2/2/90

PEER REVIEW FILES

CHEMICAL NAME: Cypermethrin(-Minus)
CASWELL NO.: 271DD
CAS NO.: 52315-07-8
REVIEWER: Doherty

CURRENT AGENCY DECISION

C (HED)

TUMOR TYPE / SPECIES

Benign lung adenomas (increase in both adenomas & adenomas/carcinomas combined; Alderly Park SPF Swiss strain mice (F).

REVIEWER PEER REVIEW PACKAGE	PEER REVIEW MEETING DATE	PEER REVIEW DOCUMENTS	PEER REVIEW CLASSIFICATION
5. / /	5. / /	5. / /	5.
4. / /	4. / /	4. / /	4.
3. 09/19/88	3. 09/12/88	3. 09/27/88	3. C
2. 01/19/87	2. 07/22/87	2. 09/06/88	2. C
1. 04/16/86	1. 05/01/86	1. 02/17/88	1. Add data needed

SAP MEETING	SAP CLASSIFICATION
2. / /	2.
1. / /	1.

QUALITATIVE/QUANTITATIVE RISK ASSESSMENT DOCUMENT	GENETIC TOXICITY ASSESSMENT DOCUMENT
2. / /	1. /
1. /	

MISCELLANEOUS:

Stamped 2/2/90; EPA-007517; about 200 p.; mna.

Peer Review Documents
(Memo dates)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

SEP 27 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Ad Hoc Peer Review of Cypermethrin-Minus.

FROM: John Doherty
Insecticide Rodenticide Branch
Health Effects Division (TS-769)

TO: George LaRocca
Product Manager #15
Registration Division (TS-767)

THROUGH: Edwin Budd
Section Head
Insecticide Rodenticide Branch
Health Effects Division (TS-769)

THROUGH: Reto Engler
Science Analysis and Coordination Branch
Health Effects Division (TS-769)

The Health Effects Division Peer Review Committee met on September 12, 1988 to discuss the toxicity studies required to register a modified technical grade of cypermethrin to be called cypermethrin-minus that differs from the currently registered product cypermethrin in that it contains an enrichment of the insecticidally active isomers.

A. Individuals in Attendance

1. Peer Review Committee: (Signature indicates concurrence with the peer review unless otherwise stated.)

Reto Engler _____

William Burnam _____

Judith Hauswirth _____

Marcia VanGemert _____

Richard Levy _____

2. Scientific Reviewers: (Non-committee members responsible for presentation of the background information; signatures indicates technical accuracy of the panel report).

Edwin Budd Edwin R. Budd 9/15/82

John Doherty _____

3. Peer Review Members in Absentia. (Committee members who were not able to attend the discussion; signatures indicate concurrence with overall conclusions of the committee.)

Theodore Farber Theodore Farber

John A. Quest Absent Excused

Esther Rinde Esther Rinde

B. Material Reviewed:

The material reviewed consisted of (1) a copy of a presentation made by Dr. William Hymans of the FMC Corporation describing the product chemistry of the products cypermethrin and cypermethrin-minus and other information related to the proposed new product; (2) a copy of a memo from J. Doherty for EPA Reg. No.: 279-3026 AND 279-3027 concerning FMC Corporation's proposal to conduct toxicity studies with cypermethrin-minus.

C. Overview of the Issue.

The FMC Corporation has proposed to register their product cypermethrin-minus which contains an enrichment of the insecticidally active isomers of cypermethrin with a concomitant lower concentration of the noninsecticidally active isomers. The currently registered product consists of 8 isomers with percentage compositions ranging from 11-14%. The product cypermethrin-minus will also consist of 8 isomers but four insecticidally inactive ones will be present at a concentration of 1% each. The remaining 4 isomers, two of which are regarded as being the most insecticidally active, will be present at a concentration of 24% each. The registrant has already agreed to

conduct several study types to support the registration of cypermethrin-minus. The registrant proposed that the other toxicity studies needed to support the registration of cypermethrin-minus could be utilized from the existing toxicity data base for cypermethrin. The main issue which the Peer Review Committee needed to discuss was whether or not a new mouse oncogenicity study with cypermethrin-minus would be required. Cypermethrin was previously determined by the Toxicology Branch Peer Review Committee (report dated Feb. 17, 1988) to be a weak category C oncogen (with no quantitative estimation of human risk being necessary).

D. Conclusions of the Ad Hoc Peer Review Committee.

1. Requirement for a new mouse oncogenicity study.

The Ad Hoc Peer Review Committee unanimously agreed that a new mouse oncogenicity study with the technical grade of cypermethrin-minus need not be conducted. The following reasons were indicated as justification for this conclusion.

a. Dietary and user exposure of humans to the most active isomers will not be significantly changed.

b. No new isomers will be introduced into the product.

c. All isomers in the proposed product cypermethrin-minus have already been tested for oncogenicity when the mouse oncogenicity study was conducted with cypermethrin.

2. Additional recommendations regarding non-oncogenic toxicity testing.

The Ad Hoc Committee also commented that the acute dermal and inhalation toxicity studies, the primary eye and dermal irritation studies and the dermal sensitization studies need not be conducted with technical grade cypermethrin-minus (but should be conducted with the end use product). An acute oral toxicity study with technical grade cypermethrin-minus should still be conducted.

The Ad Hoc Committee concurred with the registrant's proposal to submit a 90-day feeding study with rodents, a teratology study, a 2-generation reproduction study and a battery of mutagenicity studies. The remaining study types can be utilized from the existing toxicity data base with cypermethrin.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Ad Hoc Peer Review of Cypermethrin.

FROM: John Doherty
Insecticide Rodenticide Branch
Health Effects Division (TS-769)

TO: Reto Engler, Chief
Science Analysis Coordination Branch
Health Effects Division (TS-769)
and
Addressees

THROUGH: Edwin Budd, Section Head
Review Section I
Insecticide Rodenticide Branch
Health Effects Division (TS-769)

As per the memorandum dated September 6, 1988 an "ad hoc" peer review meeting to discuss issues related to toxicity testing requirements for a technical grade of cypermethrin with its composition enriched in the insecticidally active isomers will be convened on September 12, 1988.

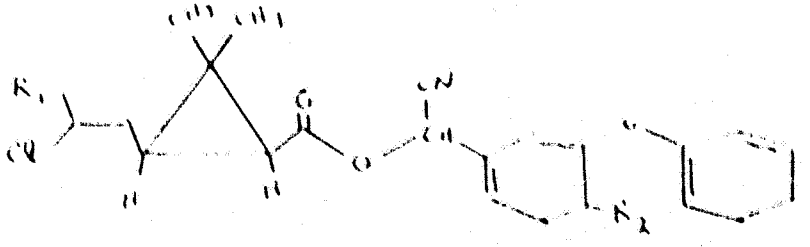
Attached are two documents which should be read prior to the meeting. These are:

1. Information provided by Dr. William Hymans of the FMC Corporation presenting the product compositions of cypermethrin and cypermethrin-minus and citing the examples of Pydrin/Asana and Karate/Alphamethrin as precedent examples of "bridging" toxicity data bases to support the registration of technical pyrethroid products of varying isometric composition.

2. Memo from J. Doherty to George LaRocca for EPA Reg No. 279-3026 and 279-3027 concerning FMC Corporation's proposal to conduct toxicity studies with cypermethrin-minus.

Addressees:
T. Farber
W. Burnam
J. Hauswirth
M. VanGemert
J. Quest
E. Rinde
R. Levy

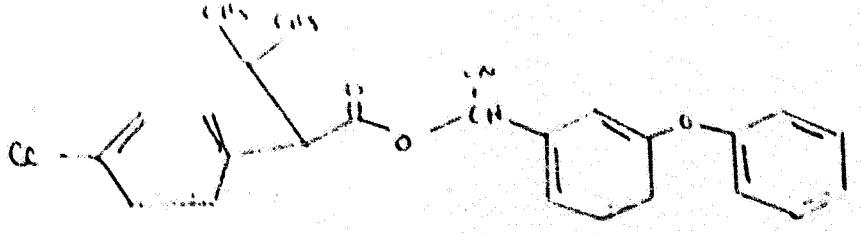
PYRETHROID CHEMICAL STRUCTURES



R_1 = Cl R_2 = H CYPERMETHRIN (AMMO/CYMBUSH)

R_1 = Cl R_2 = F CYFLUTHRIN (BAYTHROID)

R_1 = CF_3 R_2 = H CYHALOTHRIN (KARATE)



FENVALERATE (PYDRIN/ASANA)

CYHALOTHRIN PRECEDENT

- KARATE IS THE CYHALOTHRIN EQUIVALENT OF ALPHAMETHRIN

- OUR UNDERSTANDING IS THAT IT'S REGISTRATION WAS SUPPORTED BY LONG TERM TOXICITY TESTING ON A DIFFERENT ISOMER MIX THAN THAT WHICH WAS REGISTERED.

FENVALERATE PRECEDENT

EPA REGISTERED S-FENVALERATE

- WITH THE SAME CROP TOLERANCES AS APPLIED TO FENVALERATE

- BRIDGING TOXICOLOGY WITH A SUBCHRONIC RAT STUDY (UPON WHICH THE ADI WAS SET) AND A CHRONIC DOG STUDY BOTH OF WHICH WERE PERFORMED WITH A TEST SUBSTANCE THAT CONTAINED ONLY 75% OF THE ACTIVE ISOMER.

PROPOSED TOXICITY TESTING WITH CYPERMETHRIN-N TO BRIDGE TO CYPERMETHRIN

- ACUTE BATTERY (TECHNICAL AND FORMULATION)
- MUTAGENICITY BATTERY
- SUBCHRONIC RAT STUDY
- TERATOLOGY STUDY USING ONE SPECIES
- TWO-GENERATION RAT REPRODUCTION STUDY (CYPERMETHRIN ADI WAS ESTABLISHED BASED ON RESULTS OF A RAT REPRODUCTION STUDY)

FENVALERATE PRECEDENT

EXPOSURE TO MAN AND THE ENVIRONMENT

- EXPOSURE OF 2S-4S ISOMER

  FENVALERATE: 0.2 LBS AI/A X 25% = 0.05 LBS AI/A

  S-FENVALERATE: 0.05 LBS AI/A X 100% = 0.05 LBS AI/A

- EXPOSURE IS IDENTICAL

  CONSEQUENCES.....

PERCENT COMPOSITION OF CYPERMETHRIN PRODUCTS

NAME	ISOMER	CYPE	CYPE-M	CYPE-S	ALPHA METHRIN
CIS-1	1S-CIS-S	14	1	22	2
	1R-CIS-R	14	1	3	2
CIS-2	1R-CIS-S*	11	24	[illegible]	48
	1S-CIS-R	11	24	[illegible]	48
TRANS-1	1S-TRANS-S	14	1	[illegible]	0
	1R-TRANS-R	14	1		0
TRANS-2	1R-TRANS-S*	11	24	22	0
	1S-TRANS-R	11	24	3	0

* INSECTICIDALLY ACTIVE ISOMERS

FENVALERATE PRECEDENT

BIOLOGICAL ACTIVITY/USE RATES

BIOLOGICAL ACTIVITY

- PERCENT ACTIVE ISOMER IN FENVALERATE = 25%
- PERCENT ACTIVE ISOMER IN S-FENVALERATE = 100%
- BIOLOGICAL ACTIVITY RATIO = 100/25 = 4

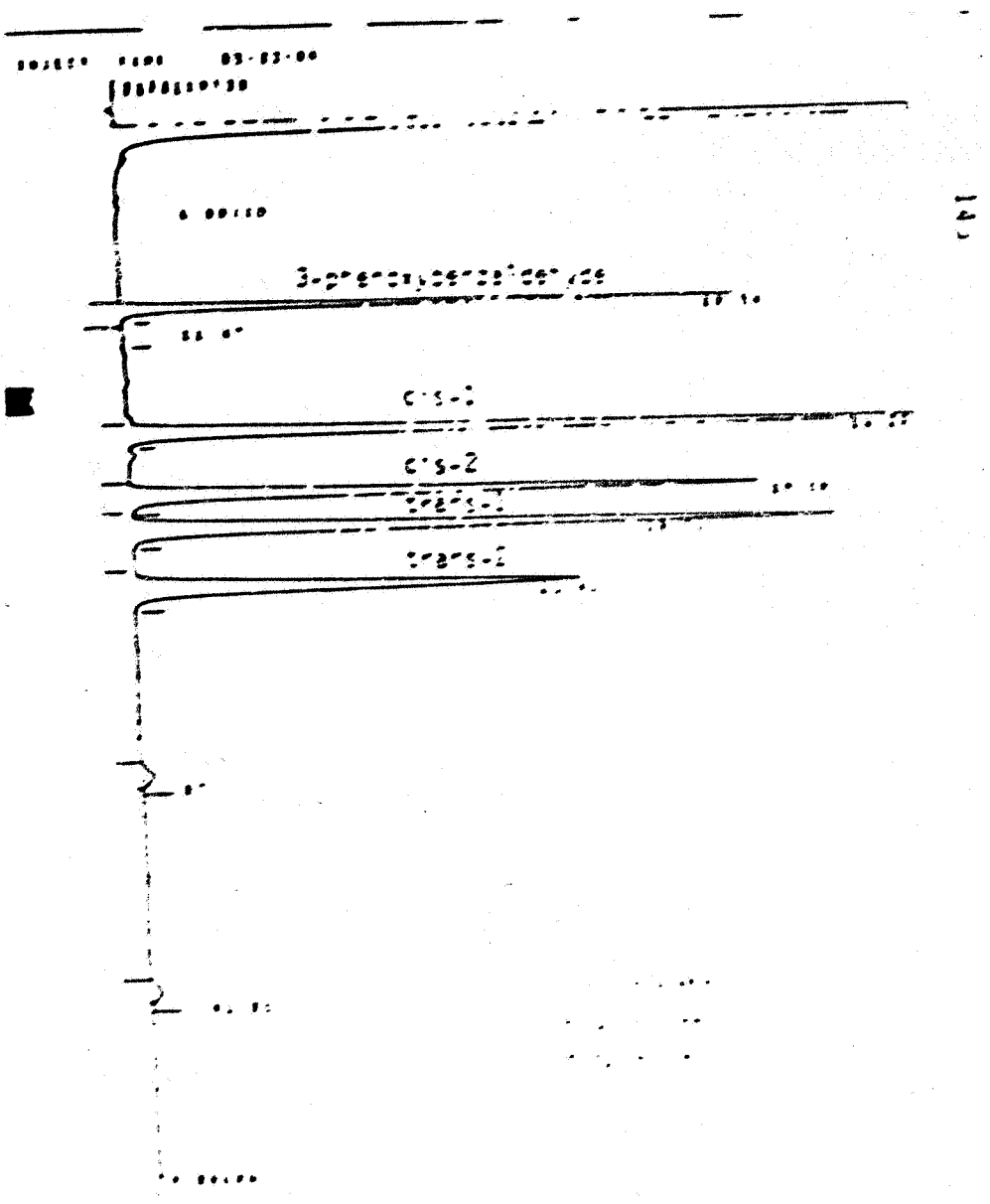
LABEL USE RATE

- FENVALERATE = 0.2 LBS AI/A
- S FENVALERATE = 0.05 LBS AI/A

Appendix C

007701

Normal Phase HPLC Spectrum of Cobermethrin Technical



FENVALERATE PRECEDENT

PERCENT COMPOSITION

ISOMER	FENVALERATE	S-FENVALERATE
2S-αS*	25	100
2R-αR	25	0
2S-αR	25	0
2R-αS	25	0

* ACTIVE ISOMER

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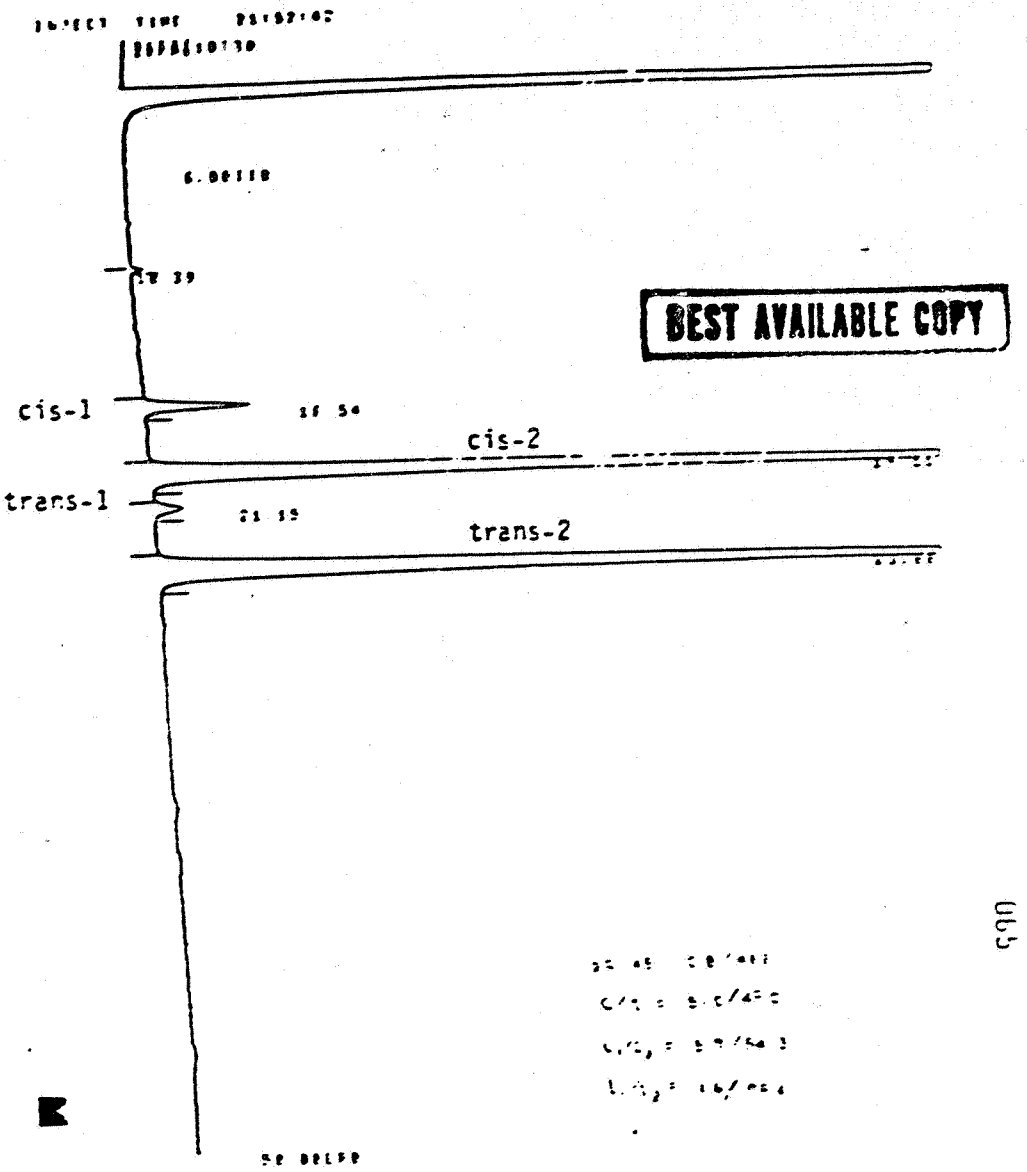
Appendix C

Normal Phase HPLC Spectrum of Cypermethrin-Minus



EXPOSURE TO MAN AND THE ENVIRONMENT

* EXPOSURE (LBS AI/A) = USE RATE (LBS AI/A) X ISOMER % CONTENT

Ex. 1R-CIS-S ISOMER

CYPE: 0.1 LBS AI/A X 11% = 0.011 LBS AI/A

CYPE-M: 0.045 LBS AI/A X 24% = 0.011 LBS AI/A

* EXPOSURE IS IDENTICAL

CONSEQUENCES:

-- EXISTING CYPE TOLERANCES SHOULD COVER CYPE-M

-- DATA BASE SUPPORTING CYPE SHOULD BRIDGE TO CYPE-M

BIOLOGICAL ACTIVITY/USE RATES

BIOLOGICAL ACTIVITY

* PERCENT ACTIVE ISOMER IN CYPE = 22%
* PERCENT ACTIVE ISOMER IN CYPE-M = 48%
* BIOLOGICAL ACTIVITY RATIO = 48/22 = 2.2

USE RATE

* MAXIMUM USE RATE FOR CYPE = 0.1 LBS AI/A
* MAXIMUM USE RATE FOR CYPE-M = 0.1/2.2 = 0.045 LBS AI/A

007707

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. NOs.: 279 3026 and 279 3027. Cypermethrin and Cypermethrin Minus: FMC Corporation's proposal to conduct toxicity studies with Cypermethrin Minus.

TOX CHEM Nos.: 271DD (Cypermethrin)
271DE (Cypermethrin-minus)
TOX PROJECT No.: 8 0801
Record Nos.: 223396
223397

FROM: John Doherty
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: George LaRocca
Product Manager #15
Registration Division (TS-767)

THROUGH: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

The FMC Corporation (refer to letter from Susan E. Burkart dated April 8, 1988, attached) is seeking to register anew technical grade cypermethrin product called cypermethrin-minus. According to the FMC Corporation, cypermethrin minus "is identical to cypermethrin in the common (chemical) name, cis/trans isomer ratio, optical activity, isomer composition, and technical CSF impurity profile". Cypermethrin minus differs from cypermethrin in that the "concentration of inactive isomers has been decreased significantly, and that of the active isomers has been increased approximately two fold". The result of the modification is that the new product is more insecticidally active and less product will have to be used.

The FMC Corporation is proposing to conduct only selected toxicity studies with cypermethrin minus and is requesting to utilize existing studies conducted with cypermethrin to support the registration of cypermethrin minus.

The following table list each study type that would be required for the registration of cypermethrin minus assuming that cypermethrin minus will be registered for the same uses for which cypermethrin is currently registered. The table also lists the testing status for each study type which is based either on Dr. Burkart's letter of April 8 or a meeting held on February 23, 1988.

Study Type	Testing Status
81 1. Acute Oral toxicity rats	New Study*
81 2. Acute Dermal toxicityÚÚ rabbits	New Study
81 3. Acute Inhalation toxicityÚÚ rats	New Study
81 4. Eye Irritation rabbits	New Study
81 5. Dermal Irritation rabbits	New Study
81 6. Dermal Sensitization guinea pigs	New Study
82 1. Subchronic oral rodent	New Study
82 1. Subchronic oral nonrodent	Existing**
82 2. 21 day repeated dose dermal	No Plans***1
82 4. Subchronic inhalation 90 day	No Plans2
83 1. Chronic toxicity rat and dog	Existing
83 2. Oncogenicity rat	Existing
83 2. Oncogenicity mouse	Not resolved
83 3. Teratogenicity one species	New Study
83 3. Teratogenicity other species	Existing
83 4. 2 Generation Reproduction rat	New Study
84 2. Mutagenicity and Genetic toxicity Battery	New Studies
85 1. Metabolism	Existing

See the following page for footnotes.

*New Study: A study with cypermethrin minus as the test material is proposed to be conducted and submitted.

**Existing: Data from an existing study conducted with cypermethrin will be used to meet this study requirement for cypermethrin minus.

***No plans: No indications that the registrant plans to conduct a study of this type or to utilize cypermethrin data were made.

1. The FMC Corporation has not submitted a 21 day dermal toxicity study with cypermethrin. TB records indicate that this study was submitted by the ICI Corporation. No provisions were made known to TB which indicated that ICI studies could be utilized to support the registration of cypermethrin minus. This study type (21 day dermal toxicity study) is required of all pesticides unless it can be demonstrated that the pesticide will not come in contact with human skin.

2. A 90 day subchronic inhalation toxicity study will be required if cypermethrin minus will be used indoors in situations that will require constant inhalational exposure.

Toxicology Branch Comments.

The FMC Corporation's proposal to provide the new studies with cypermethrin minus as indicated above to support the registration of cypermethrin-minus is acceptable to Toxicology Branch (TB) but certain additional toxicity data are also required as indicated below.

1. In a previous memo concerning the toxicity data requirements for cypermethrin-minus, TB specifically indicated that the FMC Corporation must prepare a rational for requesting a waiver for the mouse oncogenicity study (refer to J. Doherty memo dated March 23, 1988). No specific mention was made of the mouse oncogenicity data requirement in Dr. Burkart's letter of April 8, 1988. Thus the issue of the requirement for a mouse oncogenicity study with cypermethrin-minus or whether this study type can be utilized from the existing data base with cypermethrin is not resolved. The concern for the requirement for a mouse oncogenicity study relates to the fact that cypermethrin is currently considered as a type C oncogen based on there commendation of the TB Peer Review COmmittee.

On Wednesday August 31, 1988 a meeting was held at the request of the FMC Corporation to further discuss the requirement for a mouse oncogenicity study (refer to notes of the

meeting prepared by J. Doherty and dated September , 1988). At this meeting Dr. Farber proposed that this issue be presented to an "ad hoc" HED Peer Review Committee for further consideration. This committee would consider the cypermethrin data base in total and make a recommendation regarding the need for a mouse oncogenicity study with cypermethrin minus. Dr. Farber also indicated that the classification of cypermethrin as a type C oncogen may be presented to the SAP for comment.

3. The subchronic rat oral (90 day) study must include a special assessment of the nervous system to assess for possible effects of cypermethrin-minus on axons such as swelling and splitting.

4. The registrant should be advised that pending receipt and review of the "new studies" to be conducted with cypermethrin-minus, TB may deem it necessary to require certain additional studies if there are indications of toxicity problems revealed by the studies scheduled for submission.

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

SEP 6 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Ad Hoc Peer Review on Cypermethrin

FROM: Reto Engler, Chief
Science Analysis Coordination Branch
Health Effects Division (TS-769)

TO: Addressees

Cypermethrin like the other pyrethroids has several stereo-isomers. Some isomers are more active (as insecticides) and also more toxic. As companies develop, isomer mixtures with a higher percentage of the active isomer, the question arises whether most or all major studies need to be repeated, or whether "bridging" studies are sufficient. The issue becomes further complicated in those cases where oncogenic effects were seen in previous studies.

A meeting to discuss the need for additional studies on an "improved" Cypermethrin isomer mixture is scheduled for Monday, September 12, 1988, at 10:30 in Dr. Farber's office. The previous Peer Review is attached.

Attachment

Addressees

T. Farber
W. Burnam
J. Hauswirth
M. vanGemert
J. Quest
E. Rinde
R. Levy
E. Budd
J. Doherty

pc#1 9/6/88 sp

007707

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

FEB 17 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Cyperzethrin

FROM: John A. Quest, Ph.D. JAQuest
Team Leader, Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Robert Taylor, Product Manager #25
Registration Division (TS-767)

The Toxicology Branch Peer Review Committee met on May 1, 1986 and on July 22, 1987 to discuss and evaluate the data base on Cypermethrin. Attention was focused on the oncogenic potential of the chemical in Alderly Park SPF Swiss strain mice. The hiatus between meetings was due to the time needed for the Peer Review Committee to receive additional information (i.e., historical tumor data, MTD information, and neurotoxicity data).

A. Individuals in Attendance

1. Peer Review Committee: (Signature indicates concurrence with the peer review unless otherwise stated.).

Diane Beal

Donald Barnes

William Burnam

[redacted]

Theodore M. Farber

Bernice Fisher

Judith Hauswirth

C. J. Nelson

John A. Quest

Esther Rinde

Robert Zendzian 2/4/88

2. Scientific Reviewers: (Non-committee members responsible for presentation of data; signature indicates technical accuracy of panel report.)

John Doherty

Edwin R. Budd

3. Peer Review Members in Absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with overall conclusions of the Committee.)

Anne Barton

Robert Belliles

B. Material Reviewed:

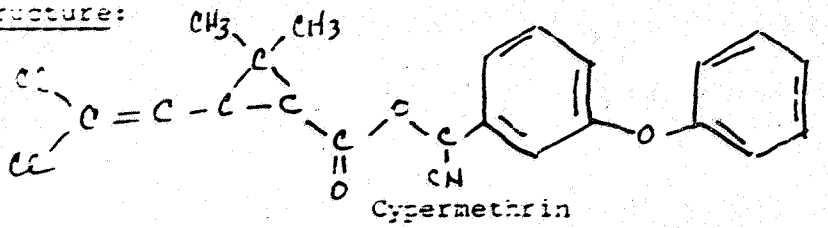
The material reviewed consisted of: (1) a background summary of available toxicology information on Cypermethrin; (2) various memoranda related to risk assessments and tolerance requests on Cypermethrin; (3) DER's of rat and mouse oncogenicity studies, a chronic dog study, and two 3-generation reproduction studies on Cypermethrin; (4) data on DER's of mouse oncogenicity studies with Permethrin, a structural analogue of Cypermethrin; (5) the one-liner data base on Cypermethrin; (6) information on historical control data for the mouse oncogenicity study; and (7) a qualitative risk assessment of tumors in female mice. Copies of these documents are attached to this memorandum.

C. Overview of Toxicology Issues:

Cypermethrin is a pyrethroid insecticide. The chemical has been developed by ICI Americas and the FMC Corporation; and both firms have requested that tolerances be established for use of Cypermethrin in/on raw agricultural commodities and as a food additive. The primary issue of concern to the Peer Review Committee in classifying the oncogenic potential of Cypermethrin was the finding of an

elev[illegible]idence of benign alveologenic tumors in the [illegible]ale Alderley Park SPF Swiss strain mice at the [illegible]se level that was tested.

Structure:



Cypermethrin

[± alpha-cyano-3-phenoxybenzyl(±)cis,trans,3-(2,2-dichloro-vinyl)-2,2-dimethyl cyclopropane carboxylate]

B. Evaluation of Oncogenicity Studies of Cypermethrin:

1. Mouse Oncogenicity Study:

Cypermetnrin was administered in the diet to 70 SPF Swiss strain mice (Alderley Park stock)/sex/dose level at doses of 0 (two separate control groups of N=70 animals/sex each), 100, 400 and 1600 ppm for 97 weeks (males) and 101 weeks (females). The study was conducted by ICI Central Toxicology Laboratory. The two separate sets of control groups were run concurrently in the study and were combined for statistical purposes. In each control and treatment group, 9-10 males and females/group underwent interim sacrifice at 52 weeks. The following incidence pattern of alveologenic lung tumors was observed in female mice (Table 1). No tumor response related to Cypermetnrin administration was observed in male mice.

Table 1: Lung Tumors in Female SPF Swiss Mice Administered Cypermetnrin in Diet

		Dose Level (ppm)			
Alveologenic Tumor Type	Sex	0	100	400	1600
Adenoma	Females	10/127(7.8%)	6/64(9.4%,	7/64(10.9%)	14/61(22.9%)b,c
Carcinoma		2/127(1.6%)	0/64(0%)	1/64(1.5%)	0/61(0%)
Combined		12/127(9.4%)	6/64(9.4%,	8/64(12.5%)	14/61(22.9%)a,c

a= p < 0.05, b= p < 0.01; Fisher's Exact Test, c= Statistically significant positive dose-related trend (p<0.[illegible]); Cochran - Armitrage Trend Test

Note: The denominators exclude animals that were examined, but died before the appearance of the first tumor (at week 46 in the 400 ppm dose group) in the study.

Cypermethrin produced a statistically significant increase in alveologenic adenomas, and in adenomas plus carcinomas combined, in female mice at the highest dose level (1600ppm) tested. There were also significant positive dose-related trends for these tumor combinations in female mice. No significant increases in carcinomas were observed. The Peer Review Committee noted the following additional information in regard to the increased lung tumorigenic response in female mice: (a) most of the adenomas were observed at terminal sacrifice and there was no decrease in latency for the time to tumor occurrence; (tumors were first seen at week 53 in the control females and at weeks 52 to 53 in the high dose females); (b) the incidences of lung tumors produced at the highest dose level of Cypermethrin exceeded the historical control incidences for lung adenomas (mean=9.6%; range=0 to 15.7%), and adenomas/carcinomas combined (mean 11.3%; range = 0 to 15.7%), in several contemporary studies conducted in female Swiss Alderley Park mice at ICI Laboratories between 1977 to 1985; (c) no compound - related nonneoplastic changes were observed in the lungs of treated female mice; (d) alveolar adenoma is a relatively common tumor in mice; (e) there were more malignant lung tumors in the control female mice than there were in the treated female mice (i.e. 2 carcinomas occurred in controls vs. 1 carcinoma in the treated groups); and (f) the highest dose level of Cypermethrin tested (i.e. 1600 ppm) was considered, based on weight gain decrements, to approximate (but not to exceed) a MTD level in both female and male mice.

2. Rat Oncogenicity Study:

Cypermethrin was administered in the diet to 52 SPF Wistar derived albino rats/sex/dose level at doses of 0 (control group no. 1), 0(control group no.2), 20, 150 and 1,000/1,500 ppm for 2 years. The high dose level was increased from 1,000 ppm to 1,500 ppm at study week 7. The study was conducted by ICI Central Toxicology Laboratory. The two separate sets of control groups were run concurrently in the study. Additional satellite groups of 12 males and 12 females/group underwent interim sacrifice at 52 weeks. No evidence of an oncogenic response was observed at any organ site in male or female rats with Cypermethrin. The highest dose level of

Cypermethrin tested in rats was considered to approximate, but not to exceed, a MTD level on the basis of decrements in body weight gain in both males and females.

3. Rat Oncogenicity Study:

Cypermethrin was administered in the diet to male and female SPF Wistar rats at dose levels of 0, 1, 10, 100 and 1,000 ppm for 2 years. The study was conducted by the Shell Toxicology Laboratory, and was considered by the Toxicology Branch to be of limited usefulness because an insufficient number of rats received the test chemical for the full 2 year dosing period. That is, the study was initiated with 96 rats of each sex in the control group and 48 rats of each sex in each dose group; However, interim sacrifices were performed on 12 rats/sex from the control group and 6 rats/sex from each dose group at 6 months and 12 months, and on 24 rats/sex from the control group and 12 rats/sex from each dose group at 18 months. Thus, the total number of rats that were scheduled to remain on test for the full 2 year feeding period were 48 rats/sex in the control group and 24 rats/sex in each dose group.

The only toxicological effects associated with Cypermethrin administration in this study were a slight depression in body weight gain (<10%) and lower food consumption at the 1,000 ppm dose level. No evidence of an oncogenic response was observed with Cypermethrin.

C. Additional Toxicity Data:

1. One-Year Dog Study:

The Committee briefly reviewed the results of a 1-year study of Cypermethrin in Beagle dogs that was conducted by ICI Central Toxicology Laboratory. The chemical was administered orally (capsule) to 6 dogs/sex/dose level at doses of 0, 1, 5 and 15 mg/kg/day. The NOEL was 1 mg/kg/day. The LEL was 5 mg/kg/day based on an increased incidence in the passage of liquid stools in both male and female dogs. In addition, dogs receiving the highest dose level (i.e. 15 mg/kg/day) exhibited an even greater increase in the passage of liquid stool plus a loss in appetite, tremors, gait changes, incoordination, disorientation and hypersensitivity. No other toxicological or nonneoplastic histopathological effects were observed.

2. Metabolism Studies:

Several studies were conducted in mice and rats, and in dogs in some cases, using single or repeated oral doses of ^{14}C-Cypermethrin. The results obtained were generally similar for the 3 species tested. Following oral ingestion of the compound, blood T 1/2 values ranged from 3 to 5 hours in rats. Tissue levels of radioactivity (RA) at 7 days after dosing were highest in fat, intestines, liver, kidney and skin in rats, and the residual level of RA in fat had a T 1/2 of 10-20 days in mice. The metabolism of Cypermethrin was similar in mice, rats and dogs; the compound was rapidly metabolized and excreted in the urine whereas it was essentially excreted unchanged in the feces. The metabolic pathway in urine consisted of hydrolysis of the esteratic site of Cypermethrin to yield dichlorovinyl cyclopropane carboxylate and 3-phenoxybenzoic acid. Conjugated forms (glucuronide, taurine and glycine) of the parent compound and the 3-phenoxy-moiety were also found. The Toxicology Branch reviewer noted that the major metabolites of Cypermethrin were similar to those of Permethrin, a structually related pyrethroid insecticide. The reviewer also noted that during the metabolism of Cypermethrin the cyano (CN-) group is eliminated from the molecule but that there was no evidence that cyanide toxicity resulted from ingestion of the chemical. In terms of excretion, approximately 90% of an administered RA dose was recovered from urine (range of 28 to 66%) and feces (range of 24 to 59%) at 7 days after dosing in mice and rats. Excretion of Cypermethrin by biliary and respiratory routes were of neglible significance.

3. Mutagenicity Studies:

Six mutagenicity studies were preformed with Cypermethrin. All were negative. These included 2 Ames tests using S.typhimurium (strains TA-1535, TA-1537, TS-1538, TA-98 and TA-100) and E. Coli (strains WP2 and WP2 uvrA) with or without metabolic activation, a Saccharomyces cerevisia yeast assay in vitro with or without metabolic activation, a host mediated assay in mice, a chromosome abberation study in Chinese Hamster bone marrow cells, and a dominant lethal assay in mice.

4. Reproduction/Teratology Studies:

Cypermethrin was evaluated for adverse reproductive activity in two 3-generation studies in rats. In the first study, the chemical was administered at dose level of 0, 50, 150 and 1000/750 ppm. The high dose level (1000 ppm) was reduced to 750 ppm at week 13 of the study because of observable signs of neurotoxicity (e.g. ataxia, increased sensitivity to sound, and high-stepping gait) in the F_0 treatment group. Other effects seen in this study included reduced food consumption and weight gain in mature rats (150 and 1000/750 ppm dose levels), and reduced offspring weight at days 0 to 28 postpartum (1000/750 dose level). No adverse reproductive effects were observed. Some Committee members made the observation that Cypermethrin produced signs of neurotoxicity in this reproduction study at a dose of 1000 ppm, but not in either one of the 2 rat oncogenicity studies discussed above (see sections D.2 and D.3.) at doses of 1000 to 1500 ppm. The committee had no definitive answer for this finding, but speculated that cis-trans ratio differences in the Cypermethrin administered in the different studies may have accounted for the greater toxicity in the reproduction study as opposed to the long term studies. In the second study, cypermethrin was administered at dose levels of 0, 10, 100 and 500 ppm, and no adverse effects were observed.

Cypermethrin was also examined for adverse activity in teratology studies in rats (dose levels of 0, 175, 35 and 70 mg/kg) and rabbits (dose levels of 0, 10 and 30 mg/kg). The only effect noted among the two studies was a reduced weight gain of the dams in the rat study at 35 mg/kg. No teratogenic effects occurred in either study.

5. Structure Activity Considerations

Cypermethrin is a close structural analogue of Permethrin. The latter compound differs from Cypermethrin only in the absence of the cyano (CN^-) group on the alpha carbon position. The Committee briefly considered oncogenicity data from 3 studies of Permethrin in mice.

(1). Charles River CD-1 mice received Permethrin in the diet for 24 months at doses of 0, 20, 500 and 2000 ppm in males and 0, 20, 2500 and 5000 ppm in females. A significant ($p<0.05$) increase in bronchiolar adenomas (12/75 or 16% at 0 ppm; 14/75 or 19% at low dose; and 28/75 or 37% at both the mid and high doses) and in liver hepatomas (3/75 or 4% at ppm; 2/75 or 2% at low dose; 15/75 or 29% at mid dose; and 17/75 or 23% at nigh dose) occurred at the mid and high dose levels in female mice. No significant increase in tumors occurred in male mice. The highest dose level tested in female mice appeared to approximate a MTD level (i.e. increased lung and liver tumors occurred which were correlated with increases in lung and liver weights), whereas the highest dose tested in males exceeded the MTD (i.e. increased mortality occurred).

(2). CFLP mice received Permethrin in the diet for 92 weeks at doses of 0, 10, 50 and 250 mg/kg/day (approx. 67, 333 and 1667 ppm, respectively). A significant ($p<0.01$) positive trend for lung tumors (primarily adenomas) occurred in female mice (3/96 or 3% at 0 ppm; 5/71 or 7% at low dose; 7/74 or 9% at mid dose; and 15/74 or 20% at high dose). The increase incidence at the high dose level was also significant ($p<0.01$). In addition, alveolar epithelial metaplasia occurred at the high dose level in females. No compound-related tumors occured in males. The highest dose level tested in this study appeared to approximate a MTD level in females (i.e. metaplasia and tumors of the lung occurred), but not in males (i.e. no remarkable toxicity occurred in males).

(3). ICI Swiss mice (Alderley Park stock) received permethrin for 23 months at doses of 0, 250 1000 and 2500 ppm. There were increases in lung adenomas in males (10 in controls vs. 17 at high dose) and females (11 in controls vs. 15 at high dose) but neither denominators for the dose groups nor statistical analyses of the data were provided. It could not be concluded whether any of the increases were compound related. The highest dose levels tested in this study did not appear to approximate a MTD level. The only changes seen at that dose were confined to the liver (i.e. increased liver weight, hepatocyte eosinophilia, enhanced microsomal enzyme activity, and increased smooth endoplasmic reticulum content), and these changes may be related to the metabolism of the compound.

In summary, permethrin produced statistically significant increases in lung tumors (adenomas) in female mice in two studies in which the highest dose level tested appeared to approximate a MTD level. In a third study, the chemical produced only slight increases in lung adenomas in male and female mice at the highest dose level tested, but this dose did not approximate a MTD level in this study. The Committee noted that the lung tumors described above for permetnrin in female mice were similar to those produced by cypermethrin in female mice (see Section D.1. above). The Committee also noted that Permethrin has not yet undergone a Peer Review weight-of-the-evidence determination for issues such as oncogenesis and MTD evaluation.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on Cypermethrin to be of importance in a weight of the evidence determination of oncogenic potential.

1. Administration of Cypermethrin in the diet of female SPF Swiss mice for 101 weeks at concentrations of 0, 100, 400 and 1600 ppm was associated with statistically significant positive dose - related trends for lung adenomas/carcinomas combined, and for lung adenomas per se. In addition, the elevated incidences of lung adenomas/carcinomas combined, and of lung adenomas per se, produced by the highest dose level of Cypermethrin in treated female mice (i.e. 1600 ppm) were also significantly elevated when compared to control female rates by the Fisher Exact test. The 1600 ppm dose level of cypermethrin was considered to approximate a MTD level in female mice.

2. The elevated incidences of lung adenomas/carcinomas combined (14/61 or 22.9%) and adenomas per se (14/61 or 22.9%) associated with the administration of the 1600 ppm dose of cypermethrin in female mice were above the historical control incidences of lung adenomas/carcinomas combined (range of 0 to 15.7%) and adenomas per se (range of 0% to 15.7%) observed in recent studies conducted by the registrant (ICI Laboratories) in the same strain of female mice.

3. There was no evidence for the occurrence of nonneoplastic changes in the lungs of treated female mice, and no evidence for a progression of benign tumors to malignancy. The only individual lung tumor type that was significantly increased in treated female mice at the highest

dose level tested was the adenoma; lung carcinomas were not increased at 1600 ppm of Cypermethrin (see Table 1). In fact, more carcinomas were observed in control than in treated female mice (Table 1).

4. There was no reduction in the latency period for the time-to-tumor (i.e. lung adenomas) appearance in female mice.

5. Cypermethrin was not oncogenic when administered in the diet of male SPF Swiss mice for 97 weeks at concentrations of 0, 100, 400 and 1,600 ppm. The 1600 ppm dose level was considered to approximate a MTD level in male mice

6. Cypermethrin was not oncogenic when administered in the diet of female and male SPF Wistar rats for 2 years at concentrations of 0, 20, 150 and 1,500 ppm. The 1,500 ppm dose level was considered to approximate a MTD level in both sexes of rats. (A similar result was obtained in another 2 year study in Wistar rats of both sexes using dietary levels of 0 to 1000 ppm Cypermethrin, but this study was considered to be limited because only 24 animals/sex were scheduled to receive the test chemical for the full 2 year dosing period).

7. The metabolism of Cypermethrin was tested in mice, rats and dogs and was found to be similar in all 3 species. The plasma T 1/2 values after oral dosing were relatively short (3 to 5 hours), and the chemical was rapidly metabolized and excreted in urine but excreted essentially unchanged in feces. Two findings of interest to the Committee were: (1) the compound was not shown to be localized to any unusual extent in lung tissue or to be excreted to any significant extent by the respiratory route; and (2) the major urinary metabolites of Cypermethrin (i.e. dichlorovinyl cyclopropane carboxylate, 3 phenoxybenzoic acid, and conjugates of the parent compound and the 3-phenoxy-moiety) are similar to those produced by the structurally - related analogue, Permethrin.

8. The structural congener, Permethrin, has been reported to be associated with lung adenomas in females (but not in male) CRCD-1 and CFLP mice at doses approximating the MTD level. However, the Committee has not yet performed a weight of the evidence evaluation of the data on Permethrin.

9. No evidence for a mutagenic effect of Cypermethrin was found in six short term genetic toxicity tests (see section B.3. for details).

10. No evidence for a teratogenic effect of Cypermethrin was found in rats and rabbits at doses up to 70 and 30 mg/kg, respectively. No adverse reproductive effects were seen in a pair of 3-generation studies in rats at doses ranging from 500 to 750 ppm.

G. Classification of Oncogenic Potential:

The Committee concluded that the data available for Cypermethrin provide limited evidence of oncogenicity for the chemical in female mice. According to EPA Guidelines for Carcinogen Risk Assessment (CFR September 24, 1986), the Committee classified Cypermethrin as a Category C oncogen (possible human carcinogen with limited evidence of carcinogenicity in animals). That is, Cypermethrin produced benign lung adenomas (reflected as an increase in both adenomas, and adenomas/carcinomas combined) at the highest dose level tested in only one sex and species of animal (female mice). Although the observed increase in lung adenomas exceeded historical control values for similar tumors by a small margin, the Committee did not consider the finding to be of major import for several reasons. These included the facts that lung adenomas are tumors of relatively common occurrence in mice, they did not show progression to carcinomas, they did not occur with a reduced latency, they did not appear in male mice or in rats of either sex even though MTD levels of Cypermethrin were tested, and the compound itself was not mutagenic. Although some preliminary data was available to the Committee indicating that a structurally similar chemical, Permethrin, also causes lung tumors in female mice, this information has not yet been fully evaluated by the Committee.

In summary, the Committee categorized Cypermethrin as a weak Category C oncogen. The evidence (common tumor, one species, one sex, no increase in the proportion of malignant tumors or decrease in the time to tumor occurrence, and lack of mutagenic activity) was not considered strong enough to warrant a quantitative estimation of human risk.

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

FEB 17 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Cypermethrin

FROM: John A. Quest, Ph.D. JAQuest
Team Leader, Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Robert Taylor, Product Manager #25
Registration Division (TS-767)

The Toxicology Branch Peer Review Committee met on May 1, 1986 and on July 22, 1987 to discuss and evaluate the data base on Cypermethrin. Attention was focused on the oncogenic potential of the chemical in Alderly Park SPF Swiss strain mice. The hiatus between meetings was due to the time needed for the Peer Review Committee to receive additional information (i.e., historical tumor data, MTD information, and neurotoxicity data).

A. Individuals in Attendance

1. Peer Review Committee: (Signature indicates concurrence with the peer review unless, otherwise stated.).

Diane Beal

Donald Barnes

William Burnam

Reto Engler

Theodore M. Farber

Bernice Fisher

Judith Hauswirth

C. J. Nelson

John A. Quest

Esther Rinde

Robert Zendzian

2. Scientific Reviewers: (Non-committee members responsible for presentation of data; signature indicates technical accuracy of panel report.)

John Doherty

Edwin R. Budd

3. Peer Review Members in Absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with overall conclusions of the Committee.)

Anne Barton

Robert Beliles

B. Material Reviewed:

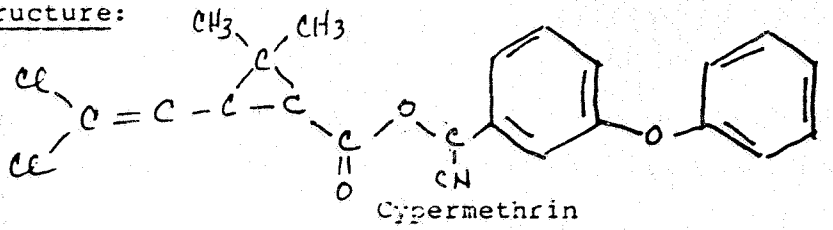
The material reviewed consisted of: (1) a background summary of available toxicology information on Cypermethrin; (2) various memoranda related to risk assessments and tolerance requests on Cypermethrin; (3) DER's of rat and mouse oncogenicity studies, a chronic dog study, and two 3-generation reproduction studies on Cypermethrin; (4) data on DER's of mouse oncogenicity studies with Permethrin, a structural analogue of Cypermethrin; (5) the one-liner data base on Cypermethrin; (6) information on historical control data for the mouse oncogenicity study; and (7) a qualitative risk assessment of tumors in female mice. Copies of these documents are attached to this memorandum.

C. Overview of Toxicology Issues:

Cypermethrin is a pyrethroid insecticide. The chemical has been developed by ICI Americas and the FMC Corporation; and both firms have requested that tolerances be established for use of Cypermethrin in/on raw agricultural commodities and as a food additive. The primary issue of concern to the Peer Review Committee in classifying the oncogenic potential of Cypermethrin was the finding of an

elevated incidence of benign alveologenic tumors in the lungs of female Alderley Park SPF Swiss strain mice at the highest dose level that was tested.

Structure:



Cypermethrin

[± alpha-cyano-3-phenoxybenzyl(±)cis,trans,3-(2,2-dichloro-vinyl)-2,2-dimethyl cyclopropane carboxylate]

D. Evaluation of Oncogenicity Studies of Cypermethrin:

1. Mouse Oncogenicity Study:

Cypermethrin was administered in the diet to 70 SPF Swiss strain mice (Alderley Park stock)/sex/dose level at doses of 0 (two separate control groups of N=70 animals/sex each), 100, 400 and 1600 ppm for 97 weeks (males) and 101 weeks (females). The study was conducted by ICI Central Toxicology Laboratory. The two separate sets of control groups were run concurrently in the study and were combined for statistical purposes. In each control and treatment group, 9-10 males and females/group underwent interim sacrifice at 52 weeks. The following incidence pattern of alveologenic lung tumors was observed in female mice (Table 1). No tumor response related to Cypermethrin administration was observed in male mice.

Table 1: Lung Tumors in Female SPF Swiss Mice Administered Cypermethrin in Diet

		Dose Level (ppm)			
Alveologenic Tumor Type	Sex	0	100	400	1600
Adenoma	Females	10/127(7.8%)	6/64(9.4%)	7/64(10.9%)	14/61(22.9%)b,c
Carcinoma		2/127(1.6%)	0/64(0%)	1/64(1.5%)	0/61(0%)
Combined		12/127(9.4%)	6/64(9.4%)	8/64(12.5%)	14/61(22.9%)a,c

a= $p < 0.05$, b= $p < 0.01$; Fisher's Exact Test, c= Statistically significant positive dose-related trend ($p<0.01$); Cochran - Armitrage Trend Test

Note: The denominators exclude animals that were examined, but died before the appearance of the first tumor (at week 46 in the 400 ppm dose group) in the study.

Cypermethrin produced a statistically significant increase in alveologenic adenomas, and in adenomas plus carcinomas combined, in female mice at the highest dose level (1600ppm) tested. There were also significant positive dose-related trends for these tumor combinations in female mice. No significant increases in carcinomas were observed. The Peer Review Committee noted the following additional information in regard to the increased lung tumorigenic response in female mice: (a) most of the adenomas were observed at terminal sacrifice and there was no decrease in latency for the time to tumor occurrence; (tumors were first seen at week 53 in the control females and at weeks 52 to 53 in the high dose females); (b) the incidences of lung tumors produced at the highest dose level of Cypermethrin exceeded the historical control incidences for lung adenomas (mean=9.6%; range=0 to 15.7%), and adenomas/carcinomas combined (mean 11.3%; range = 0 to 15.7%), in several contemporary studies conducted in female Swiss Alderley Park mice at ICI Laboratories between 1977 to 1985; (c) no compound - related nonneoplastic changes were observed in the lungs of treated female mice; (d) alveolar adenoma is a relatively common tumor in mice; (e) there were more malignant lung tumors in the control female mice than there were in the treated female mice (i.e. 2 carcinomas occurred in controls vs. 1 carcinoma in the treated groups); and (f) the highest dose level of Cypermethrin tested (i.e. 1600 ppm) was considered, based on weight gain decrements, to approximate (but not to exceed) a MTD level in both female and male mice.

2. Rat Oncogenicity Study:

Cypermethrin was administered in the diet to 52 SPF Wistar derived albino rats/sex/dose level at doses of 0 (control group no. 1), 0(control group no.2), 20, 150 and 1,000/1,500 ppm for 2 years. The high dose level was increased from 1,000 ppm to 1,500 ppm at study week 7. The study was conducted by ICI Central Toxicology Laboratory. The two separate sets of control groups were run concurrently in the study. Additional satellite groups of 12 males and 12 females/group underwent interim sacrifice at 52 weeks. No evidence of an oncogenic response was observed at any organ site in male or female rats with Cypermethrin. The highest dose level of

Cypermethrin tested in rats was considered to approximate, but not to exceed, a MTD level on the basis of decrements in body weight gain in both males and females.

3. Rat Oncogenicity Study:

Cypermethrin was administered in the diet to male and female SPF Wistar rats at dose levels of 0, 1, 10, 100 and 1,000 ppm for 2 years. The study was conducted by the Shell Toxicology Laboratory, and was considered by the Toxicology Branch to be of limited usefulness because an insufficient number of rats received the test chemical for the full 2 year dosing period. That is, the study was initiated with 96 rats of each sex in the control group and 48 rats of each sex in each dose group; However, interim sacrifices were performed on 12 rats/sex from the control group and 6 rats/sex from each dose group at 6 months and 12 months, and on 24 rats/sex from the control group and 12 rats/sex from each dose group at 18 months. Thus, the total number of rats that were scheduled to remain on test for the full 2 year feeding period were 48 rats/sex in the control group and 24 rats/sex in each dose group.

The only toxicological effects associated with Cypermethrin administration in this study were a slight depression in body weight gain (<10%) and lower food consumption at the 1,000 ppm dose level. No evidence of an oncogenic response was observed with Cypermethrin.

E. Additional Toxicity Data:

1. One-Year Dog Study:

The Committee briefly reviewed the results of a 1-year study of Cypermethrin in Beagle dogs that was conducted by ICI Central Toxicology Laboratory. The chemical was administered orally (capsule) to 6 dogs/sex/dose level at doses of 0, 1, 5 and 15 mg/kg/day. The NOEL was 1 mg/kg/day. The LEL was 5 mg/kg/day based on an increased incidence in the passage of liquid stools in both male and female dogs. In addition, dogs receiving the highest dose level (i.e. 15 mg/kg/day) exhibited an even greater increase in the passage of liquid stool plus a loss in appetite, tremors, gait changes, incoordination, disorientation and hypersensitivity. No other toxicological or nonneoplastic histopathological effects were observed.

2. Metabolism Studies:

Several studies were conducted in mice and rats, and in dogs in some cases, using single or repeated oral doses of 14 C-Cypermethrin. The results obtained were generally similar for the 3 species tested. Following oral ingestion of the compound, blood T 1/2 values ranged from 3 to 5 hours in rats. Tissue levels of radioactivity (RA) at 7 days after dosing were highest in fat, intestines, liver, kidney and skin in rats, and the residual level of RA in fat had a T 1/2 of 10-20 days in mice. The metabolism of Cypermethrin was similar in mice, rats and dogs; the compound was rapidly metabolized and excreted in the urine whereas it was essentially excreted unchanged in the feces. The metabolic pathway in urine consisted of hydrolysis of the esteratic site of Cypermethrin to yield dichlorovinyl cyclopropane carboxylate and 3-phenoxybenzoic acid. Conjugated forms (glucuronide, taurine and glycine) of the parent compound and the 3-phenoxy-moiety were also found. The Toxicology Branch reviewer noted that the major metabolites of Cypermethrin were similar to those of Permethrin, a structually related pyrethroid insecticide. The reviewer also noted that during the metabolism of Cypermethrin the cyano (CN-) group is eliminated from the molecule but that there was no evidence that cyanide toxicity resulted from ingestion of the chemical. In terms of excretion, approximately 90% of an administered RA dose was recovered from urine (range of 28 to 66%) and feces (range of 24 to 59%) at 7 days after dosing in mice and rats. Excretion of Cypermethrin by biliary and respiratory routes were of neglible significance.

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Cypermethrin was evaluated for adverse reproductive activity in two 3-generation studies in rats. In the first study, the chemical was administered at dose level of 0, 50, 150 and 1000/750 ppm. The high dose level (1000 ppm) was reduced to 750 ppm at week 13 of the study because of observable signs of neurotoxicity (e.g. ataxia, increased sensitivity to sound, and high-stepping gait) in the F_0 treatment group. Other effects seen in this study included reduced food consumption and weight gain in mature rats (150 and 1000/750 ppm dose levels), and reduced offspring weight at days 0 to 28 postpartum (1000/750 dose level). No adverse reproductive effects were observed. Some Committee members made the observation that Cypermethrin produced signs of neurotoxicity in this reproduction study at a dose of 1000 ppm, but not in either one of the 2 rat oncogenicity studies discussed above (see sections D.2 and D.3.) at doses of 1000 to 1500 ppm. The committee had no definitive answer for this finding, but speculated that cis-trans ratio differences in the Cypermethrin administered in the different studies may have accounted for the greater toxicity in the reproduction study as opposed to the long term studies. In the second study, cypermethrin was administered at dose levels of 0, 10, 100 and 500 ppm, and no adverse effects were observed.

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Cypermethrin is a close structural analogue of Permethrin. The latter compound differs from Cypermethrin only in the absence of the cyano (CN-) group on the alpha carbon position. The Committee briefly considered oncogenicity data from 2 studies of Permethrin in mice.

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(2). CFLP mice received Permethrin in the diet for 92 weeks at doses of 0, 10, 50 and 250 mg/kg/day (approx. 67, 333 and 1667 ppm, respectively). A significant ($p<0.01$) positive trend for lung tumors (primarily adenomas) occurred in female mice (3/96 or 3% at 0 ppm; 5/71 or 7% at low dose; 7/74 or 9% at mid dose; and 15/74 or 20% at high dose). The increase incidence at the high dose level was also significant ($p<0.01$). In addition, alveolar epithelial metaplasia occurred at the high dose level in females. No compound-related tumors occured in males. The highest dose level tested in this study appeared to approximate a MTD level in females (i.e. metaplasia and tumors of the lung occurred), but not in males (i.e. no remarkable toxicity occurred in males).

(3). ICI Swiss mice (Alderley Park stock) received permethrin for 23 months at doses of 0, 250 1000 and 2500 ppm. There were increases in lung adenomas in males (10 in controls vs. 17 at high dose) and females (11 in controls vs. 15 at high dose) but neither denominators for the dose groups nor statistical analyses of the data were provided. It could not be concluded whether any of the increases were compound related. The highest dose levels tested in this study did not appear to approximate a MTD level. The only changes seen at that dose were confined to the liver (i.e. increased liver weight, hepatocyte eosinophilia, enhanced microsomal enzyme activity, and increased smooth endoplasmic reticulum content), and these changes may be related to the metabolism of the compound.

In summary, permethrin produced statistically significant increases in lung tumors (adenomas) in female mice in two studies in which the highest dose level tested appeared to approximate a MTD level. In a third study, the chemical produced only slight increases in lung adenomas in male and female mice at the highest dose level tested, but this dose did not approximate a MTD level in this study. The Committee noted that the lung tumors described above for permetnrin in female mice were similar to those produced by cypermethrin in female mice (see Section D.1. above). The Committee also noted that Permetnrin has not yet undergone a Peer Review weight-of-the-evidence determination for issues such as oncogenesis and MTD evaluation.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on Cypermethrin to be of importance in a weight of the evidence determination of oncogenic potential.

1. Administration of Cypermethrin in the diet of female SPF Swiss mice for 101 weeks at concentrations of 0, 100, 400 and 1600 ppm was associated with statistically significant positive dose - related trends for lung adenomas/carcinomas combined, and for lung adenomas per se. In addition, the elevated incidences of lung adenomas/carcinomas combined, and of lung adenomas per se, produced by the highest dose level of Cypermethrin in treated female mice (i.e. 1600 ppm were also significantly elevated when compared to control female rates by the Fisher Exact test. The 1600 ppm dose level of cypermethrin was considered to approximate a MTD level in female mice.

2. The elevated incidences of lung adenomas/carcinomas combined (14/61 or 22.9%) and adenomas per se (14/61 or 22.9%) associated with the administration of the 1600 ppm dose of cypermethrin in female mice were above the historical control incidences of lung adenomas/carcinomas combined (range of 0 to 15.7%) and adenomas per se (range of 0% to 15.7%) observed in recent studies conducted by the registrant (ICI Laboratories) in the same strain of female mice.

3. There was no evidence for the occurrence of nonneoplastic changes in the lungs of treated female mice, and no evidence for a progression of benign tumors to malignancy. The only individual lung tumor type that was significantly increased in treated female mice at the highest

dose level tested was the adenoma; lung carcinomas were not increased at 1600 ppm of Cypermethrin (see Table 1). In fact, more carcinomas were observed in control than in treated female mice (Table 1).

4. There was no reduction in the latency period for the time-to-tumor (i.e. lung adenomas) appearance in female mice.

5. Cypermethrin was not oncogenic when administered in the diet of male SPF Swiss mice for 97 weeks at concentrations of 0, 100, 400 and 1,600 ppm. The 1600 ppm dose level was considered to approximate a MTD level in male mice

6. Cypermethrin was not oncogenic when administered in the diet of female and male SPF Wistar rats for 2 years at concentrations of 0, 20, 150 and 1,500 ppm. The 1,500 ppm dose level was considered to approximate a MTD level in both sexes of rats. (A similar result was obtained in another 2 year study in Wistar rats of both sexes using dietary levels of 0 to 1000 ppm Cypermethrin, but this study was considered to be limited because only 24 animals/sex were scheduled to receive the test chemical for the full 2 year dosing period).

7. The metabolism of Cypermethrin was tested in mice, rats and dogs and was found to be similar in all 3 species. The plasma T 1/2 values after oral dosing were relatively short (3 to 5 hours), and the chemical was rapidly metabolized and excreted in urine but excreted essentially unchanged in feces. Two findings of interest to the Committee were: (1) the compound was not shown to be localized to any unusual extent in lung tissue or to be excreted to any significant extent by the respiratory route; and (2) the major urinary metabolites of Cypermethrin (i.e. dichlorovinyl cyclopropane carboxylate, 3 phenoxybenzoic acid, and conjugates of the parent compound and the 3-phenoxy-moiety) are similar to those produced by the structurally - related analogue, Permethrin.

8. The structural congener, Permethrin, has been reported to be associated with lung adenomas in females (but not in male) CRCD-1 and CFLP mice at doses approximating the MTD level. However, the Committee has not yet performed a weight of the evidence evaluation of the data on Permethrin.

9. No evidence for a mutagenic effect of Cypermethrin was found in six short term genetic toxicity tests (see section E.3. for details).

10. No evidence for a teratogenic effect of Cypermethrin was found in rats and rabbits at doses up to 70 and 30 mg/kg, respectively. No adverse reproductive effects were seen in a pair of 3-generation studies in rats at doses ranging from 500 to 750 ppm.

G. Classification of Oncogenic Potential:

The Committee concluded that the data available for Cypermethrin provide limited evidence of oncogenicity for the chemical in female mice. According to EPA Guidelines for Carcinogen Risk Assessment (CFR September 24, 1986), the Committee classified Cypermethrin as a Category C oncogen (possible human carcinogen with limited evidence of carcinogenicity in animals). That is, Cypermethrin produced benign lung adenomas (reflected as an increase in both adenomas, and adenomas/carcinomas combined) at the highest dose level tested in only one sex and species of animal (female mice). Although the observed increase in lung adenomas exceeded historical control values for similar tumors by a small margin, the Committee did not consider the finding to be of major import for several reasons. These included the facts that lung adenomas are tumors of relatively common occurrence in mice, they did not show progression to carcinomas, they did not occur with a reduced latency, they did not appear in male mice or in rats of either sex even though MTD levels of Cypermethrin were tested, and the compound itself was not mutagenic. Although some preliminary data was available to the Committee indicating that a structurally similar chemical, Permethrin, also causes lung tumors in female mice, this information has not yet been fully evaluated by the Committee.

In summary, the Committee categorized Cypermethrin as a weak Category C oncogen. The evidence (common tumor, one species, one sex, no increase in the proportion of malignant tumors or decrease in the time to tumor occurrence, and lack of mutagenic activity) was not considered strong enough to warrant a quantitative estimation of human risk.

#23 10/20/87 sp
rew:11/23/87 sp

Reviewer's Peer Review Package for 2nd Meeting

1/19/87

007707

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

[redacted]

FILE COPY

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Second Peer-Review on Cypermethrin

FROM: Reto Engler, Chief
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

TO: Addressees

Attached is a package for your review concerning Cypermethrin. This chemical was previously review (May 1, 1986). In order to refresh your memory we are also including a summary and assessment on Cypermethrin contained in the original package.

A meeting to discuss the weight-of-the-evidence on Cypermethrin is scheduled for Wednesday, July 22, 1987, at 10:30 AM in Dr. Farber's office (Rm. 821 CM-2).

Attachment

ADDRESSEES

T. Farber
W. Burnam
E. Rinde
J. Hauswirth
J. Quest
L. Kasza
R. Levy
J. Doherty
E. Budd
A. Kocialski
B. Fisher
R. Beliles
D. Beal
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D. Barnes

#19 6/16/87 sp

47

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cypermethrin: Peer Review Meeting II.

TOX CHEM No. 271DD

FROM: John Doherty John Doherty April 30, 1987
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Reto Engler
Chief, Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769) Budd 5/1/87

A. Background Information.

In response to the requests made at Peer Review Meeting I for cypermethrin, the following topics have been reevaluated and additional historical control data have been submitted by the ICI Corporation.

1. Discussion of the Maximum Tolerated Dose (MTD) in the rat chronic feeding/oncogenicity study.

2. Discussion of the MTD in the mouse oncogenicity study

3. Neurotoxicity in the multi-generation reproduction study.

4. Historical control data for the Alderley Park mouse (strain Alpk/AP).

5. Non-neoplastic pathology in mouse lung in the mouse oncogenicity study (Alderley Park strain).

6. Pathological findings in the rat lung in the rat oncogenicity study (Wistar strain).

7. Revised statistical assessment of lung tumor data in the mouse oncogenicity study.

? received only Female Stat + Hist/ Controls

Items 1-6 are discussed on the following pages. The report from the statistical work group (item 7) is being prepared separately by the biostatistics team of TB. As of April 29, 1987, this report has not been completed.

B. Summary of information pertinent to the oncogenic classification of cypermethrin.

The following overview should assist the review committee in its classification of cypermethrin.

i. Implicating factors:

Cypermethrin has been demonstrated to statistically significantly increase the frequency of bronchioalveologenic tumors in the lungs of female mice. The increase in frequency of lung tumors occurs at but not in excess of the MTD.

Cypermethrin is structurally related to permethrin which also has been demonstrated to be associated with increased incidences of the same type of lung tumor in female mice.

ii. Mitigating Factors

No other oncogenic response in another organ in female mice, in male mice or in rats has been recognized. The rat studies were determined to have been studied at dose levels which included the MTD.

In the mouse oncogenicity study, the increase in tumors in females occurred at a relatively high dose level (229 mg/kg/day). At lower dose levels which were below the MTD, no increase in lung tumors was noted.

The tumor type (bronchioalveologenic adenoma) is a common tumor type in female mice occurring at a frequency of about 10% in untreated control mice. At the highest test dose level, the increase in tumors presumably caused by cypermethrin was 20% frequency.

Although this type of tumor is common in mice, it is rare in humans.

There was no increase in malignancy (none of the tumors in the high dose group were malignant) or a decrease in latency. There were no test chemical related increases in lesions that were considered possibly pre-neoplastic (such as hyperplasias) or non-neoplastic in the lung.

TB does not consider that cypermethrin has been demonstrated to be mutagenic.

1. Discussion of the Maximum Tolerated Dose (MTD) in the rat chronic feeding/oncogenicity study.

In the rat 90 day subchronic study (ICI Report #CTL/P/327, Jan 1980), rats were dosed with 0, 75, 150 or 1500 ppm of cypermethrin. The test rats in the group receiving 1500 ppm initially showed a slower weight gain and correspondingly less food consumption. After the first three weeks on their test diets, these rats gained weight at the same rate as the controls. The final weights of both the male and female in the high dose groups were depressed.

The liver of the rats dosed with both 150 ppm (males only) and 1500 ppm (males and females) showed proliferation of hepatic smooth endoplasmic reticulum and increased hepatic aminopyrene demethylase activity. These changes were considered by both the testing laboratory and TB to be adaptive responses to cypermethrin and not true toxic responses.

TB considers that the MTD was reached in the highest test dose level in the 1982 rat study (ICI Study #CTL/P/669 June, 1982). In this study, Wistar rats were dosed with either 0,0 (two control groups), 20, 150, or 1500 ppm of cypermethrin (cis/trans ratio of 55:45). The significant effects noted in the high dose test group were decreased body weight gain in males (-12%) and females (-18% to -20%). Body weight depressions in the mid dose group females were 4-5% below control groups.

The high dose test group females had increased liver weight at 52 weeks but not at termination. No other group had increased liver weight. Smooth endoplasmic proliferation was also evident in the high dose group in both sexes which was most evident at 52 weeks but also present at 104 weeks. The mid dose group females were also reported as having a slight increase in smooth endoplasmic reticulum at termination.

The liver of the rats in the high dose group also had elevated levels of aminopyrine-N-demethylase activity at both 52 and 104 weeks. This enzyme was not reported as being elevated in the other test dose groups.

Both the increase in liver weight and aminopyrine-N-demethylase are considered to be adaptive responses to cypermethrin rather than true toxic responses.

No other symptoms of sufficient magnitude were noted to indicate that the high dose was in excess of the MTD. Refer to body weight gain tables attached.

Overall, the depressions in body weight gain noted in this study indicate that cypermethrin was studied at a dose level that was <u>at</u> but not in excess of the MTD.

There were no indications that cypermethrin was related to induction of either neoplastic or non-neoplastic lesions in the lung. Summary tables for the non-neoplastic and neoplastic findings in this study are attached.

2. <u>Discussion of the MTD in the mouse oncogenicity study</u>.

The protocol for the mouse oncogenicity study (ICI Study #CTL/P/687 June, 1982) states that "the dose levels were based on the results of a preliminary 28 day feeding study in the mouse together with our general knowledge of pyrethroid toxicology".

The 28 day preliminary study data were not reviewed by TB. A 28 day preliminary study is considered by TB to be of too short a duration to adequately assess for predicting the MTD. A 90 day study is more suitable.

Thus, the relationship of the highest test dose level to the MTD is best judged by review of the toxicity response noted in the definitive oncogenicity study.

In the definitive study depression in body weight gains were the only outstanding systemic response to cypermethrin noted (except for lung tumors).

Inspection of TABLE 8 (males) and TABLE 9 (females) attached indicates that in males body weight gains were statistically significantly depressed chiefly during the first eleven weeks of the study. The difference reached statistical significance only occasionally afterwards although there was a constant weight difference (decrease) between the high dose group and the controls until termination of the study. During the first 11 weeks depressions in body weight reached -23% (week 1) and to 7 to 10% during weeks 2-11. Afterwards the difference between the controls and the high dose groups was between 5-10% and at weeks 80 to 96 the difference was 12-14%.

Similarly among the females, statistically significant increases were noted most frequently during the first 13 weeks of the study and only occasionally thereafter. At week 1, body weight for the high dose group was -18% below the controls. At other times the body weight was between -3 and up to -16% lower. At 100 weeks (termination) the high dose group was 15% lower than the controls.

The low and mid dose groups were essentially similar to the controls with some occasional and inconsistent differences noted.

In conclusion, the increased incidences in lung tumors in the high dose test groups are thus associated with a dose level that is <u>at</u> but not in excess of the MTD.

3. <u>Neurotoxicity in the multi-generation reproduction study</u>.

There are two multi-generation reproduction studies available. In the first study (Shell Toxicology Laboratory, Study No. TLGR 0188.78, Feb. 1979), cypermethrin was studied at 0, 10, 100, and 500 ppm. No obvious effects indicative of neurotoxicity were reported based on either behavioral responses or the limited amount of histopathology presented.

In the second study (ICI/CTL, Study No. CTL/P/683, 1982) cypermethrin was tested at dose levels of 0, 50, 150 and 750 ppm. The high dose test group was originally started at 1000 ppm, but due to evidence of neurotoxicity (increased sensitivity to sound, ataxia and high stepping gait, and possibly one death), the test level was reduced to 750 ppm. Lowering the dosage level to 750 ppm eliminated the signs of neurotoxicity apparently induced by cypermethrin.

Comments. The observation of neurotoxicity as reported in this study at the dose level of 1000 ppm is not consistent with other studies particularly the rat subchronic and chronic feeding studies. The rat chronic feeding study was started at 1000 ppm but after 3-6 weeks of feeding at this level with only six male rats displaying clinical signs associated with pyrethroid toxicity during the first week of dosing, the dose level was raised to 1500 ppm.

The differences may be in the ratio of cis and trans isomers and in the individual lots used for each study. The cis isomer of cypermethrin and pyrethroids in general is recognized as being more toxic to nerve preparations than the trans isomer. The study reports, however, indicate that the cis/trans ratios and the purity percentages were similar for both the chronic feeding study and the multi-generation study showing the neurotoxicity effects. Since the purity was reported at <95%, there may have been a contaminant present in the lots used for the multi-generation study but not the chronic feeding study.

Both the multi-generation study and the chronic feeding study utilized the same strain of Wistar rat. The strain of rat utilized for the 90 day study was not described as a Wistar but as an Alderley Park strain. Overall species differences would not explain the neurotoxicity.

Lastly, it is possible that the neurotoxicity noted was related to the age of the test animals. Recently presented data (Sheets, Crofton and Reiter, SOT Annual Meeting, 1987) indicate that the type II pyrethroids (to which cypermethrin belongs) are more toxic to younger rats (weanlings) then they are to adult rats.

Overall TB has no satisfactory explanation for the neurotoxicity being noted in the multi-generation reproduction study but not in the chronic feeding/oncogenicity study.

4. Historical control data for the Alderley Park mouse (strain Alpk/AP).

Information on the incidence of potential preneoplastic and neoplastic lesions in the lung for the Alderley Park strain of mouse are attached. The data were derived from seven studies conducted between 1975 and 1985. Five of the mouse studies were by the dietary route. One study each was by the inhalational and by skin painting. The identities of the test chemicals used for these studies were not provided. All of the studies except one were conducted at the ICI Laboratory.

The other study was conducted at Life Science Research facilities (England).

The average frequency (as percent of mice on study, not adjusted for mice at risk) for development of lung tumors in females for the 34 data sets (including mice that were dosed with test chemicals) was determined to be 10.9 +/-6. For females that were in the control groups only, the average was determined to be 10.2 +/-4.9.

In the cypermethrin high dose test group, the corresponding frequency was 20% and the frequencies for the two control, low and mid dose groups were 7.2, 10.0, 8.6 and 11.4 percent. Thus, the high dose group in the cypermethrin study was twice the historical control value.

In only a single study (study B) were the response frequencies in the range of 20% or greater. In study B, the mid dose group had a frequency of 20.3% and the high dose group was 30.5%. Since the control frequencies for this study were 15.3% and 8.5%, the increased frequency in the high dose group suggests a test chemical related effect.

TB concludes that the 20% frequency of lung tumors noted among females in the high dose test group for the cypermethrin study is in excess of the expected range when compared with the historical control data submitted.

5. Non-neoplastic pathology in mouse lung in the mouse oncogenicity study (Alderley Park strain).

The study reports contained tabulated data on non-neoplastic pathology for the terminal kill and one year interim sacrifice mice only (copies of summary tables attached). TB perused the individual animal pathology sheets to assess for the presence of non-neoplastic lesions in the mice which died or were sacrificed moribund during the in-life phase of the study.

Overall there were few incidences of non-neoplastic lesions that were considered to be truly or suggestive of being preneoplastic lesions. The non-neoplastic lung pathology consisted of occasional and sporadic findings of common lesions such as congestion, focal (and otherwise) alveolar macrophage proliferation, pneumonitis, and several other types of singular or infrequent (2-3 occasions) incidences, none of which showed a dose response relationship to the presence of cypermethrin in the diet.

In conclusion, there was no evidence of increases in preneoplastic lesions associated with cypermethrin in the diet.

6. Pathological findings in the rat lung in the rat oncogenicity study.

There were no indications of increased incidences of either neoplastic or nonneoplastic lesions being associated increased levels of cypermethrin in the diet in the rat chronic feeding oncogenicity study (ICI Report #CTL/P/669 June 1982. Refer to copies of the incidence reports attached.

[Note: There were also no indications of test chemical related non-neoplastic or neoplastic lesions in the Shell Research Laboratories Study. The summary tables are not included here because the ICI study was conducted at higher dose levels and included more test animals per dose level and is considered a more definitive study.]

Attachments

1. Body weight gain tables for the rat chronic feeding/ oncogenicity study.

2. Body weight gain tables for the mouse oncogenicity study.

3. Historical control data for the Alderley Park Strain of mouse (ICI submission CTL/P/1614 dated August 19, 1986).

4. Non-neoplastic findings in the mouse oncogenicity study.

5. Summary of neoplastic and non-neoplastic findings in the rat chronic feeding/oncogenicity study.

Cypermethrin Review

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cypermethrin: Historical control data for the mouse oncogenicity study.

TOX CHEM No. 271DD

FROM: John Doherty
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Richard Levy, Leader
Biostatistics Team
Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Edwin R. Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: William Burnam
Deputy Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Attached is a report from the ICI Corporation summarizing the historical control data from several studies on the incidences of lung neoplasms. This information is relevant to the statistical assessment of cypermethrin.

As per the suggestion of Mr. Burnam, the report is being forwarded to you for inclusion in the revised statistical assessment of increased lung tumor incidences in the cypermethrin mouse oncogenicity study. It is our understanding that models for statistical evaluation currently in use within Toxicology Branch incorporate historical control data in the overall assessment.

[illegible] PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cypermethrin: Historical control data for the mouse oncogenicity study.

TOX CHEM No. 271DD

FROM: John Doherty 3/26/87
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Richard Levy, Leader
Biostatistics Team
Mission Support Staff
Toxicology Branch
Hazard Evaluation Divisio.. (TS-769)

THRU: Edwin R. Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769) 3/26/87

THRU: William Burnam
Deputy Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769) 3/24/87

Attached is a report from the ICI Corporation summarizing the historical control data from several studies on the incidences of lung neoplasms. This information is relevant to the statistical assessment of cypermethrin.

As per the suggestion of Mr. Burnam, the report is being forwarded to you for inclusion in the revised statistical assessment of increased lung tumor incidences in the cypermethrin mouse oncogenicity study. It is our understanding that models for statistical evaluation currently in use within Toxicology Branch incorporate historical control data in the overall assessment.

87

Reto 007707

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

FILE COPY

JUN 11 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cypermethrin, Mouse Study Females Qualitative Risk Assessment - Reevaluation With Historical Controls

Caswell No. 271DD

FROM: Bernice Fisher, Biostatistician for B. Fisher C. Nelson 6/11/87
Scientific Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: John Doherty Ph.D.
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Richard Levy, M.P.H., Leader - Biostatistician Team
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Richard A. Levy 6-11-87

and

Reto Engler, Ph.D., Chief
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Reto Engler 6/11/87

Background

A long-term feeding study, 97 weeks for males and 101 weeks for females, consisting of five groups of 70 male and 70 female, Swiss strain mice, was conducted by ICI Central Toxicology Laboratory (June 1982). The administered dose levels of cypermethrin were 0 (2 concurrent controls), 100, 400, and 1600 ppm. From the study group, 8 to 10 animals were selected for an interim sacrifice at 52 weeks.

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At the suggestion of Dr. Doherty, survival and the lung neoplasms (carcinomas and/or adenomas), in female mice, were used for the qualitative reevaluation of cypermethrin. In addition, Dr. Doherty submitted historical control data (see attachment) from seven studies. However, only five out of the group were pertinent, since in the other two, a dietary route of administering cypermethrin, was not used.

Data Analysis

The two concurrent control groups of female mice were combined because they had similar survival patterns (tested by the Thomas, Breslow and Gart computer program) and no significant difference in the lung tumor rates (Fisher's Exact test).

Survival in the female mice was not significantly impaired with increasing doses of cypermethrin (Thomas, Breslow and Gart computer program). See table 1. for survival summary.

The Cochran-Armitage test for trend was used on the observed lung tumor data and on a Tarone (1982) modification of the concurrent control data (table 2). The modified data adjusts the concurrent control based on historical control data. In both cases, the results indicated that there was a significant ($p < .01$) increase in tumor rates with increasing doses of cypermethrin. This outcome occurred both for the carcinoma and/or adenoma groups and the adenoma alone data set. Since there were only three carcinomas (two in the controls and one in the mid-dose group), the adenoma data group had the greater weight in determining the significant trend of tumors with dose increments of cypermethrin.

In the pairwise comparisons, only the high (1600 ppm) dose groups versus the controls, evaluated by Fisher's Exact test, produced significant differences. For carcinoma and/or adenoma group, $p = .013$ (raw data) and $p=.016$ (modified data); and for the adenoma only group, $p = .005$ (raw data) and $p=.004$ (modified data). See Table 2 for details. The modified data made little difference in the trend test or the Fisher exact test.

Attachment

Cypermethrin

Table 1. Cypermethrin, Mouse Study - Females
Mortality Rates+

Dose	Weeks					
ppm	0-51	52-53[a]	53-78	79-99	100-102	Total[b]
0	17/139	0/18	29/104	51/75	6/24	105/121 (87)
100	10/70	0/10	19/50	19/31	1/12	49/60 (82)
400	10/70	0/10	15/50	22/35	1/13	48/60 (80)
1600	13/70	0/11	13/46	25/33	1/8	52/59 (88)

+ Number of Deaths/Number of Animals Alive at Beginning of Time Period
a Interim Planned Kill - weeks 52 and 53
b Excludes Interim Planned Kills

Table 2. Cypermethrin, Mouse Study - Females
Lung Tumor Rates+ and
Cochran-Armitage Trend Test and Fisher
Exact Test Results

A. Lung Tumor Rates+
(Carcinoma and/or Adenoma)

Dose	Weeks				
ppm	46[a]-78	79-99	100-102	Total	Tarone Modified
0	4/52	5/51	3/24	12/127[b] (9)**	16/156 (10)**
100	1/33	3/19	2/12	6/64 (9)	6/64 (9)
400	3/29	5/22	0/13	8/64 (13)	8/64 (13)
1600	3/28	7/25	4/8	14/61 (23)*	14/61 (23)*

B. Lung Tumor Rates+
(Adenomas only)

Dose	Weeks				
ppm	46-78[a]	79-99	100-102	Total	Tarone Modified
0	3/52	4/51	3/24	10/127[b] (8)**	13/157 (8)**
100	1/33	3/19	2/12	6/64 (9)	6/64 (9)
400	2/29	5/22	0/13	7/64 (11)	7/64 (11)
1600	3/28	7/25	4/8	14/61 (23)**	14/61 (23)**

+ Number of Tumor-Bearing Animals/Number of Animals Examined
() Percent
[a] Appearance of first tumor (week 46 - adenomas)
[b] Excludes animals that were examined, but died before the appearance of the first tumor in the study

Note: The above time intervals are for display only.

Significance of Trend Analysis denoted at Control.

Signficance of pairwise comparison with control denoted at Dose level.

* $p < .05$

** $p < .01$

References

Cox, D.R. (1972) Regression Models and Life Tables (with discussion). 9. Roy. Stat. Soc. Ser. B 34, 187-220.

Tarone, R.E. (1982) The Use of Historical Control Information in Testing for a Trend in Proportions. Biometrics 38, 215-220.

Tarone, R.E. (1975) Tests for Trend in Life Table Analysis. Biometrics 62, 679-682.

Thomas, D.G.; Breslow, N.; Gart, J.J. (1977) Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research. 10, 373-381.

MEMORANDUM

SUBJECT: Cypermethrin: Historical control data for the mouse oncogenicity study.

TOX CHEM No. 271DD

FROM: John Doherty 3/26/87
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Richard Levy, Leader
Biostatistics Team
Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Edwin R. Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: William Burnam
Deputy Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Attached is a report from the ICI Corporation summarizing the historical control data from several studies on the incidences of lung neoplasms. This information is relevant to the statistical assessment of cypermethrin.

As per the suggestion of Mr. Burnam, the report is being forwarded to you for inclusion in the revised statistical assessment of increased lung tumor incidences in the cypermethrin mouse oncogenicity study. It is our understanding that models for statistical evaluation currently in use within Toxicology Branch incorporate historical control data in the overall assessment.

Cypermethrin Review

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Pages 94 through 104 are not included in this copy.

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WASHINGTON, D.C. 20460

APR 16 1986

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Cypermethrin

FROM: Reto Engler, Chief
Mission Support Staff
Toxicology Branch/HED (TS-769)

TO: Addressees

Attached for your review is the background information on Cypermethrin, prepared by Dr. John Doherty. A meeting to discuss this chemical and develop a weight-of-the-evidence position has been scheduled for May 1, 1986 at 10:30 AM in Dr. Farber's office (CM-2, Room 821).

Attachment

ADDRESSEES:

T. Farber
W. Burnam
J. Quest
E. Rinde
J. Doherty
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[illegible] Kocialski
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[illegible]

[illegible]

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

APR 9 1986

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Cypermethrin: Data Package for Peer Review.

FROM: John Doherty
Ecology Branch
Hazard Evaluation Division (TS-769)

TO: Karl Englund
Prod. Mission Support Staff
Ecology Branch
Hazard Evaluation Division (TS-769)

Attached are several documents related to the reviews of Cypermethrin which constitute the data package for the peer review of this chemical.

This peer review is somewhat special and the issues and questions raised in the memo by Mr. Herbert Harrison, Chief Invertebrate Toxicology Branch (attached) should be addressed at the meeting.

The following items are attached:

1. Memo dated March 31, 1986 from Mr. Herbert Harrison.

2. Document entitled "Cypermethrin: Assessment of Chronic and Reproductive Effects A Summary" prepared by J.D. Doherty and dated March 5, 1984.

3. Memorandum dated March 27, 1984 from E.R. Budd entitled "Cypermethrin Residues in Cottonseed, Meat, and Milk. Risk Assessment"

4. Memorandum dated [illegible], 1983 from J.D. Doherty entitled "Environmental fate [illegible] of pesticide products [illegible] cypermethrin."

5. Memorandum dated Sept. 30, 1983 from J.D. Doherty entitled "PP #4F2262 and PP# 3H5334 concerning cypermethrin on cotton and related tolerances."

This memo contains the original reviews of the rat, mouse and dog chronic toxicity and oncogenicity studies.

6. Memorandum dated Jan. 20, 1983 from J.D. Doherty entitled "PP 2F2262 and PP 3H5334. Request for a tolerance for cypermethrin in cottonseed and in meat and milk. EPA Reg. Information 279-[illegible] and 10182-AU for CYMBUSH 2E (preparation [illegible] and CYMBUSH 3E (preparation [illegible].

This memo contains the original review of the [illegible] chronic feeding study and the reviews of the metabolism studies. Only relevant sections of the review are attached.

7. Copy of the "Red Sheet" for cypermethrin.

Please advise me as to what additional information will be required to prepare for the peer review meeting.

007707

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MAR 31 1986

MEMORANDUM

SUBJECT: Cypermethrin

FROM: Herbert J. Harrison, Chief
Insecticide-Rodenticide Branch (TS-767C)

TO: Theodore M. Farber, Chief
Toxicology Branch (TS-769C)

As you know, the Policy Group gave the Insecticide-Rodenticide Branch (IRB) the responsibility for preparing a Federal Register (FR) Notice setting forth the Agency's decision not to use quantitative risk assessments when considering cypermethrin products for registration. However, before IRB can draft the FR Notice there are a couple of items we need from you and/or your branch.

First, we need your schedule for developing the oncogenic classification for cypermethrin. Before we can draft the FR Notice we must know what classification the cypermethrin oncogenicity falls within.

Secondly, after the schedule for classifying the oncogenicity of cypermethrin has been developed, how long will it take you to provide IRB with a statement setting forth the scientific basis for why the Agency is not required to do a qualitative risk assessment for cypermethrin. This is critical to the developement of the FR Notice.

Your immediate attention to these items would be greatly appreciated.

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TOX

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

OCT 27 1981

MEMORANDUM

SUBJECT: PP#2F2503. Cypermethrin in or on cottonseed, meat and milk. Risk Assessment.

Tox. Chem. No. 375DD

TO: Tim Gardner, PM#17
Registration Division (TS-767)

FROM: Edwin R. Budd, Acting Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

FMC Americas Inc. has proposed that tolerances be established for residues of the insecticide cypermethrin parent only as follows:

0.5 ppm in or on cottonseed

0.05 ppm in the meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep

0.05 ppm in milk

Toxicology data submitted in support of this tolerance has been reviewed by Toxicology Branch and in the basis of this and all other available toxicological data, it is our opinion that there is sufficient evidence to conclude that, at a dietary level of 1500 ppm in the diet for a lifetime, cypermethrin exhibits a low oncogenic potential in female mice. See the attached document titled "Cypermethrin: Assessment of Chronic and Oncogenic Effects, A Summary" by John Doherty, Ph.D., dated April 21, 1981 for a discussion of the evidence and rationale which led to this conclusion. Accordingly, a risk assessment for the proposed use of cypermethrin on cotton was performed by Section III, Toxicology Branch Evaluation. This risk assessment is summarized below.

Estimated Human Exposure to Cypermethrin

1. Dietary Exposure to General Population

Residue Chemistry Branch (see attached memorandum by John Doyle, Ph.D., dated January 26, 1984) has stated that maximum residues of cypermethrin ("parent plus metabolites" reported or calculated as CL 43774 in the concerned raw agricultural commodities are as follows:

Commodity	Maximum Residue, ppm*	Proposed Tolerance, ppm
Cottonseed	0.45	0.5
Milk	0.002	0.05
Meat	0.02	0.05
Fat	0.49	0.05
Meat byproducts	0.02	0.05

*Note that these are "actual residues", not the proposed tolerance levels.

Starting with these maximum residues, the contribution of residue in each commodity to the average daily dietary intake (for humans) was calculated by Toxicology Branch. For this purpose, the residues in meat, fat and meat byproducts were combined into a single commodity, red meat. The "representative maximum residue" for this commodity was chosen to be 0.01 ppm.

Commodity	Maximum Residue, ppm	Food Factor[1]	Average Daily Dietary Intake of Residue, mg/day[2]
Cottonseed	0.45	0.0075	0.001013
Milk	0.002	0.053	0.000859
Red Meat	0.01	0.0135	0.001621
		Total	0.003494

1. Correction factor for average total daily dietary intake of 1.5 kg for all foods.

2. Calculated by multiplying the "food factor" average daily dietary intake of commodity, in percent; 1.15% for cottonseed (i.e. 1.15% of 1.5 kg) for milk and dairy products, 1.35% for red meat.

By dividing the average daily dietary intake of residue (0.003494 mg/day) by the average human body weight (60 kg), the average dietary exposure to residues, in units of mg/kg/day, is obtained.

$$\frac{0.003494 \text{ mg/day}}{60 \text{ kg}} = 0.000058 \text{ mg/kg day "actual residues"}$$

In addition, starting with the proposed tolerance levels, the contribution of residue in each commodity to the average daily dietary intake (for humans) was also calculated in a similar manner.

Commodity	Proposed Tolerance, ppm	X 1.5	Average Daily Dietary Intake of Residue, mg/day
Cottonseed	0.5	0.75	0.001125
Milk	0.05	0.075	0.021465
Red meat	0.05	0.075	0.008108
		TOTAL	0.030698

and

$$\frac{0.030698 \text{ mg/day}}{60 \text{ kg}} = 0.000512 \text{ mg/kg/day "tolerance residues"}$$

2. Occupational Exposure to Cotton Field Workers

Exposure Assessment Branch (see attached memorandum by Robert Hitch, dated March 2, 1984) has calculated annual exposure estimates to cypermethrin for cotton field workers as follows:

	Annual Exposures (mg/yr)			
	Typical Case		Range	
	Dermal	Inhalation	Dermal	Inhalation
For Aerial Application				
Mixers/Loaders(1)	960	negligible	20-4800	negligible
Pilots(2)	1.5	0.1	1-2	negligible - 0.
For Ground Application				
Mixers/Loaders(3)	420	negligible	8.3-2000	negligible
Applicators(4)	0.9	negligible	0.2-1.8	negligible - 0.
Total Ground(5)	420.9	negligible	8.5-2001.8	negligible - 0.

(1) Mixing cypermethrin with water for aerial application and loading it into the airplane.

(2) Pilot applying cypermethrin in water.

(3) Mixing/loading cypermethrin with water for ground application.

(4) Ground application of cypermethrin in water by tractor.

(5) It is assumed that applicators working from tractors do their own mixing and loading.

The following quotation is from the Exposure Assessment Branch memorandum referred to above (p. 6).

> "The Exposure Assessment Branch has no surrogate data for pesticides which have been aerially applied in oil. It is recommended that a field study be submitted to the Agency prior to further consideration of registration applications involving Ultra Low Volume (ULV) application of cypermethrin in oil. Of particular concern is the possibility that exposures to humans due to this use may differ substantially from the exposures expected for aqueous spray mixes."

Starting with the reported annual exposures (in mg/yr), average daily lifetime exposures were calculated by Toxicology Branch by dividing by 2 (adjustment for occupational exposure of one-half a lifetime), then by 365 days (to give mg/day) and then by 70 kg, average body weight of worker (to give mg/kg/day). When exposures were presented for both dermal and inhalation exposure, they were combined.

	Annual Exposure, mg/yr	Average Daily Lifetime Exposure, mg/kg/day
For Aerial Application		
Mixers/Loaders		
typical case	960	1.9×10^{-2}
minimum	20	3.9×10^{-4}
maximum	4800	9.4×10^{-2}
Pilots		
typical case	1.6	3.1×10^{-5}
minimum	1.0	2.0×10^{-5}
maximum	2.17	4.2×10^{-5}
For Ground Application		
Mixers/Loaders		
typical case	420	8.2×10^{-3}
minimum	8.3	1.6×10^{-4}
maximum	2000	3.9×10^{-2}
Applicators		
typical case	0.9	1.8×10^{-5}
minimum	0.2	3.9×10^{-6}
maximum	1.9	3.7×10^{-5}
Total Ground(1)		
typical case	420.9	8.2×10^{-3}
minimum	8.5	1.7×10^{-4}
maximum	2001.9	3.9×10^{-2}

(1) Assuming applicators working from tractors do their own mixing and loading.

Calculation of Q_1^* (Multi-stage and One-Hit Models)

Q_1^* values were calculated utilizing the multi-stage and one-hit models, based on incidence data for lung tumors from the ICI-1982 mouse oncogenic study on cypermethrin. The dietary dosage levels in this study in ppm were adjusted to dosage levels in mg/kg/day by dividing by 7 and then to human equivalents by use of a surface area adjustment based on a 60 kg human weight and a 50 gm mouse weight. The Q_1^* for the multi-stage model (low-dose only) was 0.019. The Q_1^* for the one-hit model (all doses) was 0.013.

Risks of Oncogenicity for Humans

The following table presents the calculated risks of oncogenicity for humans resulting from the application of cypermethrin to cotton. These risks were calculated by multiplying the average daily lifetime exposure for each group at risk by the Q_1^* value for the multi-stage model and separately for the one-hit model.

Estimated Human Exposures to Cypermethrin and Related Risks of Oncogenicity Calculated by Application of the Multi-Stage and One-Hit Models to Mouse Lung Tumor Data

Group at Risk	Average Daily Lifetime Exposure (mg/kg/day)	Multi-Stage $Q_1^* = 0.019$ (low dose only)	One-Hit $Q_1^* = 0.013$ (all doses)
General Population			
Dietary exposure			
"actual residues"	5.8×10^{-5}	1.1×10^{-6}	1.0×10^{-5}
"tolerance residues"	5.1×10^{-4}	9.7×10^{-6}	9.2×10^{-5}
Cotton Field Workers			
Aerial Application			
Mixers/Loaders			
typical case	1.9×10^{-2}	3.6×10^{-4}	3.4×10^{-4}
minimum	3.9×10^{-4}	7.4×10^{-6}	7.0×10^{-6}
maximum	9.4×10^{-2}	1.8×10^{-3}	1.7×10^{-3}
Pilots			
typical case	3.1×10^{-5}	5.9×10^{-7}	5.6×10^{-7}
minimum	2.0×10^{-5}	3.8×10^{-7}	3.6×10^{-7}
maximum	4.2×10^{-5}	8.0×10^{-7}	7.6×10^{-7}
Ground Application			
Mixers/Loaders			
typical case	8.2×10^{-3}	1.6×10^{-4}	1.5×10^{-4}
minimum	1.6×10^{-4}	3.0×10^{-6}	2.9×10^{-6}
maximum	3.9×10^{-2}	7.4×10^{-4}	7.0×10^{-4}
Applicators			
typical case	1.8×10^{-5}	3.4×10^{-7}	3.2×10^{-7}
minimum	3.9×10^{-6}	7.4×10^{-8}	7.0×10^{-8}
maximum	3.7×10^{-5}	7.0×10^{-7}	6.7×10^{-7}
Total Ground			
typical case	8.2×10^{-3}	1.6×10^{-4}	1.5×10^{-4}
minimum	1.7×10^{-4}	3.2×10^{-6}	3.1×10^{-6}
maximum	3.9×10^{-2}	7.4×10^{-4}	7.0×10^{-4}

007707

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

FEB 24 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#2F2623 and FAP#2H5334. Toxicology Branch Update on the Mouse Oncogenicity Study and Dog Chronic Feeding Study. *Cypermethrin.*

Tox Chem. No. 271DD

TO: T. A. Gardner, PM#17
Registration Division (TS-767)

THRU: William L. Burnam, Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Background:

In a previous review of this petition (see J. Doherty review for PP#2F2623 and FAP#2H5334 dated September 16, 1983) Toxicology Branch (TB) indicated that the mouse oncogenicity study showed increased incidences of benign alveologenic tumors in the females particularly in the high dose test group and that there were questions concerning the NOEL for the 1-year dog feeding study. In order to help resolve problems concerning the oncogenic potential of cypermethrin in mice, TB requested that the registrant prepare and read slides from the lung and liver of the mice which were sacrificed at the interim kill and to provide historical control data for malignant lymphoreticular tumors for the strain of mouse used. TB also requested that a study be conducted with dogs to ascertain if the signs of gastrointestinal disturbance (passing of liquid stools and vomiting) resulted from a direct local effect of the cypermethrin or from an effect mediated through the central and/or peripheral nervous system.

The registrant has provided the additional lung and liver histopathology data, additional historical control data for lung tumors, and historical control data for malignant lymphoreticular tumors. This information is reviewed below.

The registrant has not yet decided whether or not to conduct the additional dog study. For the present time and the subject petition, the registrant was prepared, however, to accept 1 mg/kg/day as the NOEL for the 1-year dog study (see comments below).

Comments:

1. Mouse Oncogenicity Study

The pathology data provided for the lungs and liver of the mice sacrificed at the interim kill were examined. It was determined that no evidence for a decreased latency or time to tumor was demonstrated in the lungs of these interim sacrifice animals. Liver tissues showed no treatment related effects in these animals.

The mouse oncogenicity study (CTL/P/687, June 1982) may be upgraded to CORE GUIDELINES.

Toxicology Branch will prepare a summary document describing the results of the chronic feeding studies and oncogenic assessment of cypermethrin. A statistical risk assessment of cypermethrin based on the oncogenic assessment will also be prepared. These documents will be forwarded to Registration Division at a later date.

2. Dog 1-Year Feeding Study

In the letter from ICI to EPA (see R. E. Ridsdale letter dated December 9, 1983, EPA Acc. No. 072204) it was stated that ICI has not yet decided to do this study, and that "for the present time and the subject petition, we are prepared to accept 1 mg/kg/day as the NOEL for the 1-year dog study."

The letter also stated that ICI does not believe that the increased incidence of fluid feces in the 5 and 15 mg/kg/day groups is of toxicological significance, because of the absence of any histopathological changes in the alimentary tract or adverse consequences on general health. TB's position is that the increased incidences of fluid feces may be an adverse response which need not be accompanied by histopathological changes.

Thus, the NOEL for the dog study (CTL/P/703, July 6, 1982) is assigned as 1.0 mg/kg/day.

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	%	Malignant	%
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 13-42% 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

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John Doherty
Toxicology Branch

DCR-44871:J.Dohert efs:Raven:557-2226:2/14/84 PERMANENT:Client's Diskett

007707

CYPERMETHRIN: LIFETIME FEEDING STUDY IN MICE

TABLE 1

INCIDENCE OF NEOPLASTIC FINDINGS (LIVER AND LUNG ONLY) IN INTERIM KILL GROUPS AT ONE YEAR

Tissue/ Pathological Findings	Male Dose Cypermethrin					Female Dose Cypermethrin				
	0ppm Group 1 Control	0ppm Group 2 Control	100ppm Group 3	400ppm Group 4	1600ppm Group 5	0ppm Group 1 Control	0ppm Group 2 Control	100ppm Group 3	400ppm Group 4	1600ppm Group 5
ALIMENTARY SYSTEM										
Liver No. examined	9	10	10	10	9	8	10	9	10	10
Hepatocellular nodule (A) - benign	0	0	1	1	1	0	0	0	0	0
Hepatocellular nodule (B) - malignant	1	1	0	1	1	0	0	0	0	0
HAEMOPOIETIC AND LYMPHORETICULAR SYSTEM										
Malignant lymphoreticular tumours	1	1	0	0	2	1	0	1	0	2
RESPIRATORY SYSTEM										
Lungs No. examined	9	10	10	10	9	8	10	9	10	10
Alveolar/poric tumour benign	1	0	1	1	2	1	1	0	0	1
No. of animals examined	9	10	10	10	9	8	10	9	10	10

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

007707

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM JUN 7 1983

DATE:

TO: T.A. Gardner, PM# 17
Registration Division (TS-767)

WDB

SUBJECT: EPA Registration No. 10182-EUP-19. Nitrosamine Contamination of Pesticide Products Containing Cypermethrin.

Tox Chem. No. 271DD

Background

The ICI Americas Inc. has notified EPA (letter dated 4/26/83) that their products (see list below) containing the synthetic pyrethroid cypermethrin contain detectable levels of nitrosamine contaminants. These impurities have been traced to the supplier of the [redacted] the technical cypermethrin.

According to information provided by the ICI Americas Inc., the levels of the nitrosamines (chemical structures not provided) in the technical cypermethrin range from [redacted] The range for the several CYMBUSH products is [redacted] nitrosamines. A sample of DEMON WP had the nitrosamine level of [redacted] The company also indicated that certain earlier preparations of cypermethrin contained nitrosamines in excess of the ranges indicated above.

The company (ICI) has indicated that future production of cypermethrin will be made with [redacted] of nitrosamines so that technical cypermethrin will contain considerably less than 0.5 ppm of the contaminant.

Recommendations:

Toxicology Branch (TB) is not concerned at this time with nitrosamine contamination of less than 1 ppm in the

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MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

technical cypermethrin (refer to FR 45: No. 124, Wednesday, June 25, 1980). Residue Chemistry Branch (RCB), however, must confirm that the nitrosamine content is less than 1 ppm as indicated. Note: There are several other synthetic pyrethroids which use [redacted] in their manufacture (e.g., permethrin, deltamethrin, tralomethrin, etc.) and there are several different chemical companies which manufacture these chemicals. Thus, TB requests that RD obtain nitrosamine information on all synthetic pyrethroids from the several different manufacturers. The nitrosamine levels of the synthetic pyrethroid products must be assured to be less than 1 ppm (as recommended in FR 45 No. 124, Wednesday June 25, 1980).

List of ICI products containing cypermethrin:

CYMBUSH® 2E Insecticide
File Symbol 10182-AU
CYMBUSH® 3E Insecticide
File Symbol 10182-AL
CYMBUSH® 3E Insecticide
EUP No. 10182-EUP-19
CYMBUSH® OL Insecticide
EUP No. 10182-EUP-25
CYPERMETHRIN Technical
File Symbol 10182-AI
DEMON® WP
File Symbol 10182-TR
DEMON® WP
EUP No. 10182-EUP-GE

July 2, 1983

John D. Doherty, Ph.D.
Toxicology Branch
HED (TS-769)

6/2/83

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007707

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

SEP 16 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE:

TO: T.A. Gardner, PM#17
Registration Division (TS-767)

THRU: William L. Burnam, Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: PP #2F2623 and FAP #2H5334 concerning cypermethrin on cotton and related tolerances.

TOX Chem. No. 271DD

The ICI Americas Inc. is requesting to establish permanent tolerances for their insecticide cypermethrin, a synthetic pyrethroid, as follows:

PROPOSED TOLERANCES (PP #2F2623)

It is proposed that a tolerance be established for residues of (±) α-cyano-(3-phenoxyphenyl)methyl (±) cis,trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (cypermethrin) in or on the following raw agricultural commodities.

0.5 ppm in or on cottonseed.

0.05 ppm in the meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep.

0.05 ppm in milk.

PROPOSED FOOD ADDITIVE TOLERANCE (FAP #2H5334).

It is proposed that 21 CFR be amended by the establishment of a food additive tolerance for residues of (±) -cyano-(3-phenoxyphenyl)methyl (±)cis, trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (cypermethrin) in or on the following agricultural commodity:

5 ppm in cottonseed oil.

This review contains data sent to TOX Branch on September 3, 1982 and May 4, 1983.

Recommendations:

Toxicology Branch (TB) cannot recommend in favor of establishing permanent tolerances for cypermethrin at this time.

Comments:

1. The mouse oncogenicity study with cypermethrin presented data indicating an increased incidence of benign alveologenic tumors in the lungs of females particularly in the high dose test group. In order to fully assess this possible oncogenic finding in lung tissue the registrant is requested to submit the following additional data regarding the mouse study:

   a. The lung and liver tissue from the mice in the interim sacrifice groups (9-10 mice/sex/group at 52 weeks) should be examined as follows:

      i. gross pathological examination including palpation of the lung tissue.

      ii. 5 sections from each lung (cut in an identical manner from all animals) should be prepared for microscopy and read.

      iii. 1 section from the liver of each of these mice should also be prepared and assessed microscopically.

   b. Historical control data for malignant lymphoreticular tumors should be submitted for the strain of mouse used for this study. Ideally, these data should be on mice from the same supplier which were studied in the same laboratory as were the mice in this study. Recent or concurrent data is most preferable.

TB is requiring information on the development of malignant lymphoreticular tumors in this strain of mouse because it was noted that as many as 55 to 75% of the female mice and 20 to 48% of the male mice in this study with cypermethrin developed this type of tumor. Although there was no indication that the presence of cypermethrin in the diets increased the incidence of this type of tumor, TB feels it necessary to assess further the general health status of the animals used in this study and the potential influence of these tumors on the development of the lung tumors observed in this study.

After the requested data (above) is received by TB, all pertinent data relating to the question of potential oncogenicity in the lungs of female mice will be re-evaluated and a request will be made to the TB statistician for statistical analysis. A future memorandum will then address the issue of potential oncogenicity of cypermethrin in more detail.

Note to PM: The mouse oncogenicity study has been retained by TB for future reference.

2. For the dog 1-year oral dosing study, the results showed that at 5 and 15 mg/kg/day there were highly increased incidences of "liquid stools." It is uncertain as to whether or not this effect was due to the method of treatment (test chemical administered orally in a corn oil solution in a gelatin capsule) or due to the test chemical actually stimulating the central nervous system or peripheral nervous system to promote a gastrointestinal disturbance.

Certain other synthetic pyrethrins are known or suspected to cause similar gastrointestinal disturbances via direct action on the nervous system. The answer to this question will influence the assignment of a NOEL to this study--and, consequently, calculation of the ADI and MPI since the dog is more senstiive than the rat to cypermethrin in chronic studies.

In order to resolve the problem of the source for the stimulus responsible for the production of the liquid stools, the registrant is requested to conduct the following study:

Beagle dogs should be dosed intravenously (i.v.) with cypermethrin in a suitable vehicle and their reactions noted including the frequency and condition of the bowel movements for the following 72 hour period. At least two groups of 3 dogs should be used: a control group dosed i.v. with vehicle and the test group dosed i.v. with cypermethrin in vehicle. The group dosed with cypermethrin should show some signs of nervous system stimulation but the dose should not be so high as to

kill the dogs within the 72 hour testing period. The dogs used in this study should be on their normal diets (and not fasted prior to dosing) and should have access to water at all times. Dosing should be made a short time after the dogs have been fed. The data should be tabulated to show the signs of response to cypermethrin (or vehicle) in parallel with any signs of bowel movements.

The results of this experiment will assist TB in determining a NOEL for the dog 1-year oral toxicity study. More specifically, demonstration that the effect (liquid stools) may be caused by intravenous injection would imply that cypermethrin acts directly on the central nervous system or on the peripheral system. In this case, the NOEL may be assigned as 1.0 mg/kg/day. On the other hand, failure of the intraveneous injection to affect the dogs' gastrointestinal system would imply that the effect is due to some other (presumably local) action. In this case, the NOEL may be assigned as 5.0 mg/kg/day.

3. The rat chronic feeding/oncogenicity study and the rat three generation reproduction study were reviewed and found to be CORE GUIDELINES. No oncogenic effect was noted in rats at doses up to and including 1500 ppm. The NOEL for this study was determined to be 150 ppm (7.5 mg/kg/day). Although a NOEL was established for this study, TB must use the NOEL eventually established for the dog 1 year oral dosing study to calculate an ADI and MPI for cypermethrin because the dog has been shown to be the more sensitive species.

4. EPA Acc. No. 071069 contains a cover letter, dated 9/1/82, from Dr. R. E. Ridsdale of ICI which contains comments on a previous review by TB concerning the use of cypermethrin on cotton (see J. Doherty review dated Oct. 28, 1981). The following comments are in response to the issues raised by Dr. Ridsdale.

4a. Neurotoxicity. TB has determined that cypermethrin does not present a practical neurotoxicity hazard to man as indicated by review of the recently submitted chronic feeding and oncogenesis rat and mouse studies.

4b. TB concedes that the product studied for the acute inhalation LC_{50} determination was GFU-061. Because the procedures used in this study did not generate a uniform spray mist the actual LC_{50} of the product when used as a spray mist could not be assessed and the study is CORE SUPPLEMENTARY.

Based on the overall toxicity of cypermethrin and because the spray mists generated will not be a respirable size, an additional inhalation LC_{50} study with this product is not required.

4c. A TB review of the products 10182-AL and 10182-AU was sent to RD on January 10, 1983. In that review, TB required that the acute oral LD_{50} studies on both these formulations be repeated (or additional information on the available studies be submitted); proposed a label change on 10182-AL; and noted that one inert in 10182-AL was not cleared.

4d. TB acknowledges receipt of the information that the cis:trans ratio of the technical cypermethrin used for the rat and rabbit teratology studies was 50:50.

STUDIES REVIEWED

Study	Result	CORE Classification
3 Generation Reproduction- rats CTL/P/683 July 9, 1982.	NOEL for adverse reproductive effects = 750 ppm (HDT). NOEL for systemic effects = 50 ppm. LEL = 150 ppm, decreased body weight gain in maturing pups.	GUIDELINES
1 year oral dosing (gelatin capsule) - dogs CTL/P/703 July 6, 1982	Tentative conclusion: NOEL = 1.0 or 5.0 mg/kg/day. G-I tract disturbances at 5.0 mg/kg/day. Definite nervous system effects at 15 mg/kg/day (HDT). (An additional study has been requested to help determine the toxicological significance of the G-I tract disturbances.)	GUIDELINES
2 year chronic feeding/ oncogenicity - rats CTL/P/669 June 1982	NOEL = 150 ppm. LEL = 1500 ppm, weight loss, general changes in blood elements and cholesterol levels. Not oncogenic up to and including 1500 ppm (HDT).	GUIDELINES
Lifetime oncogenicity - mice CTL/P/687 June 1982	Potentially positive oncogenic response in lung tissue. [Increased incidence of benign adenomas in females (only), statistically significant at 1600 ppm (HDT) (only).]	RESERVED

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_0 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.

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 0, 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 similar 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. It 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).

A. Cypermethrin: 2 year feeding study in rats

ICI Central Toxicology Labs., #CTL/P/668, June, 1982. EPA Acc. No. 071070 and 071071, TAB SOC.

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 ± 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 male group.

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 hemoglobin 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 lesions 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.

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.

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 hemoglobin, hemotocrit and RBC count were noted for males in the 1600 ppm test group at the interim sacrifice but not at the terminal sacrifice.

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

c. Platelets counts 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. Neutrophil 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 sacfifice for both the high dose group males and females.

The overall conclusion of the nematology 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.

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 Affected (2)
ntrol-1	61	66	43	44	61	90	55	54
ntrol-2	60	80	40	40	60	82	47	46
) ppm	60	93	49	49	61	69	40	44
) ppm	60	60	31	41	60	74	43	45
)0 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	3.3
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	1.7
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 (~ 3-9%) 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. FB 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 l.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 noncncogenic 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.

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Toxicology Branch
Hazard Evaluation Division
TS769

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Doherty

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

JAN 10 1983

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: Franklin Gee, Product Manager #17
Registration Division (TS-767)

SUBJECT: PP 2F2623 and FAP 2H5334. Request for a Tolerance for Cypermethrin on Cottonseed, and in Meat and Milk. EPA Registrations 10182-~~EUP~~-AL and 10182-~~EUP~~-AU for CYMBUSH 2E (preparation GFU-070) and CYMBUSH 3E (preparation GFU-061)

TOX Chem. No. 271DD

Background:

The ICI Americas, Inc. is requesting to establish tolerances as follows:

Proposed Tolerances

It is proposed that a tolerance be established for residues of (+)α-cyano-(3-phenoxyphenyl)methyl (±) cis,trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (cypermethrin) in or on the following raw agricultural commodities:

0.5 ppm in or on cottonseed

0.05 ppm in the meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep.

0.05 ppm in milk

Proposed Food Additive Tolerance

It is proposed that 21 CFR be amended by the establishment of a food additive tolerancce for residues of (+)α-cyano-(3-phenoxyphenyl)methyl (+) cis, trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (cypermethrin) in or on the following agricultural commodity:

5 ppm in cottonseed oil.

Registration is also sought for CYMBUSH 2E preparation GFU-070) and CYMBUSH 3E (preparation GFU-061).

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Toxicity studies on the insecticide WL 43467: A two year feeding study in rats.

Shell Toxicology Laboratory, TLGR.0189.78, Feb. 1979, EPA Acc. No. 070564, TAB 23c.

Five groups of male and female Wistar rats SPF obtained from the Shell Breeding Labs were dosed with 0, 1, 10, 100 and 1,000 ppm of cypermethrin (cis/trans ratio 1:1 from batch #30 and 98% purity). There were 96 control males and females and 48 test group males and females for each dose level. The experimental protocol required that interim sacrifices of 12 male and female controls and 6 males and females from each dose group be sacrificed at 6, 12, and 18 months. Thus, there were 48 controls of each sex and 24 test group rats of each sex for each dose level scheduled to receive the test diet for the two year period.

Results:

1. **Clinical observations - No behavioral effects of this test chemical were noted or reported. The clinical observations reported were stated as being in all dose groups and not related to the presence of the test chemical.**

2. **Body weight and food consumption - A NOEL for depression of body weight is set at 100 ppm although only minor depressions (<10%) were noted at 1,000 ppm. The high dose group also showed signs of reduced food intake in the first year of the study.**

3. **Survival - The following table shows the survival rate for each group and includes only those rats which were scheduled for the 24 month interval.**

	Males	Females
Controls	33/48 (69)*[1]	20/48 (42)
1 ppm	12/24 (50)[1]	8/24 (33)
10 ppm	13/24 (54)	9/24 (38)
100 ppm	17/24 (71)	10/24 (42)
1000 ppm	17/24 (71)	12/24 (50)

* Survivors/starters (%)
[1] Toxicology Branch calculation differs slightly from the report (Table 3).

Although survival is usually 50% or greater (except for the 1 and 10 ppm group females), the number of survivors is less than the desirable 25 individuals for each sex at each dose level.

4. **Clinical Chemistry - Assayed at 6, 12, 18 and 24 months. Parameters measured were protein, urea, alkaline phosphatase, aspartate amino transferase, alanine amino transferase and Na^+, K^+ and Cl^-.**

No consistent dose related deviations were noted. Occasional deviations in urea, Na^+, K^+, and Cl^- were noted but these changes could not be definitely linked to ingestion of cypermethrin.

Not all of the parameters currently recommended for assay were determined for this study.

5. Hematology - Assayed at 6, 12, 18 and 24 months. Parameters measured included Hb, HCT, RBC, WBC, mean cell volume, mean cell hemoglobin prothrombin time and KCCT time. WBC counts included differential leucocytes, absolute value of neutrophils and lymphocytes.

   No consistent dose related deviations were noted for these parameters.

6. No urinalysis data were presented. (The protocol did not require urinalysis.)

7. Organ Weights - Determined at 6, 12, 18 and 24 months for the brain, heart, liver, spleen, kidneys, and testes (no ovaries).

   No consistent dose related deviations were noted. Occasional deviations in the testes, kidneys, heart and liver weights, but the magnitude and inconsistency of these variations is not considered to be of toxicological concern.

8. Gross Necropsy - The summary of the findings reports that there were no compound-related gross necropsy changes noted. <u>This report is unsubstantiated</u> by a listing of the gross observations or a tabulation for each group.

9. Pathology - Microscopic examination was performed on all rats in the 24 month group, but on only those rats in the 0, 100, and 1,000 ppm groups (except those dying spontaneously) for the interim sacrifice groups. The following lists the tissues for analysis.

<u>Tissues examined microscopically</u>

Brain* (cerebrum, cerebellum, mid brain, medulla)
Heart* - ventricles
Liver*
Spleen*
Kidneys*
Testes*
Ovaries
Stomach
Pancreas
Mesenteric lymph nodes
Prostate or uterus
Thyroid/parathyroid with oesophagus and trachea
Thymus (if present)
Eye and lachrimal glands
Lungs
Pituitary
Adrenals

Small intestine (3 levels)
Large intestine (2 levels)
Salivary glands (sub-maxillary)
Urinary bladder
Sciatic nerves
Any other macroscopic lesions in any tissue

Tissues stored for reference

Knee joint and femur
Muscle (femoral)
Mammary gland (posterior site with skin)
Seminal vesicles
Spinal cord (thoracic)
Tongue
Bone marrow smear from femur

Non-neoplastic findings were not tabulated but are presented with each animal.

Neoplastic Findings

1. 6 month group - No neoplasia reported.

2. 12 month group - Four control female rats, 2 - 100 ppm group and 0 - 1,000 ppm group rats developed tumors. Males were reported as being unaffected. No test chemical effect is obvious.

3. 18 month group - Among the males there were 7, 2, and 2 rats affected with tumors for the control, 100 and 1,000 ppm test groups. Among the females there were 19, 10, and 7 rats affected with tumors for the control, 100 and 1,000 ppm test groups. No effect due to treatment was evident. Of the 36 rats with neoplasia among the females, 35 were pituitary neoplasms. The distribution for pituitary adenomas was 19/24, 9/12 and 7/12 for the control, 100 and 1000 ppm groups.

4. 24 month group - The following table lists the tumors (of any kind) reported in each group for those rats which lived after 18 months or longer.

	Males	Females
Controls	25/48*	54/48
1 ppm	9/24	28/24
10 ppm	14/24	37/24
100 ppm	9/24	27/24
1000 ppm	13/24	27/24
Total	70	143

* Tumors/number of rats available.

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Among the males, there were 25 (36%) rats with pituitary adenomas, 12 (17%) rats with tumors in the skin. All other neoplasms were scattered among the different organs and were of low frequency (2 or less per group). No indication of an oncogenic effect was noted in males.

Among the females, there were 114 pituitary adenomas (66%). For example, there were 39/48, 19/24, 23/24, 16/24 and 17/24 females affected for the control, 1, 10, 100 and 1000 ppm groups. The mammary glands had a total of 25 neoplasms (14%). All other neoplasms (34 incidences) were isolated occasions (<2 per group). No evidence of a neoplastic effect of cypermethrin was evident.

Lungs - There were 3 incidences of lung adenocarcinoma, one in the male (high dose group) and two in the female test groups (1 control and 1 in the 100 ppm group).

Liver - There was a single incidence of liver adenoma (10 ppm female group).

Thyroid - No adenomas were reported. There were two incidences of parafollicular carcinoma reported, one among the males (10 ppm group) and one among the females (10 ppm group).

Conclusion - This sudy is CORE SUPPLEMENTARY and cannot be used to satisfy either the chronic feeding or oncogenesis in rats data requirements. The following is a list of deficiencies.

1. Insufficient number of rats surviving for 24 months.

2. No tabulation of gross necropsy observations.

3. No parallel table of gross necropsy information with microscopic findings (i.e., individual pathology reports).

4. No tabulation of non-neoplastic findings.

5. Not all parameters for blood chemistry determinations were measured and no urinalysis was conducted.

Metabolism and pharmacokinetics of 14C labelled cypermethrin in rats, mice and dogs.

11 studies dealing with the metabolism and pharmacokinetics in rats, mice and dogs were presented for review and are listed below. For the purposes of this review, the results are summarized in terms of identification of metabolites, half life of the chemical in the body following administration, and tissue retention of the radioisotope.

For these studies, 4 isomers of cypermethrin were synthesized with the label in either the benzyl or cyclopropyl moiety. There were 4 isomers because of the cis and trans property of cypermethrin. The radiolabeled chemicals were synthesized in the company research laboratories.

Listed below are the studies reviewed.

Studies in Rats

A. Cypermethrin: The kinetics of cypermethrin in the blood of rats following a single oral dose.

Shell Toxicology Laboratory, TLER.80.073, August 1980, EPA Acc. No. 070564, TAB 24c

B. Cypermethrin: Excretion and retention of cypermethrin and its metabolites in rats following a single oral dose (CA 200 mg/kg).

Shell Toxicology Laboratory, TLER.80.083, October 1980, EPA Acc. No. 070565, TAB 25c

C. Cypermethrin: Bioaccumulation study in the rat (70 days)

Central Toxicology Lab (ICI), CTL/P/599, June 5, 1981, EPA Acc. No. 070565, TAB 27c

D. (^{14}C)-Cypermethrin: A study to determine the bioaccumulation of radioactivity in the rat following repeated oral administration (up to 28 days)

Hazelton Labs (Europe) # 2487-72/201, October 1980, EPA Acc. No. 070565, TAB 26c

Studies in Mice

E. The elimination of radioactivity by mice following oral dosing with ^{14}C-cis and ^{14}C-trans WL-43467 (cypermethrin.)

Shell Toxicology Laboratory, TLGR .0079. 78, October 1978, EPA Acc. No. 070565, 32c

F. The metabolites of cis and trans cypermethrin (WL 43467) in mice.

Shell Toxicology Laboratory, TLGR .0102. 78, June 1978, EPA Acc. No. 070565, 34c

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G. The elimination of residues from the fat of mice following the oral administration of (^{14}C-benzyl) W2 43487 (Cis WL-43467).

Shell Toxicology Laboratory, TLGR .0080.78, June 1978, EPA Acc. No. 070565, TAB 33c

H. Taurine conjugation in the metabolism of 3-phenoxybenzoic acid and the pyrethroid insecticide cypermethrin (WL-43467) (in mice).

Shell Toxicology Laboratory, TLGR .0135.77; Dec. 1977, EPA Acc. No. 070565, TAB 35c

Studies in Dogs

I. The metabolism of cypermethrin (WL-43467) in mammals. The fate of single oral doses of cis and trans (^{14}C-benzyl) cypermethrin in the dog.

Shell Toxicology Laboratory, TLGR .0011.79, April 1979, EPA Acc. No. 070565, TAB 36c

J. The metabolism of cypermethrin (WL-43467) in mammals. The fate of a single oral dose of (^{14}C-cyclopropyl) cypermethrin in the dog.

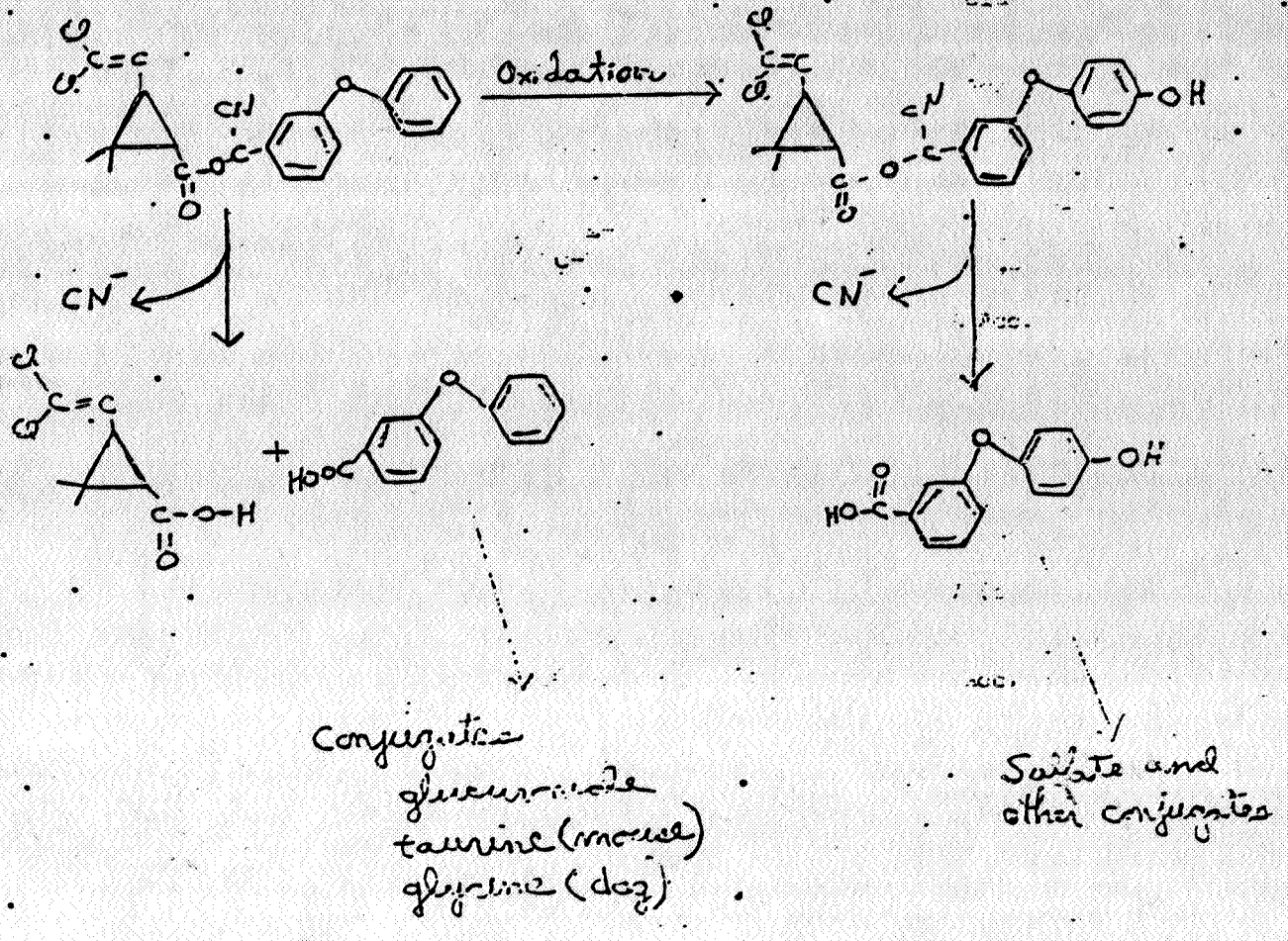
Shell Toxicology Laboratory, TLGR .79.029, April 1979, EPA Acc. No. 070565, TAB 38c

K. The metabolic fate of the cis and trans isomers of WL-43467 (cypermethrin) and of 3-phenoxybenzoic acid in dogs.

Shell Toxicology Laboratory, TLGR .79.012, April 1979, EPA Acc. No. 070565, TAB 37c

Part I: Identification of metabolites

The metabolic fate of cypermethrin following absorption was shown to be nearly the same in all three species with regard to the major metabolic pathway. In all three species cypermethrin is hydrolysed to cyclopropane carboxylic acid and 3 phenoxybenzoic acid. The principle pathway as derived from urinary metabolites is as shown:



Other minor metabolites were also demonstrated.

Note: None of these studies discussed the fate of cyanide once liberated from the parent compound.

In all three species, the radioactivity recovered in the feces was mostly unchanged cypermethrin.

Part II: Tissue Retention

In the rat, following a single oral dose (200 mg/kg of labelled cyclopropyl or benzyl cypermethrin) there were significant levels of label remaining in the tissue 7 days after dosing. In this experiment, the blood, liver, fat, muscle, brain, ovaries/testes, bone, heart, spleen, kidney, intestines, skin and residual carcass were analyzed by combustion.

In the males:

1. Following treatment with ^{14}C benzyl cypermethrin, the fat (21.16 ug/gm), skin (3.02 ug/gm), intestines (2.05 ug/gm), liver (1.08 ug/gm), and kidney (1.02 ug/gm) showed evidence of retaining at least some of the radioactivity (the data were presented as mg equivalents of cypermethrin/gm of tissue). The other tissues had less than 1.00 ug/gm.

2. Following treatment with ^{14}C cyclopropyl cypermethrin, the fat (14.97 ug/gm), intestines (11.30 ug/gm), liver (4.91 ug/gm), carcass (2.50 ug/gm), skin (2.61 ug/gm) and kidney (1.49 ug/gm) showed evidence of retaining the label. Other tissues were less than 1.0 ug/gm.

In the females:

1. The pattern of retention was similar to the male except that the ovaries retained 4.66 ug/gm of the label derived from the ^{14}C benzyl labelled material and 2.99 ug/gm of the label derived from the ^{14}C cyclopropyl labelled material.

The tissue residues in the rats dosed with 200 mg/kg of cypermethrin were subjected to methanol extraction. From 24 to 99% of the label was extracted by this solvent. The tissues which retained most of the label following extraction were the liver, bone, heart and, to a lesser extent, the skin and spleen, blood, brain and kidney depending on the location of the label in the parent compound.

Two experiments were conducted to determine the bioaccumulation of ^{14}C following daily oral (by gavage) doses of ^{14}C cypermethrin 50:50 cis/trans at the level of 2.0 mg/kg/day. The first experiment included 9 male and female rats of each sex to be dosed for 28 days and the rats were sacrificed 24 hours after the last dose. The fat (4.1 ug/gm), skin (636 ug/gm), liver (.566 ug/gm) and ovaries (.710 ug/gm) had the highest levels of radioactivity.

The second experiment included dosing 60 female rats with ^{14}C benzyl-labelled cypermethrin (50:50 cis/trans) with 2 mg/kg for up to 70 days. Groups of 3 treated and 1 untreated rat were sacrificed at days 1, 4, 7, 14, 21, 28, 35, 42, 49, 56, 63 and 70 days following dose administration. Following the last dose (day 70), the remaining 24 treated rats were sacrificed on days (2 treated rats and 1 control) 3, 8, 15, 22, 29, 36, 43 and 50 days post dosing. Samples of liver, kidney, body fat, blood, plasma, skin, and ovaries (carefully trimmed of fat) were disected out and analyzed for residues of ^{14}C. The fat and skin accumulated the most radioactivity (peaks of 3.31 ug/gm and 1.86 ug/gm respectively). These tissues also showed the slowest rate of decline of radioactivity following cessation of dosing. The

laboratory stated that the differences in the 28 day preliminary experiment (above) with respect to ^{14}C residues in the ovaries was due to carefully trimming away fat from the organ. Peak radioactivity in the liver, kidneys, blood, and plasma was always less than 1 ug/gm. The ovaries and the sciatic nerve were always less than .04 or .03 ug/gm with the controls showing a level based on background radiation of .01 ug/gm. These data also showed that cis cypermethrin was the predominant form of the residue in the fat.

In the mouse, the tissue retention of ^{14}C-benzyl labelled WL-43481 (cis cypermethrin) was studied. 10 male mice (CF strain) were dosed with 8.8 mg/kg and were sacrificed on days 8, 14, 21, 30 and 42 post dosing (2 mice on each sacrifice day). Following sacrifice, fat samples were removed and computed and analyzed for radioactivity.

The results showed that the residual ^{14}C in the fat had a half life of 15 days (10-20 days). Analysis of the fat samples by GLC showed that virtually all of the extracted radioactivity was accounted for as unchanged cis cypermethrin.

No studies were presented to demonstrate the tissue retention of cypermethrin in the dog.

Part III: Absorption and Excretion of Labelled Cypermethrin

In all three species, (rat, mouse and dog) most of the radioactivity was excreted in the urine following ingestion. The respiratory and bile routes are of minor (if any) significance.

In the rat, studies were presented repeating the results with single oral doses of 2.0 mg/kg and 200 mg/kg for both the ^{14}C benzyl and ^{14}C cyclopropyl labelled isomers (each preparation was approximately 50% cis and 50% trans). For the low dose group, the half lives based on periodically sampling the blood were reported to be:

Isomer	Sex	t 1/2
14-benzyl	Males	2.78 hr.
	Females	4.63 hr.
14-cyclopropyl	Males	4.30 hr.
	Females	4.79 hr.

For the low dose groups, sampling of the blood 3 hours or more after dosing revealed that from <1.0% to as much as 9.0% of the radioactivity remaining was as the parent compound. The rest of the radioisotope was as metabolites. The benzyl labelled material showed a higher percentage of parent compound than the cyclopropyl label.

The amount of radioactivity recovered following a single oral dose of 200 mg/kg of either ^{14}C Cyclopropyl or ^{14}C benzyl cypermethrin is shown in the following table.

Percentage of Radioactivity Recovered in 7 Days (Total)

		n	Urine	Feces	Total Recovered*
^{14}C benzyl	Males	5	28.6 ± 2.5	55.3 ± 4.6	86.7
	Females	5	32.9 ± 4.9	59.0 ± 7.3	93.9
^{14}C cyclopropyl	Males	3	41.3 ± 4.6	45.9 ± 8.2	91.4
	Females	3	55.8 ± 5.2	34.1 ± 4.3	93.4

*Total recovered is the sum of urine, feces, and including the amount in the tissues.

Following a single oral dose of 8.0 mg/kg to mice of ^{14}C benzyl cypermethrin (50% cis/50% trans) the distribution of the radioactivity is shown below (as obtained from male mice).

Isomer	% of dose recovered		
	Urine	Feces	Total
Cis	41.1	51.1	85.2
Trans	66.2	24.7	90.9

As indicated above, the absorption of isotope from the benzyl labelled material is greater than that from the cyclopropyl labelled material.

Absorption and excretion studies with dogs were somewhat limited in their usefulness because only 1 or 2 animals were used in each experiment. Thus, varying amounts of ^{14}C were recovered in the urine or the feces. Consistent with studies in other species, the <u>cis</u> isomer is recovered in somewhat greater quantities in the feces.

Study/Lab/Study #/Date	Material	EPA Accession No.	Results; LD_{50}, LC_{50}, DIS, NOEL, LEL	MRID Category	(OPP Guide) Doc. No.
Teratology - rabbit; Shell Labs; #TLGR 0010.78; 1/78	Technical 50%cis-50%trans	099855	Teratogenic NOEL >30 mg/kg (HDT) Maternal NOEL > 30 mg/kg (HDT) Levels tested-0, 10, and 30 mg/kg		Minimum 004025
Teratology - rat; Shell Labs; #78/SHL2364 ; 10/4/78	Technical 98.2%	099855	Teratogenic NOEL > 70 mg/kg (HDT) Maternal NOEL = 17.5 mg/kg Maternal LOEL = 35 mg/kg/day (decrease weight change) Levels tested by gavage in CD strain- 0, 17.5, 35 and 70 mg/kg		Minimum 004025
3-Generation reproduc. - rat; Shell Toxicol Labs; #TLGR.0188.78; 2/79	Technical 98% Pure	070564	Levels tested 0, 10, 100, 500 ppm Reproduction NOEL >500 ppm(HDT) Systemic NOEL=10 ppm(not to be used to calculate ADI) Systemic LOEL=100 ppm(decrease in day pup weight (approx. 3%)		Minimum 002191
3 Generation reproduction - rat; ICI; CTL/P/0811; 7/9/80	Tech. 51.4 cis 40.6 trans 91.5% pure	071074 071075	Reproductive NOEL = > 750 ppm (HDT) Systemic NOEL = 50 ppm Systemic LEL = 150 ppm, (decreased body weight gain in maturing pups)		Guideline 001549
90 Day feeding - rat; ICI; #CTL/P/127; 1/8/80	Technical 44:56 cis-trans	099855	Systemic NOEL = 150 ppm Systemic LEL = 1500 ppm (decreased body weight gain and possible nerve damage.) There were pharmacological effects at 150 ppm increased hepatic aminopyrene demethylase) Levels tested in SPF Alderley park strain- 0, 75, 150 and 1500 ppm		Minimum 004025
90 Day feeding - dog; Shell Labs; #1112; 11/77	Technical 50:50 cis-trans	099855	NOEL = 500 ppm LEL = 1500 ppm (diarrhea, anorexia and nerve symptoms) Levels tested in beagles- 0, 5, 50, 500 and 1500 ppm		Minimum 004025

Tox Chem No. 271DD (Cypermethrin)

Study/Lab/Study #/Date	Material	FPA Accession No.	Results: LD_{50}; LC_{50}; PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
21 Day dermal - rabbit; ICI; CTL#LB0019; 2/4/81	Technical 53:47	070564	NOEL = 20 mg/kg LEL = 200 mg/kg (HDT) -(liver pathology, possible decreases in terata weight without associated pathology)		Minimum 002391
2 Year feeding/oncogenic -rat; Sheli Toxicol.Lab; #TLGR 0189.78; 2/79	Technical 1:1, 98% Pure	070564	No conclusions drawn Levels tested 0, 1, 10, 100 and 1000 ppm		Supplemen-tary 002391
1-Year feeding - dog; ICI;CTL/P/703; 7/6/82	Tech. 53.9 cis 46.1 trans 90.6% pure	071069	NOEL = 1.0 mg/kg/day or 5.0 mg/kg/day* G-I track disturbance at 5.0 mg/kg/day LEL (more definite) = 15 mg/kg/day nervous system disturbance (hyperactivity) Levels tested - 0,1.0,5.0,15 mg/kg *An additional study has been requested to help determine the toxicological significance of the G-I track disturbance.		Guideline 003249
2-Year feeding/ oncogenic - rat; ICI; CTL/P669; 6/82	Tech. 55 cis 45 trans 89-93% pure	071070 071071	NOEL = 150 ppm LEL = 1500 ppm weight loss, general change in blood elements and cholesterol. (oncogenic NOEL > 1500 (HDT) Levels tested - 0,20,150,1500 ppm		Guideline 003249
97-101 Week oncogenic - mice; ICI; CTL/P/687; 6/82	Tech. 54 cis 46 trans 94.2-94% pure	071072 071073 071570 072204	Potentially Positive oncogenic response in lung tissue: Benign adenomas associated with females only. High dose group (1600 ppm) is stat. significant. No evidence of a decreased latency noted. Levels tested - 0,100,400,1600ppm		Reserved 003249 Guideline 003647

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Pharmacokinetics in blood - rat; Shell; # TLGR.80.073; 8/80	^{14} Cypermethrin	070564	t(1/2) was 2.78 to 4.79 hours in blood. From < 1% to 9% of radioactivity remained as parent compound. Rest of radioisotope was as metabolites		Minimum 002391
Excretion and retention-rat; Shell; #TLGR.80.073	^{14}C Cypermethrin	070565	Most of the ^{14}C recovered in the urine or feces.		Minimum 002391
Bioaccumulation - rat; ICI; CTL/P/1599; 6/5/81	^{14}C Cypermethrin	070565	Fatty tissues retain trace levels of 14C		Minimum 002391
Bioaccumulation- 70 days -rat; Hazleton (Europe); #2487-71/201; 10/80	^{14}C Cypermethrin	070565	Does tested = 2 mg/kg/day. Fat and skin accumulated most radioactivity (peaks of 1.9 and 1.86 ug/gm) t (1/2) of C^{14} in fat = 15 days.		Minimum 002391
Elimination from - mice; Shell; #TLGR 0079,78; 10/78	^{14}C Cypermethrin	070565	Most of ^{14}C recovered in urine or feces.		Minimum 002391
Metabolism - mice; Shell; #TLGR,0102,78; 6/78	^{14}C Cypermethrin	070565	Hydrolyzed to cyclopropane carboxylic acid and 3 phenoxy benzoic acid and then conjugated.		Minimum 002391
Metabolism - Shell Labs.	Labelled isomers of cypermethrin	099855	Several studies - see review		004825
Elimination from fat - mice; Shell; #TLGR.0080.70; 6/78	^{14}C Cypermethrin	070565	1/2 life for elimination from fatty tissues = 15 days		Minimum 002391
Metabolism (taurine conjugation) - mice; Shell #TLGR.0135.77; 12/77	^{14}C Cypermethrin	070565	3-phenoxybenzoic acid conjugated with taurene is a metabolite of cypermethrin in the mouse		Minimum 002391

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Pharmacokinetics in Metabolism - dog; Shell; #TLGR.0011.79; 4/79	^{14}C Cypermethrin ^{14}C Cypermethrin	070564 070565	t (1/2) was 2.78 to 4.79 hours in Rapidly metabolized		Minimum Supplementary 002391
Metabolism - dog; Shell; #TLGR.79.029; 4/79	^{14}C Cypermethrin	070565	Rapidly metabolized		002391
Metabolism - dog; Shell; #RLGP.79.012; 4/79	^{14}C Cypermethrin	070565	Rapidly metabolized		002391
Neurotoxicity - chicken; Huntingdon Res. Center; ICI #345 NT/8178 and CTL/C/1077; 7/3/81	Technical 53:47 87.8% Pure	070564	Levels tested=0, 2500, 5000, 10,000 mg/kg/day - not neurotoxic to chickens at 10,000 mg/kg (HDT)	IV	Guideline 002391
Mutagenic - ames; ICI; CTL/P/595; 11/13/80	Technical 53:47 91.5% Pure	070564	Not mutagenic to Salmonella Typhimurium strains TA-98,TA,100,TA-1535, TA-1537, TA-1538 with and without metabolic activiation		002391
Mutagenic bacterial and yeast mutagenesis (ames test); Shell; #TLGR,80,059; 6/80	Technical 98% Pure	070564	Not Mutagenic to Salmonella Typhimurium Strains TA-98,TA-100,TA-1535 TA-1537, TA-1538 with and without metabolic activation or in strains WP_2 and WP_2 uvrA of E. Coli with or without metabolic activation or in the yeast Saccharomyces cerevisiae JDI in vitro		002391
Mutagenic dominant lethal- mice ; Shell Toxicol; #TLGR.0042.77; 12/77	Technical	070564	Not mutagenic in these studies at up to 10 mg/kg for 5 consecutive days or 25 mg/kg (single dose)		002391

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL; LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic bone marrow cells - chinese hamster; in vivo; Shell Toxicol Labs; #TLGR.0136.77; 12/77	Technical	070564	No chromosome aberrations induced at 40 mg/kkg (HDT)		002391
Acute oral LD_{50} - rat; Stillmeadow, Inc; #1846-80; 10/16/80	FMC 45806 2.5 EC	243861	LD_{50} = 185 (153-223) mg/kg, males LD_{50} = 242 (178-327) mg/kg, females LD_{50} = 220 (178-271) mg/kg, combined	II	Guideline 004824
Acute oral LD_{50} - rat; Cosmopolitan Safety Evaluation, Inc; #0397A; 9/25/80	FMC 45806 2.5 EC	243861	LD_{50} = 180 (153-213) mg/kg, males LD_{50} = 137 (111-168) mg/kg, females LD_{50} = 156 (139-176) mg/kg, combined	II	Guideline 004824
Acute dermal LD_{50} - rabbit; Cosmopolitan Safety Evaluation, Inc.; #0397B; 8/1/80	FMC 45806 2.5 EC	243861	LD_{50} = > 2.0 gm/kg	III	Minimum 004824
Acute inhalation LC_{50} - rat; Toxigenics; #420-0275; 9/22/80	FMC 45806 2.5 EC	243861	LC_{50} = 2.36 (2.13-2.62) mg/kg/4hr(M) LC_{50} = .18 (1.97-2.41) mg/kg/4hr(F) LC_{50} = 2.26 (2.08-2.47) mg/kg/4hr. combined	III	Minimum 004824
Primary dermal irritation - rabbit; Cosmopolitan Safety Evaluation, Inc.; #0427E; 9/22/80	FMC 45908 2.5 EC	243861	PIS = 2.0/8.0	III	Guideline 004824
Primary eye irritation - rabbit; Cosmopolitan Safety Evaluation, Inc; #0427D; 9/16/80	FMC 45806 2.5 EC	243861	CORROSIVE	I	Guideline 004824

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Dermal sensitization - guinea pig; (Buehler); Cosmopolitan Safety Evaluation Inc; 9/28/30	FMC 45806 2.5 EC	243861	Not a sensitizer		Guideline 004824
Acute oral LD_{50} - rat	25% EC (JF6670)	241597	180 mg/kg (males and females)	II	Guideline
Acute oral LD_{50} - rat	25% EC (JF6670)	241597	250 mg/kg (males and females)	-	SUPPLE-MENTARY
Acute dermal LD_{50} - rabbit	25% EC (JF6670)	241597	> 3 ml/kg (no deaths).	III	GUIDELINE * (upgraded; only 1 dose level)
Primary dermal irritation-rabbit	25% EC (JF6670)	241597	PIS = 4.4/8.0	III	GUIDELINE
Primary eye irritation-rabbit	25% EC (JF6670)	241597	corneal opacity; reversible in 7 days.	II	GUIDELINE
Dermal sensitization - guinea pig	25% EC (JF6670)	241597	Inconclusive, but some postive results noted.	-	SUPPLE-MENTARY
Acute oral - rat; Hazleton (Europe); #2148-38/65-69; 1/80	36% w/v GFU 034A	099855	LD_{50}=270mg/kg for both sexes	II	Guideline 004825
Acute dermal - rabbit; Hazleton (Europe); #12148-38/65-69; 1/80	36% w/v GFU 034A	099855	LD_{50}>2000mg/kg	III	Minimum 004825
Primary dermal irritation - rabbit; Hazleton (Europe); #2148-38/65-69; 1/80	36% w/v GFU 034A	099855	Draize score 2.1	III	Guideline 004825

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	Tox Category	GDFF Grade / Doc. No.
Primary eye irritation - rabbit; Hazleton (Europe); #2148-38/65-69; 1/80	36% w/v GFU 034A	099855	Corneal opacity not reversed in 7 days in 5/6 rabbits	I	Guideline 004825
Dermal sensitization-guinea pig; maximization test; Hazleton (Europe); #2148-38/65-69; 1/80	36% w/v GFU 034A	099855	Mild sensitizer	--	Minimum 004825
Inhalation LC_{50} - rat; ICI ;CTL/P 536;2/14/80	36% w/v GFU 034A	099855	Equivocal(4 hrs.)	--	Supplementary 004825
Dermal sensitization - guinea pig; #CTL/P/570; 1/27/81	Technical 53:47	070565	Moderate senstizer		Minimum 002391
Acute oral LD_{50} - hen; Huntingdon Res. Center; #CTL/C/1077; 7/3/81	Technical 53:47 Batch #P25	070564	Levels tested - 0, 4, 096, 5,120, 6,400, 8,000, 10,000 mg/kg LD_{50} => 10,000 mg/kg (HDT)		Supplementary 002391
Acute oral LD_{50} - rat; Wil Labs;#Wil-81328; 3/11/82	DEMON 40WP	247845	LD_{50}= 1.817 (0.87-3.80) gm/kg for both sexes 0.808 (0.591-1.105)gm/kg for females 1.904 (1.071-3.386) gm/kg for males	III	Reserved (as of 9/22/82) 002218
Acute dermal LD_{50} - rabbit; Wil Labs; #Wil-81329; 2/9/82	DEMON 40WP	247845 250471	LD_{50} > 2000 mg/kg	III	Minimum 002218 003399
Primary eye irritation-rabbit; Wil Labs; #Wil-81330; 2/9/82	DEMON 40WP	247845	Corneal opacity reversed after 4 days, positive iris scores reversed in 3 days, positive conjunctival scores reversed in 10 days	II	Guideline 002218

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Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary dermal irrit.- rabbit; Wil Labs; 2/9/82	DEMON 40WP	247845	PIS = 1.06 Dosed with 5 gm to test material for 24 hours.	IV	Guideline 002218
Dermal sensitization - guinea pig; Wil Labs; #WIL 81332; 2/9/82	DEMON 40WP	247845	Potential sensitizer (Method of Buehler)		Minimum 002218
Acute oral LD_{50} - rat; ICI;#CTL/P/630; 7/16/81	CYMBUSH 2E (GFU-070)	070557	LD_{50} (M) = 0.35 (0.21-0.46) ml/kg LD_{50} (F) = 0.61 (0.43-0.77) ml/kg	II	Supplementary 002391
Acute dermal LD_{50} - rabbit; ICI;#CTL/P/630; 7/16/81	CYMBUSH 2E (GFU-070)	070557	LD_{50} > 2 ml/kg (only dose tested: no deaths)	III	Minimum 002391
Primary dermal irrit. rabbit ; ICI;#CTL/P/630; 7/16/81	CYMBUSH 2E (GFU-070)	070557	PIS = 4.00	II	Minimum 002391
Primary eye irritation- rabbit ; ICI;#CTL/P/630; 7/16/81	CYMBUSH 2E (GFU-070)	070557	Corneal opacity reversed by day 7	III	Guidelines 002391
Acute inhalation LC_{50}- rat; ICI;#CTL/P/639; 12/14/81	GFU-070	070557	Solvent only was vaporized Inhalation toxicity of this product was not assessed. (4 hrs.)	N/A	Supplementary 002391
Dermal sensitization - guinea pig ; #CTL/P/630; 7/16/81	CYMBUSH 2E (GFU-070)	070557	Mild to molerate sensitizer		Minimum 002391
Acute oral LD_{50} - rat; ICI;#CTL/P/584 ; 3/19/81	CYMBUSH 3E (GFU-061)	070556	LD_{50} (M) = 0.36 (0.20-.73) ml/kg LD_{50} (F) = 0.25 (0.14-.55) ml/kg	II	Supplementary (no necropsy) 002391

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Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	Tox Category	CORE Grade/ Doc. No.
Acute dermal LD_{50} - rabbit; ICI;#CTL/P/584; 3/19/81	CYMBUSH 3E (GFU-061)	070556	LD_{50} > 2.02 ml/kg	III	Minimum 002391
Primary dermal irrita. - rabbit; ICI;#CTL/P/584; 3/19/81	CYMBUSH 3E (GFU-061)	070556	PIS = 5.08	II	Guidelines 002391
Primary eye irritation - rabbit; ICI;CTL/P/584; 3/19/81	CYMBUSH 3E (GFU-061)	070556	Corneal opacity not reversed in 7 days	I	Guideline 002391
Acute inhalation LC_{50} - rat; ICI;CTL/P/536; 2/14/80	GFU-061	070556 099855	Equivocal		Supplementary 002391 (10/26/81)
Sensitization - guinea pig; ICI;CTL/P/584; #CTL/P/584; 3/19/81	CYMBUSH (GFU-061)	070556	Weak sensitizer - NOTE - unhealthy animals used, other cypermethrin products are sensitizers.		INVALID 002391
SIGNAL WORD - DANGER (Eye effects)					CYMBUSH 3E (GFU-061)
Acute oral LD_{50} - rat	Technical (90% a.i.)	241597	LD_{50} = 4123(3496-4864) mg/kg(female) (in water)	III	MINIMUM
Acute oral LD_{50} - rat	Technical	241597	LD_{50} = 1741 (1502-2019) mg/kg (F) (in corn oil)	III	MINIMUM
Acute oral LD_{50} - mice	Technical	241597	LD_{50} = 779 (654-941) mg/kg (female) (in water)	III	MINIMUM
Acute oral LD_{50} - guinea pig	Technical	241597	> 4000 mg/kg (in water) (male)	-	SUPPLEMENTARY

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORF Grade/ Doc. No.
Acute oral LD_{50} - rabbit	Technical	241597	> 2400 mg/kg (female)	-	SUPPLE-MENTARY
Acute dermal LD_{50} - rat	Technical	241597	> 4.8 gm/kg (female)	III	MINIMUM No males
Acute dermal LD_{50} - rabbit	Technical	241597	> 2.4 gm/kg (female)	III	MINIMUM
Acute intraperitoneal LD_{50} - rat	Technical	241597	1000 < LD_{50} < 2000 mg/kg	-	SUPPLE-MENTARY
Primary dermal irritation-rat	Technical	241597	Mild transient irritation 3 - 24 hour exposures of 1.2 gm/kg		SUPPLE-MENTARY
Primary dermal irritation-rabbit	Technical	241597	P.I.S. = 0.87/8	IV	Minimum
Primary eye irritation-rabbit	Technical	241597	No corneal involvement. Some irritation to 7 days.	III	Minimum
Dermal sensitization - guinea pig	Technical	241597	Moderate sensitizer.	-	SUPPLE-MENTARY
Primary eye irritation - rabbit; Central Toxicol Lab; #CPL/P/537; 2/14/80	Technical 53:47 cis=trans	099855	Not irritating	IV	Guideline 004825
Dermal sensitization-guinea pig; Central Toxicol Lab; #CPL/P/537; 2/14/80	Technical 53:47 cis=trans	099855	Not a sensitizer	--	Guideline 004825
Acute oral LD_{50}- rat; Central Toxicol Lab; #CPL/P/537; 2/14/80	Technical 53:47 cis=trans	099855	LD_{50}=247 (187-329)mg/kg - Males LD_{50}= 309 (150-500)mg/kg - Female in corn oil solvent	II	Minimum 004825

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute dermal LD_{50}-rat; Central Toxicol Lab; #CPL/P/537; 2/14/80	Technical 53:47 cis=trans	099855	LD_{50}>4920mg/kg	III	Minimum 004825
Acute dermal LD_{50}-rabbit Central Toxicol Lab; #CPL/P/537; 2/14/80	Technical 53:47 cis=trans	099855	LD_{50}>2.0mg/kg or 2460mg/kg	III	Minimum 004825
Primary dermal irritation - rat; Central Toxicol Lab; #CPL/P/537; 2/14/80	Technical 53:47 cis=trans	099855	No irritation	(IV)	Supple-mentary 004825
Primary dermal irritation - rabbit; Central Toxicol Lab; #CPL/P/537; 2/14/80	Technical 53:47 cis=trans	099855	PIS=0.71	IV	Minimum 004825
Acute oral LD_{50} - mice; ICI; CTL/P/570; 1/27/81	Technical 91.5% 53:47	070565	LD_{50} (M) = 112 (90-137) mg/kg LD_{50} (F) = 144 (112-233) mg/kg		002391 Supplemen-tary
Acute oral LD_{50} - guinea pig; ICI; CTL/P/570; 1/27/81	Technical 91.5% 53:47	070565	LD_{50} (M) > 4000 mg/kg		Supplemen-tary 002391
Acute oral LD_{50} - rabbit ; ICI; CTL/P/570; 1/27/81	Technical 91.5% 53:47	070565	LD_{50} (F) = 959 (507-2218) mg/kg		Supplemen-tary 002391
Acute IP LD_{50} - rat; ICI; CTL/P/570; 1/27/81			LD_{50} (M) = approx. 4000 mg/kg		Supplemen-tary 002391
Acute oral LD_{50} - rat; FMC Corporation; #A83-1048; 11/17/83	Ammo 2.5 oil FMC 45806	252997	LD_{50} = 2665 (2371-2958) mg/kg (M) LD_{50} = 2227 (1804-2650) mg/kg (F) LD_{50} = 2446 (2228-2664) mg/kg (M&F)	III	Guideline 003867

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary eye irritation - rabbit; FMC Corporation; #A83-1050; 11/14/83	Ammo 2.5 oil FMC 45806	252997	Washed eyes - practically non irritating Unwashed eyes mildly irritating	III	Guideline 003867
Primary dermal irritation - rabbit; FMC Corporation; #A83-1049 10/31/83	Ammo 2.5 oil FMC 45806	252997	PIS = 0 Non irritating to abraded and intact skin	IV	Guideline 003867
Acute dermal LD_{50} - rat	Ammo 2.5 oil FMC 45806	NA	This study was not performed. However, based upon the reasoning given in the review, the category of hazard for dermal absorption was determined to be Category III, so the study need not be conducted.		003867
Acute oral LD_{50} - rat; FMC Toxicol. Lab.; study #A83-860; 6/10/83	AMMO 2.5 E EPA. Reg # 279-3027 30.6% a.i.	252014	LD_{50} = 1488 (1230 - 1745) mg/kg - M 1182 (916 - 1448) mg/kg - F 1403 (1220 - 1586) mg/kg -M&F Levels tested 100*, 300*, 500*, 700, 800**, 1200*, 1500, 1800** and 2000 (* males only,** females only)	III	GUIDELINE 003798
Acute dermal LD_{50} - rabbit; FMC Toxicol. Lab.; study #A83-861; 5/31/83	AMMO 2.5 E EPA. Reg # 279-3027 30.6% a.i.	252014	> 2000 mg/kg only dose tested	III	MINIMUM 003798
Primary dermal irritation - rabbit; FMC Toxicol. Lab.; study # A83-862; 5/20/83	AMMO 2.5 E EPA. Reg # 279-3027 30.6% a.i.	242014	PIS = 1.7	III	MINIMUM 003798
Primary eye irritation - rabbit; FMC Toxicol. Lab.; study #A82-719; 5/13/82	AMMO 2.5 E EPA. Reg # 279-3026 30.6% a.i.	252014	Transient corneal opacity(<24 hours)	III	GUIDELINE 003798

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	Tox Category	CORE Grade/ Doc. No.
Dermal sensitization - guinea pig; Stillmeadow Lab; #2909-83; (FMC #A83-863); 7/6/83	AMMO 2.5 E EPA. Reg # 279-3027 30.6% a.i.	252014	Potential sensitizer 1/10 guinea pigs showed a positive senstization reaction	N/A	MINIMUM 003798
Risk assessment-mice; EPA; 3/27/84	Tech		Q^*_1 = 0.019 multi-stage Q^*_1 = 0.018 one-hit model		004466
Neurotoxicity- rat; ICI; #CTL/P/345; 2/25/80	Tech 90% 45%cis&55%trans	099855	Possible chemical related nerve fiber degeneration noted and clinical signs of nervous system effects. Levels tested 1250, 2500 and 5000 ppm		004825

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CYPERMETHRIN:

ASSESSMENT OF CHRONIC AND ONCOGENIC EFFECTS

A SUMMARY

March 1, 1984

by

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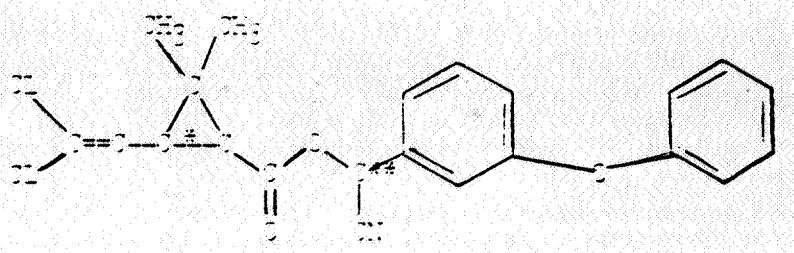
I. Introduction

Cypermethrin is the common name for (+/-) alpha-cyano-(3-phenoxyphenyl)-methyl (+/-) cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate. Cypermethrin is one of several synthetic pyrethroids which have been introduced over the past decade for a variety of insecticidal uses including both agricultural and domestic applications. Both ICI Americas Inc. and the FMC Corporation have requested establishment of tolerances for cypermethrin in/on raw agricultural commodities and as a food additive as well as registrations for their respective formulations. Cypermethrin is proposed to be marketed under the trade names CYMBUSH® and DEMON® (both ICI) and AMMO® (FMC). Technical cypermethrin is also known by the code names PP383, NRDC 149 and WL 43467. The basic toxicity data have been submitted chiefly by ICI Americas Inc. but is reportedly jointly owned with the FMC Corporation. The Shell Oil Company also has conducted many of the toxicity studies but it has not applied for tolerances or registrations. Many of the toxicity studies on the technical material were generated in European laboratories.

Review of the studies submitted to support the various uses of cypermethrin have indicated that this chemical is of moderate acute oral toxicity to rats (LD_{50} = 112-309 mg/kg) and that it is not teratogenic in rats or rabbits. The mouse oncogenicity study revealed increased incidences of benign neoplasms in the lungs of females in the high dose test group only. A similar neoplastic response was noted for permethrin, a synthetic pyrethroid which differs from cypermethrin only in the absence of the cyano group in the alpha carbon position.

This document is an overview of the long term feeding and oncogenicity studies on cypermethrin and is intended to assist in the making of regulatory decisions regarding the use of cypermethrin.



(+/-) alpha-cyano-(3-phenoxyphenyl)methyl (+/-) cis/trans-3-(2,2-dichloroethenyl) 2,2-dimethylcyclopropanecarboxylate.
*cis/trans position
**alpha carbon position

II. Availability and Usefulness of Long Term Feeding and Oncogenicity Studies

Three rodent long term chronic feeding and/or oncogenicity studies and a dog chronic feeding study have been submitted to EPA in support of requests to register products containing cypermethrin and establish tolerances for cypermethrin on various crops. These studies are listed in Table 1 below.

Table 1. List of chronic feeding and/or oncogenicity studies with cypermethrin.

Study Lab-year	Animals (No./sex/group)	Duration (weeks)	Dosage Levels
A. Rat studies			
Shell-1979	96 controls 48 each test group (including 48 controls and 24 test group rats scheduled for interim sacrifice)	104	0, 1, 10, 100, and 1,000 ppm
ICI-1982	64 (including 12 from each group scheduled for interim sacrifice)	104	0, 0*, 20, 150, and 1,500 ppm
B. Mouse Study			
ICI-1982	70 (including 9-10 from each group scheduled for interim sacrifice)	97 males) 101 females)	0, 0*, 100, 400, and 1,600 ppm
C. Dog Study			
ICI-1982	6	52	0, 1, 5, and 15 mg/kg/day (by gavage)

*For the ICI-1982 rat and mouse studies there were two separate sets of control groups run concurrently.

For these studies, the cypermethrin used ranged in purity from 88% to 96% and the ratio of the cis to trans isomers ranged from 55% cis and 45% trans to 50% cis and 50% trans. The differences in the percentage of purity for the different lots used and the small differences in the cis/trans ratio were not considered to be of sufficient magnitude to compromise interstudy comparisions. Each study was considered to have been conducted with essentially the same test substance.

Of these four studies, the ICI rat, mouse and dog chronic feeding studies were determined to be most useful for assessing the chronic feeding and oncogenic effects of cypermethrin in rodents and dogs.

The other rat study, Shell-1979, was determined to be of limited usefulness as both a chronic feeding and oncogenicity study because an insufficient number of test animals were actually dosed for the two year period.

III. Synopses of the Long-Term Feeding and Oncogenicity Studies

Shell-1979-Rat Study — Shell Toxicology Laboratory, # TLGR.1089.78, Feb. 1979. Refer to EPA Acc. No. 070564.

Five groups of male and female Wistar rats (SPF, obtained from the Shell Breeding Labs) were fed diets containing either 0, 1, 10, 100 or 1000 ppm of cypermethrin (cis/trans ratio of 1:1 from batch #30 with a purity of 98%). There were 96 males and females for the controls and 48 males and females for each test dose group. Interim sacrifices of 12 male and female controls and 6 males and females from each of the dose groups were made at 6 and 12 months. 24 control rats and 12 rats from each sex from each of the dosed groups were sacrificed at 18 months. Thus, there were 48 controls of each sex and 24 test group rats of each sex for each dose level scheduled to receive the control or test diets for the full 104 week feeding period.

At termination there were 12-17 males and 8-12 females surviving in the test groups receiving cypermethrin. The only test chemical related effects noted in this study were depressions in body weight (<10% at 1000 ppm). There was also some evidence of lower food consumption during the early weeks of the study. There were no consistent dose related effects noted on the several hematology and clinical chemistry parameters investigated. No urinalyses were performed. There were also no changes in organ weights and, in particular, the liver weights were not reported to be elevated.

Microscopic examination of a comprehensive set of tissues/organs was made for all surviving rats. Only the control, 100 and 1000 ppm dose groups were examined microscopically for the interim sacrificed animals.

No single tumor type or organ showed evidence of a positive neoplastic response to treatment. In particular, there were 5 incidences of lung adenocarcinoma, two among the controls (one male and one female), two in the groups receiving 100 ppm (one male and one female), and one in the male high dose test group. There were no adenomas reported in the lung tissue. There were no indications of dose related increases in nonneoplastic or possibly preneoplastic (hyperplastic) lesions.

ICI-1982-Rat Study — ICI Central Toxicology Laboratory, #CTL/P/669, June, 1982. Refer to EPA Acc. No. 071070 and 071071.

The test animals used were Wistar derived rats (SPF, obtained from the colony maintained at the Alderley Park facility in Cheshire, England). Five groups of 52 male and 52 female rats were given diets containing either 0 (two groups of 52 of each sex), 20, 150, or 1500 ppm of cypermethrin. Satellite groups of 12 male and 12 female rats per group were also maintained and designated for an interim sacrifice at 52 weeks. For the first six weeks of the study the rats in the high dose test group received 1000 ppm. The cypermethrin used for this study had a cis:trans ratio of 55:45 (nominal) and the purity was between 88% and 93%.

At termination of the study (after 104 weeks of dosing), there were 21-28 male rats and 22-27 female rats surviving per dosage group. Evaluation of the chronic feeding aspects of this study resulted in assigning a NOEL of 150 ppm. At 150 ppm, there were slight changes in body weight and slightly increased smooth endoplasmic reticulum in liver hepatocytes. These changes were considered to be an adaptive response rather than a toxic response. The LEL was determined to be 1500 ppm. At this level, there was body weight loss, increased liver weights and increased smooth endoplasmic reticulum in hepatocytes and some hematological and other clinical changes of a small magnitude. Although liver weight was increased 21% for females in the 1500 ppm group at 52 weeks (interim sacrifice), there was no significant increase in liver weight in this test group at termination.

All of the rats on the study were scheduled to receive a complete histopathologic evaluation which routinely included some 42 tissue organ types.

There were no dose-related or treatment related nonneoplastic lesions noted.

No single tumor type or tissue/organ showed evidence of a positive neoplastic response to treatment. In particular, there was only a single incidence of an adenoma in the lungs (in a female control group).

ICI-1982-Mouse Study — ICI Central Toxicology Laboratories, CTL/P/687, June 1982. Refer to EPA Acc. No. 071072, 071073, 071570 and 072004.

The test animals were Swiss strain mice (SPF, from the Alderley Park stock). Five groups of 70 male and 70 female mice were given either 0 control (2 groups) or 100, 400 or 1600 ppm of cypermethrin in their diets. Of these, 9-10 males and females per group were selected for an interim sacrifice at 52 weeks. The test material used for this study came from two lots which had purities of 91.5% and 94.2% and the cis:trans ratio was either 53:47 or 54:46.

No test chemical effect was noted on survival, but at termination (97 weeks for males and 101 weeks for females) there were only 9-15 males and 7-1- females per group indicating that overall survival to termination was poor. However, 50% of the mice (30 or more of males or females in each group) survived through about weeks 80-84.

Evaluation of the chronic feeding aspects of this study led to the conclusion that the NOEL was 400 ppm. There was noted a slight gain in liver weight at this level but this was considered to be an adaptive response and not a toxic response. At 1600 ppm (LEL) there were noted decreases in body weight (both males and females) that were most noticeable during the early phases of the study, increases in liver weight and generalized changes in blood elements. No clinical chemistries or urinalyses were performed.

A series of approximately 45 tissues/organs from each mouse were examined histologically from all mice dying during the study and the survivors, but not the mice sacrificed at the interim kill. Lung and liver tissues from the interim kill groups were later examined in response to Toxicology Branch's request.

There were no increases in nonneoplastic lesions which were considered to be related to the test material. In particular, there was no evidence that possible preneoplastic lesions in the lungs were related to the presence of cypermethrin in the diet.

There was noted an increase in the number of benign neoplasms in the lungs of females, but not in males, as indicated in the table below:

Table 2. Lung tumors in Swiss mice fed cypermethrin for their lifetime

		Lung Neoplasms						
		Males			Females			
Group	n	Benign[1]	Malignant[1]	Total	n	Benign[1]	Malignant[1]	Total
Control-1	70	7	1	8	69	5	0	5
Control-2	70	10	1	11	70	5	2	7
Low (100 ppm)	70	11	1	12	70	6	0	6
Mid (400 ppm)	70	7	0	7	70	7	1	8
High (1600 ppm)	70	9	3	12	70	14*	0	14*

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

[1] Benign=adenoma, Malignant=carcinoma.

There was no treatment related increase in benign neoplasms among the male groups. The high dose male group had 3 incidences of mice with malignant neoplasms whereas there were only single incidences in each of the two control groups and one in the low dose group. The data for the slight increase in incidences of malignant neoplasms in the high dose male group are not statistically significant (using Fisher's One Tailed p Statistic, p=0.310) when compared with the controls. Moreover, chemically induced increased incidences of malignant lung neoplasms would be expected to be accompanied by increases in benign neoplasms (lung adenomas). In this study, the lung adenomas were uniformly distributed among the male test and control groups. It is the conclusion of Toxicology Branch that there is no evidence that cypermethrin was associated with induction of a neoplastic effect in the male mice.

As indicated in the above table, there is a statistically significant increase in the incidences of benign adenomas in the lungs of the females in the high dose test group. There were only a total of three mice affected with malignant neoplasms among the five female groups. Two of the mice affected with malignant neoplasms were in the control group. The third mouse affected with a malignant neoplasm was in the mid dose (400 ppm) group. Thus, there is no evidence that the presence of cypermethrin in the diet induced an increased degree of malignancy for lung tumors.

Most of the female mice affected with lung adenomas were in the terminal sacrifice groups. One female mouse in each of the two control groups and one female mouse in the high (1600 ppm) dose group among the mice sacrificed for the interim kill had a benign neoplasm (adenoma) in the lung. There is no evidence that cypermethrin in the diet decreased the latency for the onset of lung neoplasms in the females.

Many mice in both the male and female control and test groups developed malignant lymphoreticular tumors but there was no evidence that the frequency or time of onset was related to the presence of cypermethrin in the diet. No correlation was found between the mice having lymphoreticular tumors and lung tumors.

In this study, the high dose female test group was shown to be associated with a statistically significant increase in lung adenomas. No evidence was presented which suggested that cypermethrin decreased the latency period for the occurrence of this tumor type or increased the degree of malignancy.

ICI-1982-Dog Study ICI Central Toxicology Laboratory, #CTL/P/103, July 6, 1982. Refer to EPA Acc. No. 071069.

Cypermethrin was administered to four groups of 6 beagle dogs of each sex at dose levels of 0, 1, 5, and 15 mg/kg/day for a period of 52 weeks. The cypermethrin was dissolved in corn oil and the solution was administered to the dogs by capsule. The cypermethrin used was of 90.6% purity and the cis:trans ratio was 53.9:46.1.

No deaths or changes in body weight resulted. The dogs in the high dose group exhibited a loss in appetite, tremors, gait changes, incoordination, disorientation and hypersensitivity. There were no indications that nonneoplastic microscopic lesions were induced by cypermethrin. No consistent dose-related or toxicologically meaningful changes in clinical blood chemistries, hematology, urinalyses or organ weights were noted.

The dogs dosed with 5 mg/kg/day of cypermethrin showed a five fold (males) and ten fold (females) increase in the reported incidences of passing of liquid stools. At 15 mg/kg/day there was about a thirty fold increase in the incidences of this symptom for both sexes. Thus, the NOEL for this study was determined to be 1.0 mg/kg/day.

IV. Mutagenicity and Metabolism Studies.

A battery of mutagenicity studies were submitted all of which were negative. The mutagenesis studies submitted and reviewed (see Table 3) included bacterial (Ames test) and yeast point mutation studies, a dominant lethal study in mice and an in vivo chromosomal abberration test (Chinese hamster bone marrow cells).

Metabolism studies in rats, mice and dogs were also submitted. The results of each of these studies indicated that cypermethrin is rapidly metabolized and excreted in the urine and that little if any residue remains behind in the body. Additional metabolism studies with cows and goats were submitted and reviewed by Residue Chemistry Branch.

The metabolic pathway for the degradation of cypermethrin in mammals is primarily through hydrolysis at the esteratic site to yield dichlorovinyl cyclopropane carboxylate and 3-phenoxyphenyl benzyl alcohol, aldehyde or acid. Conjugated forms of the parent compound and the 3-phenoxy moiety are also found. The major metabolites of cypermethrin are essentially similar to those of permethrin. During metabolism of cypermethrin the cyano group is eliminated from the molecule but there is no evidence that cyanide toxicity results from cypermethrin ingestion.

V. NOEL for Nononcogenic Effects.

The nononcogenic effects noted for each of the four long term studies are summarized in Table 4.

Table 3. Mutagenicity Studies with Cypermethrin

Study	Reference	Results	Conclusion
Bacterial Reverse Mutation Assay (Ames Test)	ICI Study #CTL/P/595 Nov. 13, 1980 (EPA Acc. No. 070564)	No evidence of mutagenicity with or without metabolic activation (S9) in S. typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100.	Cypermethrin is not a mutagen under the conditions of this assay.
Bacterial Reverse Mutation Assay (Ames Test)	Shell Toxicology Lab. Study #TLGR.80.059 June 1980 (EPA Acc. No. 070564)	No evidence of mutagenicity with or without metabolic activiation (S9) in S. typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100 or in E. coli strains WP_2 and WP_2 uvrA.	Cypermethrin is not a mutagen under the conditions of this assay.
Yeast Mutation Assay in vitro	"	No evidence of mutagenicity with or without metabolic activation (S9) in Saccharomyces cerevisiae JD1.	Cypermethrin is not a mutagen under the conditions of this assay.
Host Mediated Assay in vivo	"	No evidence of mutagenicity in Saccharomyces cerevisiae inoculated into mice pretreated with cypermethrin.	Cypermethrin is not a mutagen under the conditions of this assay.
Chromosome Abberration Study (Chinese Hamster Bone Marrow Cells)	Shell Research Ltd. TLGR.0136.77, Dec. 1977. (EPA Acc. No. 070564)	No evidence of chromosome abberrations after dosing with 40 mg/kg for two days (HDT)	Cypermethrin is not a mutagen under the conditions of this asay
Dominant Lethal Assay in vivo (mice)	Shell Toxicology Lab. Study #TLGR.0042.77 December 1977 (EPA Acc. No. 070564)	No evidence of a dominant lethal mutagenic effect at 10 mg/kg for 5 days (highest dose tested).	Cypermethrin is not a mutagen under the conditions of this assay.

The first rat study (Shell-1979) is included although not as many parameters for hematology, blood chemistry or urinalysis were determined. This study shows no effects due to the test material except for slight weight loss at 1000 ppm (50 mg/kg/day). The second rat study (ICI-1982) also used the Wistar strain rat but more parameters were investigated and more rats were available at termination. Thus, the ICI-1982 rat study is considered as the best available chronic feeding study in rodents. The mouse study was designed as an oncogenicity study and not enough parameters were investigated to qualify this study as a chronic feeding study. The NOEL for the ICI-1982 rat study is 150 ppm (7.5 mg/kg/day).

The NOEL for the dog study was set at 1.0 mg/kg/day. At higher doses (5 and 15 mg/kg/day) there was clear evidence of gastrointestinal disturbance and in addition at 15 mg/kg/day the dogs exhibited tremors, gait changes, incoordination, disorientation, hypersensitivity and appetite loss.

The NOEL which Toxicology Branch recommends for determining the Acceptable Daily Intake (ADI) is 1.0 mg/kg/day based on the dog 1-year study. Customarily Toxicology Branch uses the most sensitive species in setting the ADI.

VI. Assessment of Oncogenic Effects

Review of the rat and mouse oncogenicity studies indicated an increased (statistically significant) incidence of benign lung adenomas in the high dose test group female mice. No other indications of a possible oncogenic effect in the rat and mouse oncogenicity studies were recognized by Toxicology Branch.

The definition of chemical carcinogenesis currently used by the International Agency for Research on Cancer (IARC)[1] is "the widely accepted meaning of the term 'chemical carcinogenesis' --- is the induction by chemicals of neoplasms that are not usually observed, the earlier induction by chemicals of neoplasms that are usually observed, and/or the induction by chemicals of more neoplasms than are usually found".

Cypermethrin has been demonstrated to increase the frequency of neoplasms that are usually found

In addition to or supplemental to the criteria in the above definition, the following seven criteria are discussed separately with respect to the potential of cypermethrin to induce oncogenic effects in experimental animals.

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(1) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans , Volume 12, WHO, Lyon, France, March 1980, p. 14.

Table 4 . Summary of selected nononcogenic effects of cypermethrin.

Test Dose Level (%)	Rat Shell-1979	Rat ICI-1982	Mouse ICI-1982	Dog ICI-1982
0	No Effects	No Effects	No Effects	No Effects
0.05 mg/kg/day	No Effects	NT*	NT*	NT*
0.50 mg/kg/day	No Effects	NT*	NT*	NT*
1.0 mg/kg/day	NT*	No Effects	NT*	No Effects
5.0 mg/kg/day	No Effects	NT*	NT*	-gastrointestinal disturbances (liquid stools)
7.5 mg/kg/day	NT*	-slight decreases in body weight -slightly increased smooth endoplasmic reticulum in hepatocytes** (See next highest dose level for LEL for this study).	NT*	NT*
15 mg/kg/day	NT*	NT*	No Effects	-gastrointestinal disturbances (liquid stools) -tremors, gait changes, incoordination, disorientation, hypersensitivity, appetitte loss.
50 mg/kg/day	-slight depressions in body weight gain (< 10%).	NT*	NT*	NT*

TABLE 4 (continued).

Test Dose Level (1)	Rat Shell-1979	Rat ICI-1982	Mouse ICI-1982	Dog ICI-1982
50 mg/kg/day	NT*	NT*	No Effects (except minor liver weight gain)	NT*
75 mg/kg/day	NT*	-increased smooth endoplasmic reticulum in hepatocytes -decreased body weight gain and food consumption -slight effects on several hematological parameters, minor changes in cholesterol, triglycerides, urea, and glucose -slight changes in urine volume, pH, S.G. -minor liver (increase) and kidney (decrease) weight changes.	NT*	NT*
100 mg/kg/day	NT*	NT*	-decreased body weight gain -slight effects in several hematological parameters -liver weight increases	NT*

NT*-Not tested at this level for this study.

* This increase in smooth endoplasmic reticulum is considered to be an adaptive response rather than a toxicological response to cypermethrin treatment.

(1) Dosage levels for rats and mice in ppm were converted to dosage levels in mg/kg/day based on the following conversion factors:
rats-1 ppm = 0.05 mg/kg/day
mice-1 ppm = 0.15 mg/kg/day

1. Oncogenicity in different a) species, b) strains, c) sexes and d) organs.

As indicated above, a statistically significant increased incidence of neoplasms was observed in a single species (mouse), strain (Swiss), sex (female) and in only one organ (lung).

Additional support for determining that cypermethrin has the potential to induce neoplasms in lungs of female mice is provided by a comparision of the cypermethrin data with that of permethrin, a closely related structural congener. Refer to the EPA (Toxicology Branch) document entitled "Permethrin, Assessment of Chronic and Oncogenic Effects, A Summary" by O.E. Paynter, E.R. Budd, and B.D. Litt, dated September 3, 1982. This document describes a statistically significant increased incidence of lung and liver tumors in female Charles River CD-1 (Swiss derived) mice in one study and a "suggestive" increase in lung tumors in female CFLP (Swiss derived) mice in another study. In a third study performed with ICI Alderley Park (Swiss derived) mice, the same mice used in the cypermethrin study, slightly increased incidences of lung adenomas and/or adenocarcinomas were observed in female mice, but it could not be concluded that this increase was related to treatment with permethrin. Females of the Charles River CD-1 strain, however, showed clear evidence of lung and liver oncogenicity due to exposure.

2. Presence of rare neoplasms and number of different types of neoplasms in one or more species.

Neither the two rat nor the mouse oncogenicity studies showed evidence that neoplasms, considered to be rare neoplasms, were induced by the presence of cypermethrin in the diet.

The overall net production of tumors for each of the rat studies indicated a uniform distribution of tumors among the dosed groups and the control groups. When all of the lung tumors are eliminated from the count, the overall net production of tumors in the mouse study also indicated a uniform distribution of tumors among the dosed groups and the controls.

Thus, cypermethrin was not shown to be related to the induction of rare neoplasms or to a general increase in various types of tumors.

3. Increased incidence of malignant neoplasms.

There was no evidence that the degree of malignancy for the various neoplasms observed in either of the rat oncogenicity studies was affected by the presence of cypermethrin in the diet.

In the mouse study, the type of lung tumor which showed an increased frequency at the high dosage level (only) and in females (only) were adenomas, which are benign and not malignant. There were three females with malignant lung tumors. Of these, 2 were in one control group and the third was in the group receiving 400 ppm of cypermethrin in the diet. Thus, there was no indication that cypermethrin increased the degree of malignancy of neoplasms in the female mouse lungs.

Many of the mice in the cypermethrin mouse study developed malignant lymphoreticular tumors. However, there was no correlation between the presence of cypermethrin in the diet and the incidence of the mice affected.

4. Decreased latency (time to tumor discovery).

In the mouse oncogenicity study with cypermethrin, most mice affected with lung tumors were in the terminal sacrifice group and there was no evidence that cypermethrin induced an earlier onset of lung or other neoplasms.

There was no evidence of decreased latency for development of tumors in either of the rat studies.

5. Dose response relationship.

The evidence of a positive oncogenic response in the mouse study was present only in the high dose female test group.

6. Mutagenicity tests.

Neither the bacterial and yeast point mutation studies, the dominant lethal study, nor the chromosomal abberration study (with Chinese hamsters) resulted in a positive mutagenic response. Thus, there is no evidence that cypermethrin is mutagenic. Similar negative results were obtained when permethrin was tested in a battery of mutagenesis studies.

On this basis, it is apparent that the induction of lung tumors by cypermethrin is not related to mechanisms directly involving the genetic apparatus of the cell.

7. Spontaneous tumor incidence in untreated mice (for lung tissue).

Toxicology Branch has available data from other oncogenicity studies using the same strain and source of Swiss mouse as was used for the oncogenicity study with cypermethrin. The spontaneous tumor incidence in the lungs for the controls in these studies and for the cypermethrin study are as follows:

Table 5. Spontaneous lung tumor incidence in mice at the ICI Central Toxicology Laboratory (Alderley Park stock).

Study	Number of Tumor Bearing Animals*	
	Males	Females
ICI-Permethrin Study (See Paynter, Budd, and Litt Assessment dated Sept. 3, 1982)	11/70 (15.7%)	11/70 (15.7%)
ICI-Study (data submitted to EPA Feb. 13, 1981 by the ICI and FMC Corporations in support of permethrin)	Group 1 9/59 (15.2%)	9/59 (15.2%)
	Group 2 8/60 (13.3%)	4/59 (6.8%)
ICI- Cypermethrin Study (See synopsis in this document)	Group 1 8/70 (11.4%)	5/69 (7.2%)
	Group 2 11/70 (15.7%)	7/70 (10.0%)

*Both lung adenomas and carcinomas are included for the cypermethrin and permethrin studies. The numbers provided for the third study did not indicate whether or not both benign and malignant tumors were included.

The above table indicates that the range for males is 11.4 to 15.7% and the range for females is 6.8 to 15.7%. The incidence of tumors in the high dose female test group in the oncogenicity study with cypermethrin was 20.0%. 20.0% is in excess of the available historical control data for the spontaneous incidence of tumors in the lungs of the female Swiss mouse used for the cypermethrin assay.

Current Toxicology Branch policy regarding the use of historical control data is that it should not substitute entirely for the concurrent control data. In the case with cypermethrin, there were two concurrent control groups of 70 mice and each of these gave nearly the same low spontaneous rate of lung tumor development. Use of the concurrent control data supports a conclusion that cypermethrin in the diet was related to the increased incidence of lung tumors in the high dose female test group mice.

The Task Force of Past Presidents of the Society of Toxicology has discussed the use of historical control data as follows:

"The following propositions may be taken as scientifically useful in the evaluation of a chemical carcinogenic response, with distinctions drawn between the use of concurrent control and historical control data. (1) If the incidence rate in the concurrent control group is lower than in the historical control groups, but the incidences rates in the treated groups are within the historical control range, the differences between the treated and control groups are not biologically significant. (2) If the incidence rates in the treated groups are higher than the historical control range but not statistically significantly greater than the concurrent control incidence, the conclusion would be that there is no relation to treatment, but with the reservation that this result could be a false negative resulting from some flaw. (3) If the incidence rates in the treated groups are significantly greater than in the concurrent controls, and greater than the historical control range, a treatment effect may be present which is unlikely to be a false positive test".

(Task Force of Past Presidents, Animal data in hazard evaluation: Paths and pitfalls. Fundam. and Appl. Toxicol., 2:101-107,1982)

In the case of cypermethrin, the incidence rate in the high dose female test group is greater than both the concurrent control groups and the available historical control groups. Thus, consistent with the criteria of the Task Force of Past Presidents, it is unlikely that the effect noted with cypermethrin is a false positive.

VII. Conclusions

On the basis of all available toxicological data, Toxicology Branch has determined that there is sufficient evidence to conclude that, at a dosage level of 1600 ppm in the diet for a lifetime, cypermethrin exhibits a low oncogenic potential in female mice.

The available data support nononcogenic NOEL's of 1.0 mg/kg/day in the dog (one year study) and 150 ppm in the rat.