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

004825

MEMORANDUM

DATE: OCT 28 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA No. 10182-EUP-19 and PP 1G2461 and FAP 1H5287, Experimental Use Permit and Temporary Tolerances for the Synthetic Pyrethrin Cypermethrin on Cottonseed, Cottonseed Hulls and Cottonseed Oil.
TOX Chem. No. 271DD

FROM: John Doherty 10/22/81
Toxicology Branch/HED (TS-769)

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

Action Requested:

The ICI Americas, Inc. is requesting an Experimental Use Permit to use Cypermethrin (CYMBUSH® Insecticide) on cotton in 13 states (Alabama, Arkansas, Arizona, California, Georgia, Louisiana, Missouri, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee and Texas). A combined total of 6000 acres in these states are involved. The total amount of cypermethrin as active ingredient requested for use is 12,000 lbs. The duration of this requested permit is for 2 years. The requested tolerances are 0.1 ppm cottonseed, 0.2 ppm cottonseed hulls, and 1.0 ppm cottonseed oil.

Recommendation:

1. Toxicology Branch has no objection to allowing this experimental use permit and granting these temporary tolerances providing that the following change is made in the label.

   a. The label must be changed to state that contact with this product may result in skin sensitization in some individuals. Also, the term "slightly toxic" should be deleted from the precautionary statement.

Comments:

1. Both the special neurotoxicity study and the 90-day rat feeding study provided indications that cypermethrin at high doses may cause some damage to the structure of the sciatic nerve. The sciatic nerve should be carefully analyzed for damage in the chronic feeding and oncogenesis studies for this chemical. The high, near fatal doses at which the possible adverse effects were noted in the available studies do not indicate that this use of cypermethrin will represent a hazard to the nervous system.

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2. The inhalation LC50 determination performed on formulation GFU 034A was a Supplementary study and must be repeated in order to register this formulation for other than EUP programs.

3. Acute toxicity data for the 36% cypermethrin product was submitted and reviewed. This product is an eye irritant (Category I) and the label has a "DANGER" signal word. The precautionary label statements are consistent with a corrosive eye irritant and Category II oral toxicity data. The inerts in the 36% formulation are cleared for preharvest use.

   The acute toxicity data for the 25% formulation was reviewed previously (see J. Doherty memo, dated 9/8/80). The inerts in this product are cleared for preharvest use.

4. The registrant is requested to identify the cis:trans ratio of the technical cypermethrin used for the rat and rabbit teratology studies.

8 POINT REVIEW

1. Toxicity data with technical grade cypermethrin (53:47 cis:trans ratio) considered in setting this tolerance.

a.	Acute Oral LD50, rats	LD50 = 247 mg/kg, males LD50 = 309 mg/kg, females
b.	Acute Dermal LD50, rabbits	LD50 > 2460 mg/kg
c.	Primary Dermal Irritation, rabbit	Primary irritation index, PII = 0.71 (not irritating)
d.	Primary Eye Irritation, rabbit	Mild irritation
e.	Skin Sensitization, guinea pigs (technical material)	Not a sensitizer
f.	Skin Sensitization, guinea pig (formulated product)	Mild sensitizer
g.	90-Day Oral Feeding, rats	NOEL of 75 ppm for pharmacological effects; NOEL of 150 ppm for toxic effects.

h.	13-Week Feeding, dogs	NOEL of 500 ppm - behavorial signs of nervous system effects and deaths resulted in males receiving the next highest dose of 1500 ppm.
i.	Teratology, rabbits	Not teratogenic at 30 mg/kg/day (highest dose tested).
j.	Teratology, rats	Not teratogenic at 70 mg/kg/day (highest dose tested).
k.	Metabolism Studies	

2. Data considered desirable but currently lacking. The basic data requirements to support a G type petition where the ADI used up is less than 50% have been submitted except for basic mutagenesis studies (Ames test and others).

3. Toxicology Branch was informed on 9/24/81 by Dr. R. E. Ridsdale of ICI Americas that these studies will be sent to EPA in the near future.

4. This is a new chemical. No other tolerances have been granted for this chemical (see computer printout).

5. Granting this tolerance will bring the ADI used to 1.00% from 0% (see computer printout).

6. The PADI is 0.0038 mg/kg/day, the MPI is 0.2250 mg/day (60 kg person). The rat 90-day feeding study with a NOEL of 150 ppm and a safety factor of 2000 were used to determine the PADI.

7. There are no pending regulatory actions against cypermethrin registrations.

8. Cypermethrin belongs to the chemical class of synthetic pyrethrins. Some of these chemicals have been shown to produce neoplasmas in liver and possibly also lungs in some tests. The oncogenic potential of synthetic pyrethrins is currently being evaluated by Toxicology Branch.

STUDIES REVIEWED

	Acute Toxicity Study	Result	TOX Cat.	Core Classification
1.	Acute Oral, rats (in corn oil)	LD50 = 247 mg/kg males LD50 = 309 mg/kg females	II	Minimum
2.	Acute Dermal LD50, rat	LD50 > 4920 mg/kg	III	Minimum
	Acute Dermal LD50, rabbit	LD50 > 2460 mg/kg	III	Minimum
3.	Primary Dermal Irritation, rat	Not irritating	IV	Supplementary
	Primary Dermal Irritation, rabbit	Primary Irritation Index PII = 0.71	IV	Minimum
4.	Primary Eye Irritation, rabbit	Mild irritation	IV	Guidelines
5.	Skin Sensitization, guinea pigs	Not a sensitizer	-	Guidelines

The above studies were conducted using cypermethrin 53:47 cis and trans ratio.

Subchronic Toxicity:

6.	90-Day Oral Feeding, rats (44% cis and 56% trans)	NOEL of 75 ppm for pharmacological effects. At 150 ppm some changes in the smooth endoplasmic reticulum in liver were noted. Toxicological NOEL of 150 ppm. At the highest level tested (1500 ppm) some evidence of vacuolation and splitting of nerve were noted.	Minimum
7.	13-Week Feeding, dogs (50% cis and 50% trans)	NOEL of 500 ppm - behavorial signs of nervous system effects and deaths in males receiving 1500 ppm.	Minumum
8.	Teratology, rabbits	Not teratogenic at 30 mg/kg /day (highest dose tested).	Minimum
9.	Teratology, rats	Not teratogenic at 70 mg/kg /day (highest dose tested).	Minimum

Special Neurotoxicity:

10.	Effects on Sciatic Nerve (45% cis and 55% trans), rats	Possible chemical related nerve fiber degeneration noted and clinical signs of nervous system effects.

Metabolism:

11.	^{14}C benzyl label cis cypermethrin	See review
12.	^{14}C aryl label trans cypermethrin	" "
13.	^{14}C aryl label cis and trans cypermethrin	" "
14.	^{14}C cyclopropyl label cis cypermethrin	" "
15.	^{14}C cyclopropyl label trans cypermethrin	" "
16.	^{14}C benzyl label 3 phenoxybenzoic acid	" "

Acute Toxicity of CYMBUSH Formulation (GFU 034A) - 3 lb. a.i./gallon formulation

17.	Acute Oral LD50, rats	LD50 = 270 mg/kg	II	Guidelines
18.	Acute Dermal LD50, rabbits	LD50 = > 2000 mg/kg	III	Minimum
19.	Primary Skin Irritation, rabbits	Draize score 2.1	III	Guidelines
20.	Primary Eye Irritation, rabbits	Corneal opacity not reversed in 5/6 rabbits at day 7.	I	Guidelines
21.	Acute Inhalation LC50, rats	Equivocal	-	Supplementary
22.	Skin Sensitization, guinea pig	Mild sensitizer	-	Minimum

These studies are in EPA Accession No. 099855.

No CAS Number Cypermethrin 10/1-/91

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File last updated 10/1-/91

ACCEPTABLE DAILY INTAKE DATA

Acute/Older NOEL	U.F.	cRfD	NOEL	MPI
mg/kg		mg/kg/day	mg/day(60kg)	
7.500	150.00	2000	0.050	3.2250

Current Action PP# 1G2401, IH5287

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cottonseed (41)	1.00	0.15	0.00225

MPI	TMRC	% ADI
0.2250 mg/day(60kg)	0.022 mg/day(1.5kg)	1.00

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REVIEW OF STUDIES

Cypermethrin (PP 383): Acute Toxicity and Local Irritation

Report No. CPL/P/537, Central Toxicology Laboratory, Februa[illegible] 14, 1980.

Note: These studies were conducted using cypermethrin of the composition 53:47 cis: trans ratio. A previous review (see J. Doherty review dated September 8, 1980 concerning EPA Reg. No. 10182-EUP-19) reviewed the results with a 45:55 cis:trans ratio.

1. Acute Oral Toxicity to Rats:

Groups of five male and female rats were dosed with 100, 150, 200, 250, 300, 400, 500, 640 or 800 mg/kg of cypermethrin in maize oil and observed for 14 days.

LD50,s with 95% confidence limits of
247 (187-326) mg/kg for males
309 (150-500) mg/kg for females

were determined.

Signs of toxicity included subdued behavior, excessive salivation, urinary and fecal incontinence, dehydration, ataxia, unsteady gait and piloerection. The effects were stated as being persistant in some of the survivors throughout the two week observation period.

Core Minimum. Toxicity Category II. No necropsy was performed or reported.

2. Acute Dermal Toxicity:

Part 1-rat

4.0 ml of cypermethrin/kg was applied to the prepared backs of 5 males and 5 female rats and kept in place for 24 hours. One male rat died three days after the initial application. None of the other rats died. An LD50 of > 4920 mg/kg of cypermethrin was established. Toxic signs included subdued behavior, unsteady and/or defective gait, urinary incontinence, ungroomed appearance and piloerection. The toxic effects persisted throughout the observation period although the exact symptoms and degree were not documented.

Core Minimum. An LD50 of > 4920 mg/kg was established, Toxicity Category III. No necropsy was performed. The persistant toxic signs were not documented.

Part 2-rabbit

One dose level of 2.0 ml/kg was applied to the prepared backs of 5 male and 5 female rabbits. No rabbits died. Three of the males showed some toxic responses, lacrimation, eye discharge and nervous and shaking were noted in one rabbit each.

Core Minimum. An LD50 of > 2460 mg/kg is established. No necropsy was performed. Toxicity Category III.

3. Skin Irritation:

Part 1-rat

One application of 0.1 ml of cypermethrin to five rats caused slight transient desquamation in one rat only.

Five applications of 0.1 ml of cypermethrin/rat did not cause irritation in the test animals.

Core Supplementary.

Part 2-rabbit

One application of 0.5 ml cypermethrin/test area in each of six rabbits prepared with both intact and abraded skin resulted in a primary irritation index of 0.71.

Core Minimum. Toxicity Category IV.

4. Eye Irritation:

0.1 ml of cypermethrin was instilled into the conjunctival sac of each rabbit. The eyes of 3 rabbits were rinsed after instillation (20-30 seconds). No corneal opacity developed. Except for some slight redness in the conjunctivae, the eyes were reported as being normal 7 days following instillation.

Core Guidelines. Toxicity Category IV.

5. Skin Sensitization - Guinea Pigs:

Ten control and ten test group male guinea pigs (Dunkin-Hartley) were used in this experiment. Induction was by making a topical application of 0.3 ml and undiluted test material/animal by placing a piece of paper to the shaved back of the animal. The filter paper was kept in place for six hours with a polyethylene patch and adhesive bandage. A total of 10 six hour exposures were applied over a 21 day test period. The control animals were treated with water.

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 x.04 = .3 = .5%
-150 x.04 = 6 = 1.0
-1500 x.04 = 60 1.0

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.

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.

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0, 5, 50, 500, 1500

125 125 125

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.

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.

PP 383: Effects of High Dietary Levels on Clinical Behavior and Structure of Sciatic Nerve in the Rat

Central Toxicology Laboratory, ICI, Feburary 25, 1980, CTL/P/345 (Revised).

Three groups of 10 rats (SPF - derived, male Wistar) were dosed for 14 days with cypermethrin (90% pure, 45% cis and 55% trans). For each treated rat there was a litter mate control of similar weight, housed in an adjacent cage. The dose levels of cypermethrin were 1250, 2500, and 5000 ppm.

Results:

1. The mid dose level was found to be the 14 day LD50 for this strain of rat. For example, all of the rats fed at 5000 ppm died by day 7. Only 4 rats in the mid dose group survived the 14 day period. All of the rats in the low dose group survived. All test animals lost weight and ate less relative to their controls.

2. All test groups demonstrated some signs of neurotoxicity. Slight "alligator gait" occurred in 5 of the rats receiving 1250 ppm. Two of these rats were hypersensitive to external stimuli.

   In the mid dose group, the 4 rats which survived the 14 day test period exhibited slight to extreme alligator gait.

   In the high dose group, the rats displayed varying degrees of "alligator gait" and in some cases other symptoms (convulsions, disorientation, etc.).

3. Histology - the brain, spinal cord, sciatic nerve, gastrocnemiua muscle and vagus nerve were removed and preserved in buffered formol saline. The other sciatic nerve was preserved in 3% buffered glutaraldehyde. Only the sciatic nerve was processed for examination by electron microscopy.

   a. The incidence of degenerating nerve fibers was low in all groups as indicated by myelin globules in digestion chambers. However a single rat in the mid dose group displayed an excessively high degree of degeneration.

   b. Ultrastructural change included collapse of myelinated axons, contraction of axoplasm within myelinated axons, foci of myelin debris within sheaths of myelinated axons, fragmentation of myelinated axons, and interstitial vacuolation. The rats that died as a result of the test chemical displayed sufficient autolysis to limit their value for analysis.

      In particular there were 4 animals (of the 6 examined) that showed foci of myelin debris within sheaths of myelinated axons in the 2500 ppm group. None of the 5 paired controls showed this type of lesion.

      None of the animals in the low dose group were examined histologically or by electron microscopy.

Conclusion:

This study was poorly executed in that the low dose group was not examined microscopically. The high dose group was of little value in appraising the neurotoxicity problem because of the high rate of death and autolysis among the test animals. The mid dose group demonstrated the presence of "myelin debris within sheaths" which has been interpreted by Toxicology Branch to be a toxic response. The position is supported by the observation that both of the two high dose group animals that were examined also demonstrated this lesion, whereas none of the control animals did.

The following metabolism studies were conducted at the Shell Toxicology Laboratory (TUNSTALL):

The Metabolism of WL 43467 in mammals. (1). The fate of a single oral dose of [^{14}C benzyl 43481] WL 43481 (cis WL 43467) in the rat. July, 1976

Six male and six female Wistar rats, 12 weeks of age were dosed with 0.6 mg of the cis isomer of cypermethrin labelled in the ring position of specific activity of 34.96 uCi/mg. Following dosing each rat was housed individually in a metabolism cage. Two rats of each sex were sacrificed at 24 hours, 72 hours and eight days after the initial dose administration. Urine, feces, blood and tissue samples were analyzed for radioactivity.

Results:

After 72 hours 87% or more of the radioactivity was excreted via the urine or feces. The male had a higher proportion of the labelled material in the urine. The females had a higher proportion in the feces. After 8 days, there were still traces of radiolabelled material (unidentified) in the carcass. For example, the two males retained 2.8 and 1.4%, the two females retained 2.1 and 0.9%. The fat tissue retained the most ^{14}C (< 1 ppm concentration); the liver and muscle retained .06 and .04 ppm. The structures of the urinary metabolite of cypermethrin from the cis isomer with the ^{14}C benzyl label are depicted in the figure appended to this review.

The Metabolism of WL 43467 in Mammals. The Fate of a Single Oral Dose of [^{14}C] WL 42641 (trans WL 43467) in the Rat

October, 1976.

Three male and three female Wistar rats were given a single oral dose of [^{14}C] WL 42641 (0.6 mg) in corn oil (0.8 ml) and individually housed in metabolism cages. The expired air from a rat of each sex was trapped for ^{14}C analysis. Urine and feces were collected and the rats were sacrificed 72 hours after treatment.

Results:

After 72 hours 71.4% (average) of the dose was recovered in the urine from the males, 74.4% (average) was recovered in the urine of the females. The feces contained 28.3% and 22.7% for the males and females. The male rat expired 0.03% and the female rat expired 0.04% of the administered dose as $^{14}CO_2$. From 1.4 to 3.9% of the dose was recovered in carcass of the males and from 1.6 to 4.2% was recovered in the carcass of the females. The intestines and skin retained ther highest amounts. The fat tissue retained the highest concentration, 0.18 ppm average in the male and 0.46 ppm average in the female.

The Metabolism of WL43467 in Mammals. The Fate of a Single Oral Dose of [^{14}C - cyclopropyl] WL 43467 in the Rat.

January, 1977

Three male and three female Wistar rats (430 gm males, 240 gm females) were dosed with single oral doses of [^{14}C] WL 43467 (specific activity 9.6 uCi/mg) in corn oil. Approximately 0.52 mg were administered. Each rat was placed in an individual animal metabolism cage. One male and one female were placed into air tight metabolism cages for quantitation of expired $^{14}CO_2$. The urine and feces were collected for a 72 hour period after which the rats were sacrificed with Nembutal.

Results:

Averages of 55.8% and 66.5% of the label was recovered in the urine, and 28.7% and 27.0% of the label was recovered in the faeces, less than 0.1% was recovered in the expired air; 13.3% and 5.8% of the label remained in the males and females respectively. The liver contained (.37 ppm for males and .12 ppm for females) and fat (0.31 ppm for males and 0.72 ppm for females) retained the highest concentrations of label.

Total recovery of the label was 104.2% for the males and 103.7% for the females.

The Elimination of Residues from the Fat of Rats Following Oral Administration of [^{14}C - Benzyl] WL 43481 (cis -WL 43467)

June, 1978

[^{14}C-benzyl] cypermethrin (cis) was synthesized and administered in corn oil to 8 female rats at a dosage level of 2.5 mg/kg. The rats were maintained in cages and thereafter sacrificed in groups of two on days 8, 14, 25, and 42. Following sacrifice, samples of the fat (peritoneal), liver and kidney were removed for radioassay. Analysis for radioactivity was done by combusting 50 mg of fat or 100 mg of liver or kidney. The tissues were also analysed for the presence of cypermethrin by gas chromatography.

Results:

At day 8, the fat samples had radioactivity concentrations of 0.34 and 0.31 ppm. Whereas the liver and kidney had concentrations of .018 (average of two) and 0.0085 (average of two) ppm respectively. At day 42, the fat samples had concentrations of 0.045 and 0.055 ppm and the liver and kidney were < .001 ppm.

Analysis of the residue in the fat indicated that at day 8, 88% of the radioactivity was as cypermethrin and at day 25, 100% of the radioactivity was as cypermethrin as determined by gas chromatography.

A Study of the Metabolism of 3-Phenoxybenzoic Acid and its Glucoside Conjugate in Rats

December, 1978.

The metabolism of 3-phenoxy[^{14}C] benzoic acid was studied in rats (Wistar) by administering doses of the free acid and a glucoside conjugate isolated from plants. The glucoside conjugate was prepared by applying the free acid to Spanish cotton leaves, allowing time for metabolism and isolating the glucoside metabolite. These compounds are both considered to be principle metabolites of cypermethrin and certain other synthetic pyrethrins. Following administration, the urine and faeces and body tissues were analyzed for radioactivity. Five rats of each sex were treated with the free acid and two rats of each sex were dosed with the glucoside.

Results:

After 8 days, the males and females following dosing with the free acid excreted 81.5% and 79.8% of the dose in the urine and 12.1% and 18.4% in the faeces; 7.9% and 4.1% of the dose remained in the animals for the males and females respectively.

For the glucoside conjugate, 90% and 81.35% was recovered in the urine, 7.45% and 15.0% was recovered in the faeces, and 0.9% and 0.8% remained in the animals for the males and females respectively.

Attempts were made to identify the metabolites in the urine by chromatography and mass-spectra. The proposed metabolic pathway is shown in the appended table. The gucoside conjugate and the free acid following oral administration were shown by the data presented to yield the same metabolites both qualitatively and quantitatively.

The Metabolic Fate of the cis and trans-isomers of Cypermethrin in the Rat. Metabolites Derived from the ^{14}C-Labelled Cyclopropyl Ring.

November, 1978

Animal Experiments:

A number of experiments were carried out (all on Wistar strain rats), some for confirmatory purposes, some with separate isomers and some further work because the urinary glucuronides detected in preliminary studies proved to be unstable even during frozen storage and fresh material was required. These experiments are listed in sequence for ease of reference. All dosing was via the oral route, using a ball-ended needle attached to a 1 ml syringe.

Experiment 1.
This was the experiment used to acquire excretion/retention data (see page 15 of this review. Three male and three female rats (male, 430 g; female 240 g) were given single oral doses of [^{14}C]cypermethrin (0.52 mg) in corn oil (0.8 ml). Each rat was housed in a Jencons metabowl and urine and faeces were collected for three days.

Experiment 2.
A male rat was dosed with 0.58 mg of [^{14}C]cis-cypermethrin in 0.35 ml of corn oil. A second male rat was dosed with 0.55 mg of [^{14}C]trans-cypermethrin in 0.35 ml of corn oil. Urine and faeces were collected for three days.

Experiment 3.
A male rat was dosed with 0.89 mg of [^{14}C]cypermethrin in 0.5 ml of corn oil. Urine was collected for 18 hours.

Experiment 4.
Two male rats were each dosed with 0.68 mg of [^{14}C]cypermethrin in 0.8 ml of corn oil. Urine was collected for 24 hours.

Experiment 5.
One male rat was dosed with 0.5-0.6 mg of [^{14}C]cis-cypermethrin and urine collected for 20 hours.

Experiment 6.
The bile duct of a male rat (230 g) was cannulated under anaesthesia and the animal was then dosed with 0.52 mg of [^{14}C]cypermethrin in 0.8 ml corn oil. Bile (7 ml) was collected for 4.5 hours while the rat was maintained under thiopentone anaesthesia.

Experiment 7.
A male rat was dosed orally with 0.52 mg of [^{14}C]cypermethrin in 0.8 ml of olive oil. The bile duct was then cannulated as above and bile (3.7 ml) was collected for 4 hours under anaesthesia.

Experiment 8.
A male rat was treated as described for Experiment 6, but dosed with half (0.26 mg) of the compound given above. Bile (3.2 ml) and urine (0.4 ml) were collected for 5 hours while the animal was held under anaesthesia.

Experiment 9.
This experiment was carried out 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 cis [^{14}C]cypermethrin in 0.5 ml of corn oil. Urine and faeces were collected daily for three days and composite samples (0-2 days) of urinary and faecal samples from both rats were prepared. Two other female rats were orally dosed with 0.87 mg of trans [^{14}C]cypermethrin in 0.45 ml of corn oil. Urine and faeces were collected daily for three days and composite samples (0-2 days) prepared. Composite faecal samples (2 g) were extracted by homogenisation with methanol (2 x 10 ml) at room temperature using an 'Ultra-Turax' homogeniser. The extract and solid residue were separately radioassayed (the latter, via combustion to CO_2).

When necessary, urine, faeces and bile samples (Experiment 1-9) were stored frozen at -20°C (± 5°) prior to and/or after analysis.

RESULTS

The results of these studies as demonstrated by the data presented indicated that the rapid metabolism of cypermethrin is due to the efficient cleavage of the ester linkage of both isomers and the elimination of the cyclopropanecarboxylic acid moiety largely as glucuronic acid conjugate. Hydroxylation of the methyl groups on the cyclopropane ring occurs to a limited extent. Most of the hydroxylated products observed had also suffered ester cleavage. The faecal radioactivity was due mostly to unchanged pyrethroid. In accord with this finding was the very limited elimination of radioactivity in the bile and most of the metabolites were eliminated via the kidneys and not via the biliary-intestinal-faecal route.

The appended table shows the results of chromatographic analysis of the urinary metabolites of cypermethrin.

It is noted that cypermethrin does accumulate to at leat some minor degree as indicated by their being some residues in the animals 8 days or more following administration.

Acute Toxicity Studies GFU 034A: A Formulation of Synthetic Pyrethroid Insecticide Cypermethrin (36% w/v)

Hazelton Laboratories (Europe) January, 1980; Report No. 2148-38/65-69.

1. Acute Oral Toxicity Study in Rats.

Four groups of ten fasted Wistar rats (5 male and 5 female) were dosed by gavage with 125, 177, 250 and 353 mg/kg of test material (36% cypermethrin) and observed for 14 days.

Results:

The major clinical signs reported were body tremors, ataxia and paralysis of the hind limbs. These reponses increased with increases in dose level. The rats that died, died during the first 24 hours, and the symptoms disappeared after 72 hours in the survivors. The animals that died as a result of the poisoning showed "dark red lungs". An LD50 of 270 mg/kg for both sexes was determined.

Core Guidelines. Toxicity Category II.

2. Acute Dermal Toxicity in the Rabbit.

A group of ten (5 male and 5 female) New Zealand White rabbits were prepared and administered a single dose of 2000 mg/kg of test material (cypermethrin 36%). Another group of ten rabbits (4 males and 6 females) served as a control group. The animals were observed for 14 days after dosing.

Results:

No rabbits treated with cypermethrin formulation died. One control female died. No clinical signs of intoxication resulted. Necropsy did not reveal treatment related internal lesions. This test is Core Minimum. The dermal LD50 is defined as > 2000 mg/kg or Toxicity Category III.

3. Primary Skin Irritation in the Rabbit.

0.5 ml undiluted test material (36% formulation of cypermethrin) was applied to the prepared backs of 6 New Zealand White rabbits and held in placed for 24 hours.

A primary irritation index of 2.1 (Draize method) was obtained based on appearance of erythema and oedema.

Core Guidelines. Toxicity Category III.

4. Eye Irritation Study in the Rabbit.

Nine New Zealand White rabbits were dosed in their right eyes with 0.1 ml of test material (36% cypermethrin formulation) and their eyes were examined for damage. The eyes of 3 of these rabbits were flushed with water for one minute 20-30 seconds after instillation.

Results:

Severe conjunctival irritation was noted in all rabbits. Five of the six rabbits developed diffuse opacity within 24 hours. At day seven, five of the six rabbits still showed corneal opacity.

Washing appeared to diminish the response because the corneal opacity did not presist to day 7 in flushed rabbits.

Core Guidelines. Toxicity Category I.

5. Sensitization Study in the Guinea Pig Magnusson-Kligman Guinea Pig Maximization Test. Test Article: Cypermethrin Fomulation GFU 034A.

Induction:

A group of ten female guinea pigs (Hartley-Dunkin strain) were prepared and intradermal injections of 0.1 ml of either "complete adjuvant" 50% in water, 0.1 ml of 5% v/v test article (GFU-034A), or 0.1 ml of 5% v/v test article emulsified in adjuvant. One week later the same area was again prepared and a filter paper saturated with 10% v/v solution of test article was applied to the area and held in place for 48 hours.

A positive control group (ten guinea pigs treated with benzyl penicillin) were also similarly prepared. Parallel uninducted control groups were prepared for both cypermethrin and benzyl penicillin.

Challenge Phase:

Two weeks after the induction phase, the area was again prepared and test material or benzyl penicillin was applied by holding in place for 24 hours.

Results:

Positive reactions were noted for cypermethrin treated animals in two of the ten test animals within 24 hours and in one more test animal at the 48 hour observation. The untreated controls did not develop positive responses. The test animals treated with benzyl penicillin responded by showing severe sensitization.

These data indicate that this formulation of cypermethrin is a "mild sensitizer". This study is Core Minimum. The number of induction applications was not stated.

Cypermethrin 3E (Formulation GFU 061): Four Hour Exposure by Inhalation in the Rat

ICI Central Toxicology Laboratory, Feburary 14, 1980, CTL/P/536.

Ten male and ten female Wistar-derived rats were used in this experiment. The test group, five of each sex were exposed to vapors generated by blowing air through a glass bubble containing cypermethrin formulation. The control group was exposed to air only. Exposure was for 4 hours.

Results:

No animals died as a result of exposure. The clinical signs of CNS toxicity included depression of the auditory response. Autopsy (15 days after exposure) was unremarkable.

This test is Core Supplementary. The anlayses of the atmosphere indicated a very low level of cypermethrin although a nominal concentration of 12.7 mg/l of material was present during the exposure but only 0.039 mg/l of this was as cypermethrin. The method of generating the atmosphere apparently resulted in unequal generation of the more volatile components of the formulation.

Attachment

OPP:HED:TOX: J.DOHERTY:sb 9/18/81 X73713 Rm 815 CM 2 #m3

Table 2C

Excretion Patterns For Radioactivity Following Oral Administration Of ^{14}C-Labeled Cypermethrin To Rats

Substance Administered	Number of Rats Dosed, Per Sex	Dose levels (mg/kg bodyweight)	Interval After Administration (hours)	Cumulative % Of Administered Radioactivity Excreted In				% Of Dose* Not Excreted		Reference
				Urine		Feces				
				Males	Females	Males	Females	Males	Females	
^{14}C-benzyl cis-cypermethrin	6	1.7 (males) 2.4 (females)	24 48 72	53 60 62	35 43 44	19 26 31	36 48 50	- - 6.0	- - 3.6	7C
^{14}C-benzyl trans-cypermethrin	3	2.4 (males) 3.0 (females)	24 48 72	59 69 71	62 73 74	19 26 28	16 21 23	- - 1.7	- - 2.0	8C
^{14}C-cyclopropyl 50:50 cis:trans-cypermethrin	3	1.2 (males) 2.1 (females)	24 48 72	32 53 56	48 64 66	- - 29	- - 27	- - 4.9	- - 3.0	10C

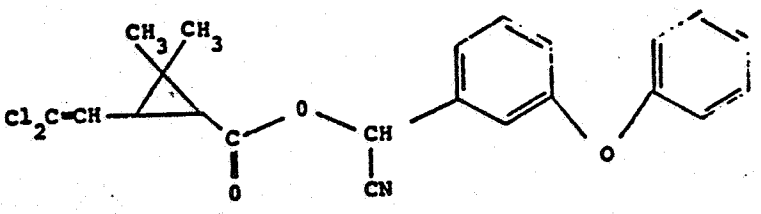
Positions of radiolabeling are shown in Figure 1C.

* excluding that remaining in the intestines.

Figure 1C

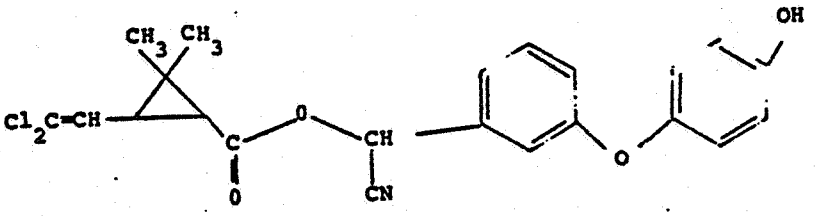
Structures Of Cypermethrin And Of Animal Metabolites

I Cypermethrin (PP383)



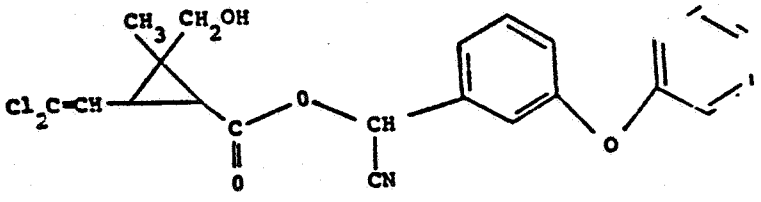
(RS)-α-cyano-3-(phenoxyphenyl)methyl (1RS)cis,trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate.

II



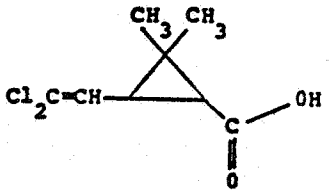
(RS)-α-cyano-3-(4-[hydroxyphenoxy]phenyl)methyl (1RS)-cis,trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate.

III



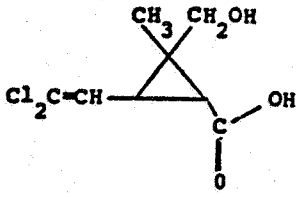
(RS)-α-cyano-3-(phenoxyphenyl)methyl (1RS)-cis,trans-3-(2,2-dichloroethenyl)-2-hydroxymethyl-2-methylcyclopropanecarboxylic acid.

IV



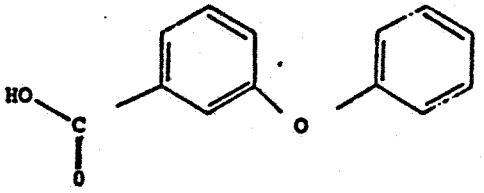
(RS)-cis,trans-3-(2,2-dichloroethenyl-2,2-dimethylcyclopropane-carboxylic acid

V



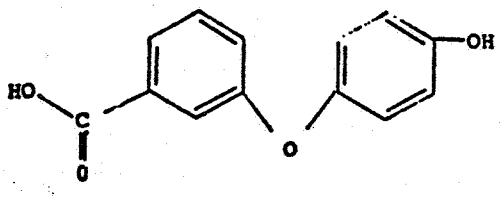
(RS)-cis,trans-3-(2,2-dichloroethenyl)-2-hydroxymethyl-2-methylcyclopropane carboxylic acid

VI



3-phenoxybenzoic acid

VII



3-(4-hydroxyphenoxy)benzoic acid.

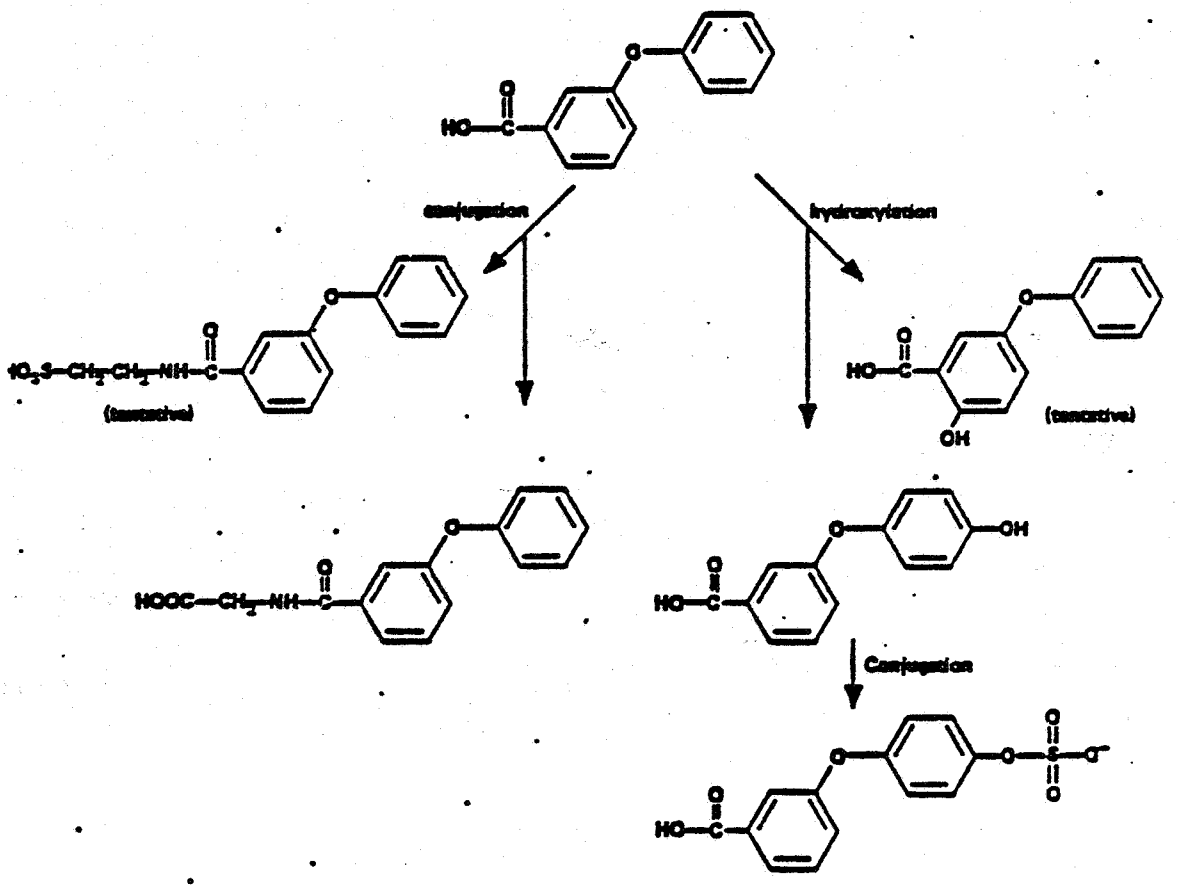


Fig 11 Summary of the metabolism of 3-phenoxy benzoic acid in rats

CYPERMETHRIN TOXICOLOGY REVIEWS

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