document No.: 003249
(attached with supporting tables)

STUDY TYPE: Chronic Oral Toxicity (capsule) - dog.
OPPTS 870.3151 (nonrodent) [§82-1 (b)

DP BARCODE: D180777
P.C. CODE: 109702

SUBMISSION CODE: S422096
TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): Cypermethrin, batch p26, 90.6% purity and 53.9% cis and 46.1% trans.

SYNONYMS:

CITATION: A.E. Kalinowski (5 other authors), 1982, "Cypermethrin: One year oral dosing study in dogs" ICI Central Toxicology Laboratory, Study No.: PD0398, July 6, 1982. MRID No.: 00112909, 42068503, 92027037. Unpublished.

SPONSOR:

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 00112909, 42068503, 92027037) cypermethrin (90.6%) dissolved in corn oil was administered to 4 groups of 6/sex beagle dogs in gelatin capsules at dose levels of 0, 1, 5 or 15 mg/kg/day for 52 weeks.

The males (4.75 fold) and females (10 fold) dosed with 5 mg/kg/day had increased incidence of passage of liquid stools starting in the first week of dosing and the incidence of this condition greatly increased to 31 fold at the 15 mg/kg/day dose level compared to controls. At 15 mg/kg/day, body tremors, gait abnormalities, uncoordination, disorientation and hyper-sensitivity to noise were evident in the first week in addition to body weight decrease. **The LOEL is 5 mg/kg/day based on gastrointestinal effects. The NOEL is 1 mg/kg/day.**
This chronic toxicity study is classified ACCEPTABLE and satisfies the guideline requirement for a chronic oral study (82-1) in the dog.

COMPLIANCE: A signed and dated Quality Assurance statement was provided. GLP, Data Confidentiality and Flagging statements were not provided.

A copy of the original DER from HED Document No.: 003249 dated September 16, 1983 is attached.

In addition to the original DER, the following tables photocopied from the study report are attached.

Appendix 7. (one page of the several pages for this appendix). Summary of frequency of principal neurotoxic effects seen in the 15 mg cypermethrin/kg/day group - male.

Presented to illustrate the incidence of tremors and abnormal gait. Only males are presented as an example.

Table 4. Incidence of fluid feces-expressed as number of observations per week for females.

Presented to support the NOEL and LOEL for this study. Females are presented because males are less affected at the LOEL (5 mg/kg/day).

Table 7. Male group mean bodyweights and body weight gain.

Presented to illustrate effects on body weight and gain. Only males are presented as an example.

Table 15. Group mean red blood cell count in females.

Presented to support the contention that there are no changes in red blood cells that may be in conjunction with a possible effect in the spleen.

Table 77. Group mean spleen weight (g) by sex.

Presented to support the contention that there are no weight changes in the spleen that may be in conjunction with a possible effect in the spleen.

Table 79. Incidence of pathological findings in all animals. (only data for spleen are illustrated to show a possible increase in "sidero-fibrotic nodules of fibrous capsular thickening".

It is noted that the high dose level has the highest incidence of this condition. There were no supporting conditions found in spleen weight or red blood cell count or hemoglobin or hematocrit that might be expected to change if there were a pathological condition of the spleen.

A. Cypermethrin: One Year Oral Dosing (Gelatin Capsule) Study in Dogs

Central Toxicology Laboratory, ICI, # CTL/P/703, July 6, 1982, EPA Acc. No. 071069, TAB 49C.

B. Substance tested: RS-α-cyano-3-phenoxybenzyl (IRS)-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcycloproanecarboxylate or cypermethrin. The material was identified as being from batch No. P26 Ref. No. C4921/187 or Y00334/017/005. The purity was stated as being 90.6% (w/w) and as being 53.9% cis: 46.1% trans. The impurities (9.4%) were not identified.

C. 4 groups of 6 beagle dogs (Alderly Park strain, 16-20 weeks old) of each sex were dosed with 0, 1, 5, or 15 mg/kg/day of cypermethrin in corn oil for 52 weeks. The test chemical was administered by gelatin capsule and the amount administered was based on the current weight of the dog. The dose level was adjusted for the 90.6% purity of the test material. Water was available ad libitum.

D. Ten preparations of cypermethrin in corn oil were made and each of these were analyzed for their content. The analysis revealed that the actual level was similar (within 10%) to the desired level.

E. Survival and reactions to the test chemical. There were no mortalities.

Males and females in the high dose (15 mg/kg) test group (only) displayed signs of nervous system stimulation in the form of body tremors, gait abnormalities and uncoordination, disorientation, and hypersensitivity to noise. These symptoms would be expected in test animals dosed with high levels of synthetic pyrethroids.

Detailed neurological examination was said to have been conducted which evaluated some 21 parameters involving reflexes, cranial nerve function, postural reactions, attitudinal reactions and assessment of temperment. The report states that these studies did not reveal additional information (about the neurotoxicity of cypermethrin) but there were no tables or other indication showing the data or extent of investigations.

The dogs dosed with cypermethrin showed increases in vomiting during the first week and the passing of liquid feces throughout the study, symptoms which have been associated with synthetic pyrethroids in other dog studies especially when gelatin capsules and corn oil are used. The incidences of the passing of liquid stools over the 52 week period is given below:

	Males	Females	
Control	28	25	
Low (1.0 mg/kg)	19	36	
Mid (5.0 mg/kg)	133	254	LEL
High (15.0 mg/kg)	875	767	

There is noted an increase of about five-fold for males and about ten fold for females in the groups dosed with 5 mg/kg/day. There is about a 30-fold increase in incidences for the groups dosed with 15 mg/kg/day. A true NOEL is 1.0 mg/kg/day for this effect.

F. Body Weight and food consumption. A NOEL is set at 5 mg/kg/day for males and females. It is noted that a trend toward lower weight gain was evident in the mid (5 mg/kg/day) male group. Loss of appetite was noted only in the high dose test group.

NOTE: For sections G, H and I below, analyses were made at pretest and in weeks 4, 8, 12, 16, 20, 26, 39 and 52. Jugular vein blood was used for hematology and clinical biochemistry. Urinalysis was performed at pretest and at weeks 8, 16, 24, 39 and 50.

G. Hematology included determinations on hemoglobin, hematocrit, RBC, MCV, mean cell hemoglobin, mean cell hemoglobin concentration, total and differential white blood cell count, platelet count and prothrombin times. No consistent dose related changes in these parameters were noted.

H. Clinical biochemistry determinations were made on BUN, glucose, triglycerides, albumin and total protein, cholesterol, Ca^{++}, K^{+}, alkaline phosphatase, alanine transaminase, aspartate transaminase, and creatine kinase. Occasional deviations from the control values were noted but there were no consistent dose related changes reported.

I. Urinalysis determinations were made on glucose, ketones, urobilinogen, pH, specific gravity and protein. No consistent dose related effects were reported.

J. Gross Pathology - The gross necropsy observations are included on the individual animal pathology sheets but the data are not tabulated in a summary table. Inspection of the individual dog pathology sheets did not reveal the presence of a specific type of grossly observable lesion associated with the treated dogs.

K. Organ weights- The liver, heart, adrenal, thyroid, brain, pituitary, lung, thymus, kidney, spleen and gonad weights were determined at sacrifice. The following changes in organ weight were noted:

a. The liver was slightly higher in weight but statistical significance was not attained. For example, the high dose group females were 6.4% higher. No definite dose related toxic chemical effect is noted. (Note: liver weight increases are known to be associated with higher doses of synthetic pyrethroids).

b. The heart weight of the high dose group males was statistically significantly lower (-6%).

c. The adrenal weight in males was 19% higher or 11% higher depending upon exclusion of a single dog from the control group with a small adrenal.

All other organs did not show statistically significant differences in weight. The overall conclusion is that a NOEL of 15 mg/kg is supported for organ weight changes. It should be noted that at 15 mg/kg the effects noted on the heart and the adrenal are not definitely related to the test material in the opinion of this reviewer.

L. Microscopic pathology. The protocol provided that all dogs were to be evaluated for 37 tissue types. The pathologist responsible for evaluation of the tissue was S.F. Moreland (Pathologist/Veterinarian). The following individual tissue types are discussed as follows.

a. No dose related changes in the structure of the liver were reported. The lesions reported were fibrosis, bile duct proliferation, increased golden pigment accumulation, necrosis and inflammatory cell infiltration, but these were in all dogs in the study.

b. The lungs of the male dogs had 1, 1, 1 and 3 incidences of granuloma (out of six dogs), but this nonneoplastic lesion is not considered to be definitely related to the presence of the test chemical. A similar increase in females was not evident.

c. The spleen had increased incidences of "siderofibrotic nodules or fibrous capsular thickening" in the high dose test groups of both males and females. In males there were 2,3,3 and 4 incidences and 2,3,3, and 5 incidences among the females for the control, low, mid and high dose test groups (out of six dogs). In the absence of changes in hematology parameters, this effect in the spleen is not considered to be a definite test chemical effect by this reviewer.

d. There were reported 0, 1, 2 and 3 incidences (of 6 dogs per group) of "focal interstitial lymphocytic infiltration" among the control, low, mid and high dose test groups in the epididymis to indicate a possible chronic inflammatory process. In other organs (e.g., the salivary gland) a similiar lesion was noted as occurring at higher incidences in the control groups.

e. There was a single tumor noted in one dog of all of the dogs on the study at termination. This was a hamartoma in a high dose test group male. One female had a benign papilloma surgically removed from its lip. Thus, cypermethrin did not give indications of being oncogenic in this dog study.

Conclusion. This study is classified as Core Guidelines. TB is unable at this time to assign a toxicological NOEL for this study. The dogs dosed with 5 mg/kg/day (the level suggested by the registrant as the NOEL) had a clearly increased incidence of liquid stools. This effect could be a result of stimulation of the central nervous system (or the peripheral nervous system) by the test material or could be the result of some other (presumably local) action.

In order to resolve this issue a study in which dogs are treated intravenously with cypermethrin and their bowel movements monitored should be conducted and submitted. For more details and a rationale for this requirement, see 2. under Comments (page 3 of this review).

CYPERMETHRIN

Page_____ is not included in this copy.

Pages 54 through 61 are not included.

The material not included contains the following type of information:

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_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

EPA Reviewer: John Doherty 7/23/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley
Review Section IV, Toxicology Branch I (7509C)

SUPPLEMENTARY DATA EVALUATION RECORD
Original DER in HED Document No.: 003249
(attached with supporting tables)

STUDY TYPE: Carcinogenicity (feeding) Study - mice. 83-2

DP BARCODE: D180777
P.C. CODE: 109702

SUBMISSION CODE: S422096
TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): Cypermethrin (91.5-94.2% purity). Cis:trans ratio 53:47 and 54:46 from batches P19, ACD/79/134 and 47.

SYNONYMS:

CITATION: S. Lindsay (5 other authors), 1982. "Cypermethrin: Lifetime Feeding Study in Mice". ICI Central Toxicology Laboratory, Study No.: CTL/P/687, June 1982. MRID No.: 00112911 and 92027038. Unpublished.

SPONSOR: Not specified.

EXECUTIVE SUMMARY:

In a carcinogenicity study (MRID 00112911 and 92027038) cypermethrin (53-54% cis and 46-47% trans) was administered to groups of 70/sex Swiss derived Alderley Park strain SPF mice at dose levels of control-1, control-2, 100, 400 and 1600 ppm (corresponding to 0, 0, 14, 57 or 229 mg/kg/day) for 97 weeks for males and 101 weeks for females.

Liver weight was increased at 57 mg/kg/day (20% absolute weight) and above in males and for females at the high dose only (15% for relative weight) at the interim sacrifice but not at the terminal. Other systemic effects were noted at 229 mg/kg/day included reduction in RBC parameters (hemoglobin, hematocrit and RBC count in males, mean cell volume and hemoglobin) and platelet counts (for males at interim but not terminal sacrifice) and neutrophils and body weight gain (i.e. about 9% at week 6 for males and 12% for females at week 11). **The LOEL is 400 ppm (57 mg/kg/day) based on liver weight. The NOEL is 100 ppm (14 mg/kg/day).**

This study was determined to be **positive for induction of benign alveologenic neoplasms.** Adequacy of dosing for carcinogenicity is based upon typically 9% decreases in males and 12% in females in the first months of the study.

This carcinogenicity study is classified ACCEPTABLE and satisfies the guideline requirement for a carcinogenicity study (83-2) in mice.

COMPLIANCE: The study is circa 1980-82 and only a signed and dated Quality Assurance statement was provided.

A copy of the original DER from HED Document No.: 003249 dated September 16, 1983 is attached.

Table 8 (males) and Table 9 (females) photocopied from the study report are attached to illustrate the effects on body weight.

00324

A. Cypermethrin: Lifetime Feeding Study in Mice

Central Toxicology Laboratory, ICI, #CTL/P/687, June 1982. EPA Acc. No. 071072 and 071073(TAB 51C) and 071570.

B. Substance tested: The test material was cypermethrin technical (PP383; WL43467) or RS-α-cyano-3-phenoxybenzyl (IRS)-cis,trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylate. The test material was obtained from the ICI Company (reference no. P19 with a purity of 91.5% w/w and cis:trans ratio of 53:47) or from the Shell Company (reference no. ACD/79/134 or Batch 57, with a purity of 94.2 or 94% and a cis:trans ratio of 54:46).

C. The test mice were obtained from the Alderley Park stock of Specific Pathogen Free Swiss derived strain. Five groups of 70 male and 70 female mice were selected and dosed as either control (2 groups) or 100 ppm, 400 ppm or 1600 ppm of cypermethrin in their diets. Of these, 9-10 males and 9-10 females per group were selected at 52 weeks for an interim sacrifice. Mice were delivered at 19 days of age and were 4-5 weeks old at the start of the study. They were housed 5/cage by sex.

D. Diet analysis. Periodic dietary analyses were made on some 23-24 occasions. Usually the achieved concentration of cypermethrin in the diet was within 10% of the expected level. Tests for homogeneity showed uniformity within the diet batch and cypermethrin was shown to be stable in the diet for over a three month period.

E. Survival and clinical responses to the test chemical. No obvious test chemical effects were reported in the behavior of the test mice. Signs of neurological effects which might be expected in animals treated with a pyrethroid were not reported as developing.

No test chemical effect on survival was noted. The males were sacrificed at week 97 when there was 72.7 to 84.7% mortality in the five groups. The females were sacrificed at week 101 when there was 76.7 to 88.9% mortality among the groups. For both sexes about 50% mortality was reached at about week 80-84. There were 13, 15, 16, 9 and 13 males and 14, 10, 9, 12 and 7 females which survived through weeks 96 or 100 respectively.

F. Body weight gain was decreased in the high dose test groups (males and females) only. Statistical significance in the difference for the high dose test groups was evident only in the first year, but a weight difference was still evident in the latest weeks. For example, at week 6 the high dose males were about 10% lower in weight than the controls, at week 80 they were 13.5% lower.. The females were 9% lower at week 6 and 7% lower at week 80. The low and mid dose groups were essentially similiar to the control groups.

Food consumption and utilization data were collected and periods of lower consumption (although not consistent) for the dosed mice were noted.

G. Hematology - Blood samples were taken from 10 male and 10 female mice at weeks 52 and at termination (where possible). The parameters investigated included determination of hemoglobin, hematocrit, total white cell count, red cell count, mean cell volume, mean cell hemoglobin and concentration, platelet count and examination of peripheral blood films. Several deviations possibly due to the test chemical were noted.

a. Reduction in <u>hemoglobin</u>, <u>hemotocrit</u> and <u>RBC</u> count were noted for males in the 1600 ppm test group at the interim sacrifice but not at the terminal sacrifice.

b. <u>Mean cell volume</u> and <u>hemoglobin</u> were significantly reduced in the females in the high dose test group at the interim sacrifice but not at the terminal sacrifice.

c. <u>Platelets counts</u> were increased for males at both the interim and terminal sacrifice for the high dose group; they were also slightly elevated for the high dose group females at the terminal sacrifice.

d. <u>Neutrophil</u> counts were significantly increased for the males and suggested for the females at interim kill but not at the terminal sacrifice.

e. Eosinophils were statistically significantly reduced at the interim and terminal sacrifice for both the high dose group males and females.

The overall conclusion of the hematology determinations is that a NOEL is set at 400 ppm. At 1600 ppm there are generalized changes in the blood elements. Note a somewhat similiar conclusion was made for the rat chronic feeding study.

H. Clinical Biochemistry - no determinations were made.

I. Urinalysis - No determinations were made.

J. Organ weights. At weeks 52 and at termination the liver, spleen, testes, kidney, lung, heart, and brain weights were determined.

The liver weight was affected at both the interim and terminal sacrifices as shown in the following table:

	Males		Females	
Group	Interim	Terminal	Interim	Terminal
Control - 1	2.83/2.79[1]	2.74/2.89	2.36/2.38	3.08/3.14
Control - 2	2.79/2.81	3.49/3.41	2.46/2.42	2.34/2.35
100 ppm	2.69/2.72	2.90/2.91	2.47/2.59	2.71/2.61
400 ppm	3.37*/3.18	2.81/2.86	2.67/2.59	2.69/2.60
1600 ppm	3.39*/3.56*	3.96/3.88	2.79/2.77*	2.47/2.67

*Statistically significant
[1] absolute weight/relative weight (as adjusted for bodyweight).

At 400 ppm the liver absolute weight is increased by 20% (at the interim sacrifice only). Increases in liver weight are an expected result of ingestion of synthetic pyrethroids.

The testis weight was decreased for the high dose test group (-18% absolute and relative) at the interim sacrifice only.

The other organs did not show consistent evidence of a compound related change in weight.

A NOEL for changes in organ weights is set at 400 ppm. At 1600 ppm there is noted an increase in liver weight. The changes in liver weight at 400 ppm (interim sacrifice only) and testis weight at the highest dose level (interim sacrifice only) are not considered consistent and definite responses to the test material.

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K. Gross Pathology - All mice were reported to be necropsied as soon as possible after death or sacrifice. No tables tabulating the incidences of the various gross pathology findings were presented. The gross pathology for each mouse is described on the individual mouse pathology data sheets. Using these sheets, the extent of followup of the gross pathology by microscopic analysis can be readily determined. In the opinion of this reviewer a satisfactory follow up of gross necropsy lesions with microscopic findings was presented.

L. Microscopic Evaluation:

A series of approximately 45 tissue types and organs from each mouse were taken and examined histologically following fixation. Microscopic examination was performed on all mice dying during the study and on the survivors.

9-10 mice from each group for each sex were sacrificed at 52 weeks for an interim kill; except for the sciatic nerves for selected control and high dose test group mice, no other histopathological analysis of the tissues was made. The tissues from the mice in the interim sacrifice groups were preserved for possible future analysis.

a. Non-oncogenic aspects

A table was prepared at the request of TB which lists and tabulates the nonneoplastic findings for this study. Inspection of this table did not indicate the presence of any dose or compound related increases of nonneoplastic lesions. Major lesions observed were typical of Alderly Park mice and occurred in all groups with similar frequencies. NOTE: This table can be found in EPA Acc. No. 071570. In particular, no evidence of changes in liver pathology were noted at any dose level.

b. Oncogenic aspects.

The following table summarizes the overall neoplastic responses for the mice in this study.

	Males				Females			
	n	Total Incidences (1)	Malignant Incidences (1)	Mice Affected (2)	n	Total Incidences (1)	Malignant Incidences (1)	Mice Affect (2)
ontrol-1	61	66	43	44	61	90	55	54
ontrol-2	60	30	40	40	60	82	47	46
00 ppm	60	93	49	49	61	69	40	44
00 ppm	60	60	31	41	60	74	43	45
600 ppm	61	68	44	47	60	74	45	48

(1) as summarized in Table 55 of the study report.

(2) as indicated in Table 56 of the study report.

n = number of mice (not including those sacrificed at the 1 year interim kill). Inspection of the above table does not indicate an overt or obvious increased incidence of neoplasms or increase in malignancy in treated mice. Certain types of neoplastic findings and selected organs are discussed below. In particular, most of the malignant tumors were in the lymphoreticular system.

1. Lungs: A statistically significant increased incidence of benign alveologenic neoplasms in the lungs of female mice was observed in the high dose test group as shown in the following table:

Alveologenic Tumors

(Total incidences in all observed mice)

	Males[1/]					Females				
Group	n	Benign	%	Malignant	%	n	Benign	%	Malignant	%
Control - 1	61	4	6.6	1	1.6	61	4	6.6	0	0
Control - 2	60	10	16.7	1	1.7	60	4	6.7	2	3.
100 ppm	60	10	16.7	1	1.7	61	6	9.8	0	0
400 ppm	60	6	10.0	0	0	60	7	11.7	1	1.
1600 ppm	61	7	11.5	3	4.9	60	13**	21.6	0	0

**Statistically significant increase P = 0.016 by TB computer using Fisher's one-tailed P statistic.

n = number of mice available for examination.

1/ In addition, one mouse in the low dose test group (males) was reported as having "secondary carcinoma (occult primary)."

Inspection of the summary Table (EPA Acc. No. 071570) for nonneoplastic lesions in the lungs did not indicate increased incidences of lesions which could be interpreted to be pre-neoplastic conditions. There were no dose dependent increases in any of the nonneoplastic lesion types in the lungs reported. Nonneoplastic lesion types were of low frequency (~ 8-9%) with regard to the number of mice affected. Thus, the lung tissue needs evaluation in terms of possible induction of a neoplastic response in females.

TB does not consider that the lungs of the male mice in this study are affected by cypermethrin.

The development of malignant tumors in the three male mice in the high dose test group (3 incidences vs only 1 in each of the controls and low dose group) is considered to be spontaneous and not conclusively linked to the presence of cypermethrin in the diet. Moreover, chemical induction of lung tumors would be expected to be expressed by both increased incidences of benign neoplasms and malignant types. In the case of male mice in this study there is no increase in benign neoplasms.

Malignant neoplasms among the females is not an issue with regards to increased malignancy being related to the presence of the test material in the diet. For example, of the three mice with malignant neoplasms in the lungs, two of these mice were in the control group - 2.

The following table shows the lack of a decreased time for onset of development of lung tumors with the presence of cypermethrin in the diet.

Group		n[1]	Average Week of Death			Week of Earliest Tumors
C-1	0	4	86.50	±	17.08	63
C-2	0	6	85.17	±	17.62	53
Mid	100 ppm	6	90.33	±	10.91	73
Low	400 ppm	8	80.25	±	16.55	46
High	1600 ppm	13	90.92	±	11.10	66

[1] n = mice with benign or malignant neoplasms

Based on these data, it appears that cypermethrin induces an increase in benign alveologenic neoplasms in female mice in the later months of the study.

The registrant/petitioner for the use of cypermethrin (The ICI Corp.) presented historical control data regarding the incidences of benign alveologenic neoplasms. These data indicated that the % of mice affected after 96-99 weeks was 6.8 - 15.7. This information is useful but does not in itself eliminate the possibility that the frequency in the high dose female group (21.6%) was due to chance alone. It should be noted that the two control groups in the study with cypermethrin had 6.6% and 6.7% of the females affected with benign alveologenic neoplasms.

2. Liver: The following table indicates the neoplastic findings in liver in this study with cypermethrin.

Liver Tumors
(Incidences of neoplasms in all observed mice)

	MALES					FEMALES				
Group	n*	Benign	%	Malignant	%	n	Benign	%	Malignant	%
Control - 1	61	11	18.0	11	18.0	61	1	1.6	2	3.3
Control - 2	60	13	21.7	9	15.0	60	2	3.3	5	8.3
100 ppm	60	10	16.7	16	26.7	61	3	4.9	2	3.3
400 ppm	60	10	16.7	12	20.0	60	4	6.7	4	6.7
1600 ppm	61	4	6.6	13	21.3	60	1	1.7	2	3.3

* Number of mice examined.

The above data do not indicate an oncogenic response to cypermethrin in the diet. Inspection of the nonneoplastic findings in the liver also did not indicate evidence of a test chemical effect.

3. Pituitary: The pituitary in females had many instances of adenomas. There were 69 incidences reported but there was no indication of a dose related effect. There were 23/59, 17/57, 6/59, 11/52, and 12/59 instances for the two control groups, the low, mid and high dose test groups respectively. The incidences among the controls were almost twice that of the dose group female animals.

4. Harderian gland: The Harderian gland developed adenomas in both males (total 31) and females (total 21) but there was no evidence of a test chemical related effect.

5. Thyroid: There were a total of 2 tumors in the thyroid reported. Both incidences were follicular carcinomas and both occurred in high dose group males. TB considers this finding not to be related to ingestion of cypermethrin.

6. Haemopoietic and lymphoreticular systems: Many mice in both the male and female test groups developed malignant lymphoreticular tumors. The distribution of the mice affected was reported to be as follows: 28, 24, 29, 17 and 24 among the male groups and 44, 35, 35, 33 and 35 among the female groups for the control-1, control-2, low, mid and high dose test groups. (60-61 mice per group were available for analysis and it is assumed that all of or nearly all of the mice were evaluated for lymphoreticular tumors). Although many mice in this study developed lymphosarcoma, these was no indication presented in the report which indicated that the lymphosarcoma present was influenced by the presence of the test material. In particular, there was no indication that the mice dosed with cypermethrin developed the lymphosarcomas at an earlier time than did the control mice.

The high rate of lymphoreticular tumors suggests that the mice may have been in poor health, particularly in the later weeks of the study. Although this strain of mice is apparently susceptible to this type of tumor, the frequency which was displayed in this study is much greater than at least one other study submitted by the ICI company with a closely related chemical (see the ICI mouse study with permethrin). It is noteworthy that most but not all of the mice with lung tumors also had malignant lymphoreticular tumors. See also 1.b. under Comments (page 2 of this review).

Conclusion: CORE Classification of this study is RESERVED pending submission and review of the histopathology data from the mice sacrificed at the interim kill. See 1.a under Comments (page 2 of this review).

Sufficient data have thus far been presented to indicate that this study shows an apparent oncogenic effect in that there is noted an increased incidence of benign alveologenic neoplasms in the female mice particularly in the high dose test group.

The NOEL for nononcogenic aspects of this study based on the limited observations made is 400 ppm. At 1600 ppm there is noted an increase in liver weight and generalized changes in the blood.

John D. Doherty, Ph.D.
Toxicology Branch
Hazard Evaluation Division
TS769

9/15/83

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Review of Documents Submitted

1. Cypermethrin: Lifetime feeding study in mice, supplement to report CTL/P/687.

   CTL, study no. PM0366, December 12, 1983 (date signed) EPA Acc. No. 072204.

The lung tissues from the mice which were sacrificed for the interim kill were palpated and 5 sections from each lung (reportedly cut in an identical manner from all mice) were prepared for microscopy and read. In addition, a single section from the liver of each mouse from groups sacrificed for the interim kill was also prepared and read.

Table 1 (xeroxed from the study report) shows the results of the neoplastic findings in the lung and liver of the mice sacrificed for the interim kill.

There were no liver tumors found in the females. There were 7 liver tumors (3 benign and 4 malignant) found in the males. The following table illustrates the revised (to include the interim sacrifice data) frequency of liver neoplasms:

	MALES					FEMALES			
	n	Benign	%	Malignant	%	Benign	%	Malignar	
									%
Control - 1	70**	11	15.7	12 (11)	17.1	1	1.4	2	2.9
Control - 2	70	13	18.6	10 (9)	14.3	2	2.9	5	7.1
100 ppm	70	11 (10)*	15.7	16	22.9	3	4.3	2	2.9
400 ppm	70	11 (10)	15.7	13 (12)	18.6	4	5.7	4	5.7
1600 ppm	70	5 (4)	7.1	14 (13)	20.0	1	1.4	2	2.9

*The number in parentheses is the original finding based on all mice except those in the interim sacrifice.
**Note-there were only 69 female mice examined.

The overall result including the mice in the interim sacrifice is that there is no evidence of an oncogenic response of cypermethrin in mouse liver in this study.

There were 10 additional benign alveologenic tumors found in the lungs of the mice in the interim sacrifice. Seven of these were in the male groups and 3 were in the female groups. The following table illustrates the frequency of lung tumors including the mice sacrificed for the interim kill.

	MALES			FEMALES		
	n	Benign	Malignant	n	Benign	Malignant
Control - 1	70	7 (4)*	1	69	5 (4)	0
Control - 2	70	10	1	70	5 (4)	2
100 ppm	70	11 (10)	1	70	6	0
400 ppm	70	7 (6)	0	70	7	1
1600 ppm	70	9 (7)	3	70	14**(13)	0

* The number in parentheses represents the original count, not including the mice sacrificed for the interim kill. Specifically, among the females were three additional benign neoplasms found in the lungs of the mice. These were in each of the control groups, and one in the high dose group.

** The high dose test group (females) is statistically significant ($p < .05$, Fisher's One Tail p Statistic) when either benign tumors or benign plus malignant tumors are compared with the control groups.

The data provided in the supplement confirm that there is no oncogenic response in the male lung tissues, but that there is a statistically significant higher frequency of neoplasms in the female high dose test group. Because two of the three neoplasms found in the female groups were in the control groups, the data in the supplement do not provide a basis that there is an earlier onset of development of the tumors in the female mouse lungs.

Microscopic examination of the mice sacrificed at the interim kill also revealed that there were 8 mice which had malignant lymphoreticular tumors. Among the males, two were in the control groups and two were in the high dose test group. Among the females, there was one mouse affected in the control groups and one in the low dose group and two mice were affected in the high dose test group. Combining the results of the interim sacrifice with the results from the other mice on the study shows that there were 29(28), 25(24), 29, 17, and 26(24) males and 45(44), 35, 36(35), 33, and 37(35) females affected for the control groups, low, mid, and high dose test groups. The number in () is the data not including the interim sacrifice. There is no evidence that the malignant lymphoreticular tumors were induced by the test material. Note: There were about 70 mice per group for all groups.

2. Incidence of malignant lymphoreticular tumors in control Swiss-derived mice.

EPA Acc. No. 072204

The registrant submitted control data from three experiments (5 groups of male and female controls). The data showed that from 6-27% of the male controls and from 18-42% of the female controls had the malignant lymphoreticular condition. By comparison, 24 to 41% of the male mice and 47 to 64% of the female mice in this oncogenicity study with cypermethrin developed this condition.

The registrant also presented graphical data which showed that mortality and bodyweights of the mice in the cypermethrin oncogenicity study were similar to other studies run at the ICI facility although the incidences of lymphoreticular tumors were lower for these studies.

TB notes that the incidences of malignant lymphoreticular tumors in the cypermethrin oncogenicity study was higher than what would be expected for this strain of mouse. There is, however, no evidence that the presence of cypermethrin induced an increase in the number of mice affected, time of onset of this condition or caused an increase in the degree of malignancy, nor was there any relationship between mice having lung tumors and malignant lymphoreticular tumors.

Because malignant lymphoreticular tumors are common in mice, the impact of this condition is not considered to be sufficient to compromise the interpretation of the study. Dr. Louis Kasza, Toxicology Branch staff pathologist, concurs with this conclusion.

Two articles from the literature were presented to further document historical control data for lung neoplasms and the malignant lymphoreticular tumor condition. These articles can be found in EPA Acc. No. 072204.

Sher, S.P.
Tumors in Control Hamsters, Rats, and Mice: Literature Tabulation.
Dated March 1982
CRC Critical Reviews in Toxicology

Sher, S.P.
Review Article: Tumors in Control Mice: Literature Tabulation.
Toxicol. Appl. Pharmacol. 30:337-359 (1974)

3/21/94
John Doherty
Toxicology Branch
Hazard Evaluation Division (TS-769)

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CYPERMETHRIN

Page_____ is not included in this copy.

Pages 75 through 77 are not included.

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EPA Reviewer: John Doherty Date: 7/15/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley Date: 7/15/96
Review Section IV, Toxicology Branch I (7509C)

SUPPLEMENAL DATA EVALUATION RECORD
Original DER HED Document No. 004825
(attached with supporting tables)

STUDY TYPE: Prenatal Developmental Study - Rat
OPPTS 870.3700 [§83-3 (a)

DP BARCODE: D180777 SUBMISSION CODE: S422096
P.C. CODE: 109702 TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): Cypermethrin technical, batch 30, WL 43467, 98.2% purity.

SYNONYMS: WL 43467

CITATION: J.M. Tesh, S.A. Tesh and W. Davies, 1978, "WL 43467: Effect upon the progress and outcome of pregnancy in the rat. Life Science Research, Study No.: 78/SHL2/364, October 4, 1978, MRID No.: 00056804, 92027039 or 92027061. Unpublished.

SPONSOR: Not provided.

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 00056804, 92027039 or 92027061, cypermethrin (98.2% purity) in corn oil was administered by gavage to four groups of 25 mated CD strain Charles River rats at dose levels of 0, 17.5, 35, or 70 mg/kg/day on days 6-15 of gestation. The rats were sacrificed at day 21 of gestation.

Dose levels of 35 (12%) and 70 (28%) mg/kg/day resulted in decreased body weight gain. The dams dosed with 70 mg/kg/day displayed neurological signs such as splayed limbs, spasms, and hypersensitivity to noise and convulsions. **The maternal LOEL is 35 mg/kg/day, based on body weight. The maternal NOEL is 17.5 mg/kg/day.**

No effects on either skeletal or visceral structures were reported. **The developmental LOEL is > 70 mg/kg/day. The developmental NOEL is > 70 mg/kg/day.**

The developmental toxicity study in the rat is classified ACCEPTABLE and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3 (a) in the rat.

COMPLIANCE: The study is circa 1978 and signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements

The original DER from HED Document No.: 004825 dated October 28, 1981 is attached.

There were no individual animal or summary tables to support the reporting of the observation for neurological signs. This is not considered essential for this older study. The study authors description is considered acceptable.

Table 2 (photocopied from the study report) "Group mean bodyweight change (g) of females during gestation" is attached to show the effects on body weight gain. This table clearly shows that on days 6-15 there was a 12% decrease in body weight gain at 35 mg/kg/day and a 28% decrease in body weight gain at 70 mg/kg/day.

Table 3 (photocopied from the study report) illustrates the in utero aspects of this study and does not indicate any adverse effects of cypermethrin treatment.

Tables 4 ("Summary of observations at foetal examination post mortem"), 5 ("Summary of abnormalities found by free-hand sectioning") and 6 ("Results of skeletal analysis") all [photocopied from the study report] are attached to illustrate the findings for visceral and skeletal analysis of the fetuses.

III. **DISCUSSION.** This study is classified as ACCEPTABLE. The study is considered to demonstrate that at dose levels which are maternally toxic, that cypermethrin dose not also cause developmental toxicity in the skeletal or visceral structures of the rat.

The study supports a NOEL and LOEL of 17.5 and 35 mg/kg/day for maternal toxicity and the NOEL and LOEL for developmental toxicity are > 70 mg/kg/day.

WL 43467: Effects Upon the Progress and Outcome of Pregnancy in the Rat (Teratology Study)

Life Sciences Research, No. 78/SHL2/364, October 4, 1978.

Four groups of 25 adult female rats of the CD strain (Charles River) were mated and later were dosed with 0, 17.5, 35.0 or 70.0 mg/kg/day of WL 43467 (98.2% pure) on days 6-15 inclusive of gestation. On day 21 of gestation, the pups were delivered by Ceasarian section. Twenty-five of the control, low and mid dose and 22 of the high dose group rat became pregnant.

Results:

1. Maternal responses. The test groups receiving 17.5 and 35.0 mg/kg/day were reported as being essentially similar in condition and appearance as the control groups. In the high dose test group, 11/25 females displayed transient neurological symptoms (splaying of legs, spasms, and hypersensitivity to noise, and some convulsions).

   The mid and high dose groups failed to gain weight as rapidly as the control.

2. Terminal Studies:

   a. The dams were reported as being unaffected as far as viable young, resorptions, implantation loss, litter weight and foetal weight were tabulated.

   b. The feotuses were also reported as being unaffected by the presence of the test chemical in either the soft tissue or skeletal structures. There were 344, 330, 335, and 307 foetuses available for examination and 2/3 were examined for skeletal defects (by microcopy) and 1/3 were examined for visceral abnormalities by free hand serial sectioning.

This test is Core Minimum. No positive control was included. Cypermethrin did not produce teratogenic effects at doses up to and including 70 mg/kg/day in the rat based on the evidence presented in this study. The exact cis and trans ratio was not stated.

CYPERMETHRIN

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Pages 81 through 85 are not included.

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[Cypermethrin/1978] Developmental Study OPPTS 870.3700 (§83-3(b)

EPA Reviewer: John Doherty 7/15/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley, DVM 7/15/96
Review Section IV, Toxicology Branch I (7509C)

SUPPLEMENTAL DATA EVALUATION RECORD
Original DER HED Document No.: 004825
(attached with supporting tables

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

DP BARCODE: D180777 SUBMISSION CODE: S422096
P.C. CODE: 109702 TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): Cypermethrin, batch No.: 30, 98.5% purity supplied by the Bioscience Division of Sittingbourne Research Centre.

SYNONYMS: WL 43467 or NRDC 149.

CITATION: K.M. Dix, 1978, "Toxicity of WL 43467: Teratological studies in rabbits given WL 43467 orally". Shell Toxicology Laboratory (Tunstall), Study No.: 1103, January, 1978, 00056805. Unpublished.

SPONSOR: Unspecified.

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 00056805), cypermethrin (98.5% purity) in corn oil was administered to banded Dutch rabbits by gelatin capsule at dose levels of 0 (empty capsule), 0 (capsule plus corn oil), 3, 10 or 30 mg/kg/day on days 6 to 18 inclusive of gestation.

There were no effects on the does of any kind reported. **The maternal LOEL is > 30 mg/kg/day. The maternal NOEL is > mg/kg/day.**

There were no treatment related effects on either the skeletal or visceral structures reported. **The developmental LOEL is > 30 mg/kg/day. The developmental NOEL is > 30 mg/kg/day.**

The developmental toxicity study in the rabbit is classified SUPPLEMENTARY and does not satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3b in the rabbit. The study is not considered upgradeable because the dose levels selected are too low.

COMPLIANCE: The study is circa 1978, signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were not provided.

The original DER (dated October 28, 1981) from HED Document No. 004825 for this study is attached.

Table 3 (photocopied from the study report) entitled "Mean bodyweights of pregnant rabbits dosed orally with WL-43467 on days 6-18 of gestation that had live fetuses at term" illustrates the lack of an effect on body weight for this study.

Table A prepared by TB-I contains the cesarian section observations.

The following tables photocopied from the study report are attached to illustrate the assessment of the skeletal and visceral structures for developmental effects.

Table 7. "Results of structural examination for skeletal abnormalities". See also Table 9.

Table 8. "Results of structural examination for visceral abnormalities". This is the best copy available and is difficult to read in some places but shows that there are no differences in counts. In several cases the numbers were written in.

Table 9. "Results of structural examination of rabbit foetuses for visceral and skeletal abnormalities". Verifies Table 8.

Table 10. "Results of structural examination of litters of rabbit foetuses"

III. **DISCUSSION.** This study is classified as SUPPLEMENTARY. The limiting factor is that the dose levels did not elicit maternal toxicity at any dose level and there was no justification for the dose levels selected (i.e. no dose range finding study data).

The study author concluded that there were no maternal or developmental effects of treatment with cypermethrin and TB-I concurs with this conclusion. Thus the NOEL and LOEL are > 30 mg/kg/day.

TABLE A Cesarean Section Observations[a]

Observation	Dose (mg/kg/day)				
	0	LDT	M1DT	M2DT	HDT
# Animals Assigned (Mated)	30	20	20	20	
# Animals Pregnant Pregnancy Rate (%)	24 (80%)	18 (90%)	18 (90%)	17 (85%)	19 (95%)
# Nonpregnant	6	2	2	3	1
Maternal Wastage # Died # Died Pregnant # Died Nonpregnant # Aborted # Premature Delivery	 1 0 0	 0 1 1	 0 1 1	 0 0 0	 1 0 0
Total # Corpora Lutea Corpora Lutea/Dam	Data not provided.				
Total # Implantations Implantations/Dam	Data not provided.				
Total # Litters	23	17	17	17	18
# Live Fetuses/Dam (total not provided)	7.3	8.2	7.2	7.4	7.6
Dead Fetuses/Dam (total not provided)	Data not provided.				
Total # Resorptions (totals not provided) Resorptions/Dam Early ("resorptions") Late ("fetal death") Total Litters with Total Resorptions (not provided)	 0.43 0.35 0.78	 0.59 0.06 0.65	 1.18 0.58 1.76*	 0.47 0.18 0.65	 0.56 0.22 0.78
Mean Fetal Weight (g) Males Females	28	28	28	29	28
Sex Ratio (% Male)	50	50	46	44	56
Mean preimplantation Loss (%)	2.04	2.12	1.35	1.29	2.28
Postimplantation Loss (%)	Data Not Provided.				

a. Data extracted from Tables 2, 4 and 5 of the study report.
* statistically significantly different from control.

Toxicity of WL 43467: Teratological Studies in Rabbits Given WL 43467 Orally

Shell Toxicology Laboratory (TUNSTALL), January, 1978.

Virgin female banded Dutch rabbits were mated with proven bucks and 30 females were grouped as controls. Groups of 20 females were dosed with corn oil capsule, 3 mg/kg, 10 mg/kg and 30 mg/kg of cypermethrin (WL 43467, 98.5% purity) on day 6 to 18 inclusive of gestation. On days 28 the rabbits were sacrificed and the pups delivered by Caesarian section following sacrifice by pentobarbitone injection. Seventeen or more rabbits in each group were pregnant and survived to term.

Results:

1. No consistent dose related effects were reported as occurring in the dams. There was a single death in each of the five groups except for the mid dose group. Weight gain was equivalent in all groups.

2. There were no chemical related effects on pre-implantation losses, resorptions, early or late foetal deaths, number of feotuses alive at birth, sex ratio of pups, average weight or length of pups.

3. Following delivery, the foetuses were placed in an incubator and kept for 24 hours to assess viability as measured by number of pups still alive after 24 hours. 40%, 51%, 32%, 36%, and 36% of the pups were alive after 24 hours for the control, corn oil control, low dose, mid dose, and high dose test groups respectively.

4. After 24 hours the remaining foetuses were killed by intraperitoneal injection of sodium pentobarbitone and examined by open disection for visceral abnormalities. Approximately 1/3 of the foetuses from each liter were decapitated and their heads were fixed in Bouin's solution. The remainder of the foetuses were trimmed and stained with alizarin red and examined for skeletal deformities.

5. There were no abnormalities noted in the skeletal system or the visceral system of the pups that indicated a dose response. There was a slight increase in renal abnormalities in the high dose group with there being 4.9%, 0%, 2.2%, 5.0%, and 8.9% mean percentage of animals affected in the control, corn oil control, low dose, mid dose, high dose groups respectively. This is not considered to be related to the ingestion of the test chemical.

   The mean percentage of foetuses showing both visceral and/or skeletal abnormalities was highest in the high dose test group. For example, the mean percentages were 12.0%, 17.4%, 10.0%, 14.0%, and 23.5% for the control, corn oil control, low dose, mid dose, and high dose test groups. This increase is not sufficient to conclude a test chemical effect. Moreover, there was no consistent lesion type which could be considered as responsible for causing the higher frequency in the high dose test group.

   This test is Core Minimum. No positive control was run concurrently. Cypermethrin was shown by the data in this study as not producing teratogenic effects at doses up to and including 30 mg/kg/day in rabbits. The cis:trans ratio was not specifically stated.

CYPERMETHRIN

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Pages 90 through 94 are not included.

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EPA Reviewer: John Doherty
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley, DVM
Review Section IV, Toxicology Branch I (7509C) 7/17/96

SUPPLEMENTARY DATA EVALUATION RECORD
Original DER in HED Document No.: 003249
(attached, with additional tables)

STUDY TYPE: Multigeneration Reproduction Study - Rat
OPPTS 870.3800 (§83-4)

DP BARCODE: D180777 SUBMISSION CODE: S422096
P.C. CODE: 109702 TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): Cypermethrin (90.6 to 93.1%). The cis/trans ratio was stated as being 53.4:46.6.

SYNONYMS:

CITATION: G.M. Milburn (4 other authors), 1982. Cypermethrin: Three generation reproduction study in the rat. ICI Central Toxicology Laboratory, Study No.: RR0143, July 9, 1982. MRID No.: 00112912, 42068504,.92027040. Unpublished.

SPONSOR: ICI

EXECUTIVE SUMMARY:

In a 3 generation reproduction study (MRID 00112912, 42068504, 92027040) cypermethrin (90.6 to 93.1%) was administered to four groups of 15 male and 30 female Wistar derived SPF strain rats at dose levels of 0, 50, 150 or 1000/750 ppm (reduced to 750 ppm after 12 weeks because of severe neurological symptoms). These dose levels correspond to 2.5, 7.5 or 50/37.5 mg/kg/day. Three successive generations were produced, each consisting of 2 separate breedings to produce six sets of litters.

At 150 ppm (7.5 mg/kg/day), parental weight gain was decreased in males (i.e. about 7% for F_2 at week 5) and females (i.e. about 4.5% for F_0 at week 8 and about 10% for F_2 week 8). At 1000/750 ppm (50/37.5 mg/kg/day) parental body weight gain was typically 10% decreased for both males and females and there was decreased mean litter weight gain during lactation (i.e. 12% to 21% for F_1B and 12 to 17% for F_1B females for days 10 to 28). At 1000 ppm (50 mg/kg/day) there were obvious clinical signs of neurotoxicity (i.e. ataxia etc). **The LOEL is 150 ppm (7.5 mg/kg/day) based on consistent decreased body weight gain in both sexes. The NOEL is 50 ppm (2.5 mg/kg/day).**

The reproductive study in the rat is classified ACCEPTABLE and satisfies the guideline requirement for a 3-generation reproductive study (OPPTS 870.3800, §83-4) in the rat.

COMPLIANCE: Study is circa 1981-2 and only a signed and dated Quality Assurance statement was provided.

A copy of the original DER as it appeared in HED Document No.: 003249 dated September 16, 1983 is attached. Several tables photocopied from the study report are also attached to support the NOEL and LOEL.

Table 8. F_o Parent Clinical Observations Days 0-22.

Table included to demonstrate that at 1000 ppm (50 mg/kg/day) there were clinical signs of neurotoxicity. No similar table for the F1 or later parental group was available in the study report.

COMMENT: One 150 ppm dosed female had "high stepping gait" on one occasion. This is noted here because this is a known typical response to pyrethroid treatment. Since only one incident for only one animal was reported and there were no similar incidents in the animals treated with 750 ppm, this incident at 150 ppm is considered a curiosity.

Table 10. F_o Parents - Group Mean Bodyweight Gain (g) From Start of Study - Females. Table 13. F_2 parents - Group Mean Bodyweight Gain (g) from Start of Study - Males. Table 14. F_2 Parents- group Mean Bodyweight gain (g) from Start of Study - Females.

Tables included to support NOEL and LOEL of 50 and 150 ppm based on consistent statistically significant decreases in body weight gain for all generations at 150 ppm (7.5 mg/kg/day).

Table 31. Intergroup Comparison of Fertility (proportion of Fertile Animals) Males. Table 32. Intergroup Comparison of Fertility (proportion of fertile animals) Females.

Tables included to demonstrate that there were no adverse effects on fertility.

Table 39. Group Mean Viable Litter Size-F_2B Litter.

Table included to demonstrate that there was no adverse effects on litter size.

Litter.

Tables included to demonstrate that weight at birth was not statistically significantly affected (for some litters it was actually slightly higher) but that weight gain during lactation was decreased at 750 ppm (37.5 mg/kg/day).

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REVIEW OF STUDIES

A. Cypermethrin: Three Generation Reproduction Study in the Rat.

Central Toxicology Laboratory, ICI, #CTL/P/683, July 9, 1982. EPA Acc. No. 071074 and 071075, TAB 52C.

B. Substance tested. The test material was cypermethrin: (RS) α-cyano-3-phenoxybenzyl (IRS)-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. Analysis of the test material reported that the purity was 90.6-93.1% and the cis:trans ratio was 53.4 to 46.6 (other lots of test material gave slightly different percentages). Three batches (P19, P24 and P26) of cypermethrin were used for this study.

C. The test rats used for this study were Wistar derived Specific Pathogen Free albino rats. They were obtained from the Alderley Park supplier.

The study comprised four groups each containing 15 males and 30 females which were dosed as either 0, 50, 150 or 750 ppm of cypermethrin in their diets. The high dose test group received 1000 ppm for the first twelve weeks of the study but this level was reduced to 750 ppm because of obvious signs of neurological effects.

D. Dietary analysis for the test substance. Data were presented which showed that the desired doses were achieved (within 10%) and that cypermethrin was stable for at least six weeks and the diet preparations were homogeneous with respect to distribution of the cypermethrin.

E. Three successive generations were produced, each consisting of two breedings. The pups from the second breeding were selected to be the parents for the succeeding generations.

F. Mortality and clinical signs. The death (sacrificed in extremis) of a single rat (high dose group male at 1000 ppm) was attributed to the test chemical. Other rats dosed with 1000 ppm showed signs of neurological disturbance characterized by increased sensitivity to sound, ataxia and high stepping gait (during first 3 weeks of study). The report states that no other "treatment related signs were seen in any other F_0 treatment group or in subsequent generations at any dose." Thus, although no tables regarding behavior (other than for

the F_1 generation) were presented a NOEL for nervous system effects is set at 750 ppm.

G. Body weight gain (mature rats).

A NOEL is set at 50 ppm. At 150 ppm there were many cases of decreased weight gain in both males and females. More pronounced effects were noted in the 1000/750 ppm test dose groups.

Food consumption was also reported to be less in the mid (occasionally) and high dose test groups.

H. Reproductive performance. For each of the six breedings, assessments were made regarding length of gestation, live born index, survival index, maternal neglect index, male fertility, and viable litter size.

Other than there being some "slightly reduced" actual pregnancy weight gains (to day 14) in the high dose test groups there were no other effects reported.

I. Offspring body weight gain was determined at days 0, 4, 10, 21 and 28 post partum. A NOEL is set at 150 ppm. At 1000/750 ppm, there were many instances of statistically significant decreases (of about -13%). There were no signs of behavioral changes in the offspring reported.

J. Pathology (mature rats) was conducted on rats which died or showed signs of reproductive impairment. Later F_0 and F_2 parents were subjected to a gross post partum examination and selected tissues (including the testes) were examined microscopically. The F_1 parents (25 females and 10 males) were subjected to a full post mortem examination including histopathology of 17 or more tissue types.

No pathological findings were attributable to the test chemical.

K. Pathology (pups). "Full" post mortem examinations were conducted on any grossly abnormal pups and five males and five females from the F_1B and F_2B litters and 10 males and 10 females per group from the F_3B litters. Selected rat pups (less than 18 days of age) were preserved for teratological examination.

No evidence of test chemical induced pathology or terata were presented in this report.

Conclusion.

This study is CORE GUIDELINES. The NOEL for adverse effects on reproductive parameters is 750 ppm (HDT). The NOEL for systemic effects is 50 ppm. At 150 ppm (LEL), body weight decreases in maturing rats were noted and at 750 ppm pup weight was also decreased.

CYPERMETHRIN

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[Cypermethrin/1979] Rat Reproduction Study OPPTS 870.3800 (§83-4)

EPA Reviewer: John Doherty 7/15/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley, DVM 7/15/96
Review Section IV, Toxicology Branch I (7509C)

SUPPLEMENTAL DATA EVALUATION RECORD
Original DER in HED Document No.: 002391
(attached with supporting tables)

STUDY TYPE: Multigeneration Reproduction Study - rat
OPPTS 870.3800 (§83-4)

DP BARCODE: D180777
P.C. CODE: 109702

SUBMISSION CODE: S422096
TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): Cypermethrin (98% purity) Batch No.: 30

SYNONYMS: WL 43467 and NRDC 149

CITATION: R.W. Hend, R. Hendy and D.J. Fleming 1979, "Toxicity studies on the insecticide WL 43467: A three generation reproduction study in rats". Shell Toxicology Laboratory, Study No.: TLGR.0188.78, February, 1979. MRID No.: 00090040. Unpublished.

SPONSOR:

EXECUTIVE SUMMARY:

In a 3 generation reproduction study (MRID 00090040) cypermethrin (98% purity) was administered to four groups of 30/sex Wistar SPF strain rats/sex/dose group in their diets at dose levels of 0, 10, 100 or 500 ppm [0, 0.5, 5, or 25] mg/kg/day. The first parental group produced two litters (F1A and F1B), the F1B litter was culled to produce the F2A and F2B litters and the F2B litter was culled to produce the F3A and F3B litters.

At 25 mg/kg/day there was decreased parental weight gain (i.e. about 3% for males and 7 % for females for the F1 generation and pup weight at day 21 of lactation (about 4% but $p < 0.01$). **The LOEL is 500 ppm (25 mg/kg/day based on decreased weight gain. The NOEL is 100 ppm (5 mg/kg/day).**

This reproductive study in the rat is classified as SUPPLEMENTARY and does not satisfy the guideline requirement for a 3 generation reproductive study (OPPTS 870.3800, §83-4) in the rat. The study is summary form only and not supported by the individual animal data.

COMPLIANCE: The study is circa 1979 and signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were not provided.

A copy of the original DER for HED Document No.: 002391 dated 12/28/82 is attached. The following Tables supporting the NOEL and LOEL are also attached.

Tables 1, 2 and 3. Mean Body Weights of F0, F1 and F2 parental generations rats fed WL 43467.

Included to demonstrate the decrease in body weight at 500 ppm (25 mg/kg/day).

Table 7. Fertility, viability, gestation and lactation indices of rats fed WL 43467 during a 3-generation reproduction study.

Included to demonstrate the overall efficiency of the study.

Table 9b. Mean Litter weight data of the rats aged 21 days fed WL 43467 during a 3 generation reproduction study and Table 9c. Mean pooled litter weight data of rats aged 21 days fed WL 43467 during a 3 generation reproduction study.

Included to demonstrate that there was a small but still statistically significant decrease ($p < 0.01$) in body weight at 100 (3%) and 500 (4%) ppm. The small decrement at 100 ppm is not considered of sufficient magnitude to be included in the LOEL. As the pups in the 100 ppm dose group matured to be the parental groups there was no statistical difference. Refer to Tables 1, 2 and 3.

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Toxicity studies on the insecticide WL 43467: A three generation reproduction study in rats.

00239

Shell Toxicology Laboratory (Tunstall) TLGR 0138.78, February 1979, EPA Acc. No 070564, TAB 22c.

The experiment was started (F_0 generation) with 4 groups of 30 male and female Wistar SPF rats (Shell Toxicology Lab, Tunstall) which were dosed for five weeks at either 0, 10, 100, or 500 ppm of cypermethrin (batch no. 30, 98% pure). After five weeks, a single male was placed with a single female to produce the F_1A and later the F_1B generations. Litter F_1A was sacrificed at weaning (21 days). One male and one female from each of the F_1B litters were selected and paired to produce the F_2A and F_2B generations. Similarly, the F_3A and F_3B generations were produced from the F_2B generation.

Results:

1. Reproductive performance - No adverse effects were noted on the general health or behavior of the rats at any dose. There were no adverse effects on the fertility index (number of pregnancies/number of matings), the gestation index (pregnancies resulting in live litters), viability index or lactation index.

2. Litter parameters - The following data were collected on each litter: date born, number of pups born alive, number of pups born dead, sex of pups at weaning, total litter weight on days 1, 4, 7, 14, and 21, individual pup body weights on day 21.

Of the several parameters measured, the only parameter which appeared to be affected in a dose related manner was the mean pup weight at 21 days. The following table illustrates the differences noted.

	Males		Females	
Dietary Concentration (ppm)	Number of observations (N)	Mean male pup weight (g)	Number of observations (N)	Mean female pup weight (g)
0	681	48.2	661	46.6
10	681	48.5	672	46.9
100	704	46.7** (-3%)	666	45.6** (-2%)
500	687	46.3** (-4%)	652	44.7** (-4%)
Standard deviation of a single observation		6.99		6.75

** $P \leq 0.01$ - Significance of the difference between treatment and control means using Williams t test.

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These data contain the weights of all pups. When the individual generations are considered (F_{1A}, F_{2B}, etc.) the statistical significance is not readily apparent.

3. Pathology - There were no consistent histopathological changes reported for either the pups when born or the parental rats.

Conclusion - This study is CORE MINIMUM. Only two pups (a male and female) from each litter were examined histologically. The data are in summary form only and individual data are not presented. A NOEL of 500 ppm (HDT) is assigned for adverse effects on reproduction. A NOEL of 10 ppm is assigned for systemic effects. However, the small depressions in pup weight (~3%) noted at 100 ppm are not considered of sufficient magnitude to require that the level of 100 ppm be used in ADI determinations for cypermethrin. (Note: decrease in pup weight is a characteristic of other pyrethroids in three generation reproduction studies.)

CYPERMETHRIN

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[Cypermethrin/1982] Chronic Feeding/Carcinogenicity - rat 83-5)

EPA Reviewer: John Doherty 7/15/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley, DVM
Review Section IV, Toxicology Branch I (7509C) mcopley 7/15/96

SUPPLEMENTARY DATA EVALUATION RECORD
Original DER in HED Document No.: 003249
(attached with supporting tables)

STUDY TYPE: Chronic Feeding/Carcinogenicity - rat [§83-5]

DP BARCODE: D180777 SUBMISSION CODE: S422096
P.C. CODE: 109702 TOX. CHEM. NO.: 268AA

TEST MATERIAL (PURITY): Cypermethrin (88 to 93% purity), lot No: Y00334/017. 55% cis and 45% trans.

CITATION: G.M. Milburn (9 other authors), 1982 "Cypermethrin: 2 Year Feeding Study in Rats". ICI, Central Toxicology Laboratory, Study No.: CTL/P669. June, 1982. MRID No.: 00112910. Unpublished.

SPONSOR: Not specified.

EXECUTIVE SUMMARY:

In a chronic toxicity/carcinogenicity study (MRID 00112910) cypermethrin (88-93% purity, 55% cis and 45% trans) was administered to 5 groups of 52/sex Wistar derived Alderley Park SPF strain rats at dose levels of control-1, control-2, 20, 150 or 1500 ppm (corresponding to 0, 0, 1, 7.5 or 75 mg/kg/day) for 2 years. Satellite groups of 12/sex were sacrificed after one year of dosing.

Definite signs of toxicity were evident at 75 mg/kg/day and these consisted of body weight gain decrease throughout the study (i.e. about 10% for males and 13% for females at week 13), *slight* effects on several hematological parameters (both red and white cells), *slight* effects on clinical chemistry parameters (decreased cholesterol and triglycerides and glucose and increased urea. Decreases in urine volume, pH and an increase in specific gravity were noted. Liver weight was increased in females. **The LOEL is 1500 ppm (75 mg/kg/day) based on body weight. The NOEL is 150 ppm (7.5 mg/kg/day).**

Cypermethrin was not considered to be oncogenic in this study. A possible association with increased testicular interstitial tumors was not considered definite.

This chronic toxicity/carcinogenicity study is classified ACCEPTABLE. and does satisfies the guideline requirement for a chronic oral feeding/carcinogenicity study (83-5) in rats.

COMPLIANCE: The study is circa 1990-82 and only a signed and dated Quality Assurance statement was provided.

A copy of the original DER from HED Document No.: 003249 dated September 16, 1983 is attached. In addition to the original DER, the following tables are attached to support the NOEL and LOEL.

Table 10 (males, one page) and Table 11 (females, 2 pages) Group Mean Body Weight Gain.

Illustrates the effects on bodyweight. Table 11 shows that although there were some statistical differences at weeks 36 to 52 for the mid dose group, this effect in not evident after week 52 and is not considered large enough (only 4-5%) a specific effect to be included in the LOEL assignment.

Table 16. Group Mean Haemoglobin. Table 20. Group Mean Haematocrit. Table 28. Group Mean Cell Volume. These tables are included to illustrate the slight and inconsistent effects on hematological parameters at the high dose group.

Table 80. Group Mean Plasma Urea. Table 84. Group Mean Plasma Glucose. Table 88. Group Mean Cholesterol. Table 96. Group Mean Plasma Triglycerides. These tables are included to illustrate the slight and inconsistent effects on clinical chemistry parameters.

Table 104. 2-Hour Dilution Test-Group Mean Urine Volume.

Table 139. Group Mean Liver Weight. Interim Kill. Table 140. Group Mean Liver Weight - Terminal Kill. Included to illustrate the marginal effects on liver weight.

Table 162. Total Incidences of Neoplasms in all Animals. Only the portion of the table illustrating testis data are shown to illustrate the tumors in the testis.

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A. Cypermethrin: 2 year feeding study in rats

ICI Central Toxicology Labs., #CTL/P/669, June, 1982. EPA Acc. No. 071070 and 071071, TAB 50C.

B. Substance tested: Cypermethrin, RS-α-cyano-3-phenoxybenzyl (IRS)-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate, cis-trans ratio of 55:45 (nominal). The substance identification number was Y00334/017. Analysis of the test substance indicated that the test material was 88 to 93% pure. The chemical nature of the impurities was not defined.

C. The test animals used were Wistar derived albino rats obtained from the Specific Pathogen Free (SPF) colony maintained at the Alderly Park facility in Cheshire, England. 5 groups of 52 male and 52 female rats were dosed with diets containing 0(two groups), 20, 150, or 1500 ppm of cypermethrin. Satellite groups of 12 male and 12 female rats were also maintained and designated for an interim sacrifice at 52 weeks. For a brief period (first six weeks) the animals requiring the highest dosage level were dosed with 1000 ppm rather than 1500 ppm. The rats were approximately 36 days old when they were initiated on their test diets.

D. Dietary analysis indicated that the test diets were usually within $\pm$ 10% of the desired levels. The cypermethrin was found to be stable for up to six weeks. Usually fresh diets were mixed at 2-3 week intervals.

E. Survival at 104 weeks was considered acceptable and is shown in the following table.

Dose Level (ppm)	Males	Females
0	27 (52%)*	24 (46%)
0	28 (54%)	22 (42%)
20	26 (50%)	23 (44%)
150	21 (40%)	24 (46%)
1500	27 (52%)	27 (52%)

* Number of survivors (as percent of 52 starters).
No test chemical effect on survival is noted.

There were some initial behavioral signs of reaction (first six days) to the test chemical (frequent face washing, increased sound sensitivity and lack of co-ordination in the hind limbs) in six high dose males. Some signs of reaction which consisted of thin appearance and hair loss were later reported as being evident in the high dose test group.

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A NOEL of 1500 ppm is set for these effects. The effects reported at this level are too indefinite and/or of transient nature to assign this level as a LEL.

F. Body weight gain was definitely considered to be decreased for the high dose male and female test groups. The mid dose test groups were also occasionally affected (statistically significant) and were on some occasions as much as 4-5% lower for females. The high dose groups were -18% (females) and -12% (males) lower at termination. Food consumption was reported to be decreased in the high dose test groups.

NOEL for body weight gain = 150 ppm. The slight effect noted in females at 150 ppm is not considered to be of sufficient magnitude or consistency to offset this assignment of a NOEL.

For sections G, H and I (below) samples were taken at pretest, week 4, week 13 and at each 13 weeks afterward until termination. 12 rats from each sex from each group were selected.

G. Hematology. The following parameters were measured: Hb, total white cell count, total red cell count, mean cell volume, mean cell hemoglobin and cell hemogloblin concentration, hematocrit, differential white cell count. At selected intervals prothrombin and kaolin/cephalin time tests were determined. Bone marrow smears were also sampled.

The high dose test group was associated with slight adverse effects on several hematological parameters. These included reduced mean cell volume (and related changes in Hb and hematocrit); slightly increased white cell count (increase in lymphocyte count with a decrease in neutrophil count). There was also a slight increase in prothrombin time.

A NOEL for hematological parameters is 150 ppm. The LEL for generalized changes is 1500 ppm (HDT).

H. Clinical Biochemistry. The following parameters were investigated: alkaline phosphatase, alanine transaminase, aspartate transaminase, plasma cholesterol, albumin, total protein, urea, glucose, and triglycerides.

Plasma cholesterol levels were decreased for the high dose test groups (both male and female) about 25%. The mid dose group was decreased occasionally but the

decrease did not reach statistical significance. Plasma triglycerides were also apparently decreased in males at 1500 ppm (there was a large variation in triglyceride data which hindered a more definite conclusion). Other parameters showing effects at 1500 ppm were urea (increased) and glucose (decreased). Other parameters were occasionally higher or lower than the controls.

NOEL for blood biochemistries = 150 ppm. The LEL for generalized changes is 1500 ppm (HDT).

I. Urine analysis. Parameters investigated included volume, pH, specific gravity, glucose, protein, bilirubin and analysis for cypermethrin metabolites.

Effects reported for the groups dosed with 1500 ppm included reduction in volume, decreased pH and an increase in the specific gravity. A slight decrease in protein was also reported. Dose related amounts of the cypermethrin metabolite, 3-(4'-hydroxyphenoxy)-benzoic acid, were assayed in the urine.

A NOEL for this aspect of the study is 150 ppm.

J. Organ weights. The adrenals, brain, heart, kidneys, liver, lung, gonads, pituitary gland and spleen were weighted at 52 weeks and at termination. The thymus was weighted at 52 weeks.

The only organ the testing laboratory considered definitely affected by treatment was the liver (females in the high dose test group only) and this effect was only evident at 52 weeks and was evident by a 21% increase in relative liver/body weight.

At 104 weeks, the female kidney weight for the high dose test group was decreased in weight - 17% absolute and relative. Spleen weight also appeared to be decreased 13% absolute and relative for the high dose test group males.

NOEL for organ weight changes = 150 ppm, LEL = 1500 ppm, liver and possibly also kidney weight changes.

K. Gross necropsy (on all rats). No table summarizing or tabulating the gross necropsy observations was presented. The gross necropsy findings are reported on the individual animal pathology reports. Using these reports it can readily be determined if gross necropsy observations were followed up histologically. Inspection of these individual animal pathology reports indicates that

followup of the gross necropsy observations by histopathological descriptions of lesions was acceptable.

The testing laboratory reported no gross lesions considered to be attributable to the test material.

L. Histopathology - A comprehensive list of some 42 tissue types were prepared for histological examination. All rats were scheduled for complete microscopic analysis.

No single tissue type was indicated in the study to be a neoplastic or nonneoplastic target organ for cypermethrin at any dose level. The following organs are commented on for various reasons as given.

1. The liver showed some increases in weight gain (in high dose females at 52 weeks). The liver has been shown to be a target organ for toxicity for other pyrethroids.

There were a total of three neoplasms reported in the liver - two incidences of hepatocellular carcinoma (one control male and 1 high dose female) and one incidence of hepatocellular adenoma (low dose group male). There were no "nodular hyperplasia" or "hyperplastic nodules" reported. Light microscopic analysis of the liver did not reveal dose related increases in commonly occurring non-neoplastic liver lesions.

Some special studies were conducted to assess for possible liver effects of cypermethrin. These were induction of hepatic aminopyrine-N-demethylase (APDM) activity and electron microscopy of the smooth endoplasmic reticulum (SER). Increased enzyme activity (up to 64%) was noted in the high dose test group (1500 ppm) especially in the females. The high dose test group was also associated with increases in the content of the smooth endoplasmic reticulum. The mid dose group females also showed a statistically significant increase (~ 20.5% increase) in SER.

Slight increases in APDM activity and in smooth endoplasmic reticulum is considered by TB to be an adaptation response to the test chemical, rather than a true toxic response.

2. The testis developed a slightly higher incidence of interstitial cell adenomas in the high dose test group among animals dying before termination.

Interstitial Cell Adenomas

Dose Group	52 weeks to termination	Termination	Total
Control - 1	2/25	5/27	7/52*
Control - 2	0/22	8/28	8/50
20 ppm	0/26	7/26	7/52
150 ppm	2/28	5/21	7/49
1500 ppm	6/24^{xx}	7/27	13/51^{NS1}

* incidences/number examined (does not include rats dying in first year).

^{xx} P=.007) Fisher's one-tailed P
^{NS1} P=.098) statistic by TB computer.

Only the rats which died prior to termination of the study showed a statistically significant increase in this tumor type (at the high dose level only).

Nonneoplastic pathology of the testis was unremarkable in that only non-dose-related lesions were present. The report indicated that there were slight increases in incidences of tubular atrophy and calcification of the testes. Testes weight changes did not show statistically significant increases. An 18% apparent increase in relative weight is reduced to 7% when one extreme value is eliminated from the high dose test group.

TB notes that at least one other synthetic pyrethroid has been demonstrated to induce testicular interstitial neoplasms in rats. However, due to the failure of the data with cypermethrin in the above table to reach consistent statistical significance, TB cannot conclude from these data that the testis is a neoplastic target organ for cypermethrin.

3. Pathology of the nervous system. At least some synthetic pyrethroids have given indications that a particular type of axonal lesion results from exposure to high doses. The sciatic nerves were routinely fixed in formol saline and examined in this study. In addition, some special examination of the sciatic and posterior tibial nerves was conducted by fixing the tissues in formol glutaraldehyde and embedding in glycol methacrylate. The nerves were cut and stained in H&E and in addition were stained by Palmgrins silver impregnation techniques for axons and the solochrome cyanin technique for myelin. Histological findings did not reveal a test chemical effect in the structure or integrity of

the nerves from rats dosed with cypermethrin. The overall incidence of l- ions in nerve tissue is shown in the following table.

Sciatic Nerve-Neuropathy

	Males				Females			
	Combined Control	20 ppm	150 ppm	1500 ppm	Combined Control	20 ppm	150 ppm	150 ppm
Number examined	102	49	47	51	102	48	50	51
minimal/slight	31	13	14	13	40	18	26	21
moderate/marked	64	32	27	33	55	23	23	28
severe	5	1	3	3	0	2	1	1

4. Examination of the pituitary revealed frequent occurrences of adenomas and occasional carcinomas but there was no evidence of a dose response. There were 66 incidences of adenomas among the male groups and 213 incidences among the females. These were distributed as 22/61, 12/64, 15/55, 10/59 and 7/57 among the males and 46/62, 46/63, 38/59, 42/62 and 41/61 among the females for the controls, low, mid and high dose test groups.

There were 2 incidences of carcinomas in the pituitary for the males (a control and low dose group) and 13 incidences among the females. There were 4, 2, 1, 2 and 4 in the control groups, low, mid and high dose groups respectively (see above for denominators.)

There was no indication that the pituitary neoplasms developed earlier in the rats dosed with cypermethrin.

Other Oncogenic Aspects

The following table indicates the total number of neoplasms in each group (not including testicular interstitial adenomas, pituitary adenomas or generalized lymphosarcomas):

	Incidences of Neoplasms*	
	Males	Females
Control-group #1	35	32
Control-group #2	30	47
20 ppm	34	28
150 ppm	27	32
1500 ppm	35	37

* Total of 64 rats in each group.

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