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

JUN 2 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Peer Review of Bifenthrin

From: Judith W. Hauswirth, Ph.D. Judith W Hauswirth 4/28/87
Acting Section Head, Section VI
Toxicology Branch/HED (TS-769C)

To: George La Rocca
Product Manger No. 15
Registration Division (TS-767C)

The Toxicology Branch Peer Review Committee met on April 10, 1987 to discuss and evaluate the weight of the evidence on Bifenthrin, with particular reference to its oncogenic potential.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated).

Reto Engler — Reto Engler

John A. Quest — John A. Quest

Esther Rinde — Esther Rinde

Louis Kasza — Louis Kasza

Judith W. Hauswirth — Judith W. Hauswirth

Robert Beliles — Robert B Beliles

Donald Barnes — Donald G Barnes

Richard Levy — Richard A. Levy

2. Reviewers: (non-panel members responsible for data presentation signatures indicate technical accuracy of panel report).

Byron T. Backus (Reviewer) — Byron T. Backus

Marcia van Gemert (Section Head) — Marcia van Gemert

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C. J. Nelson (Reviewer) cjnelson

Edwin Budd (Section Head) Edwin Budd

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

Theodore M. Farber Theodore M. Farber

Anne Barton

William Burnam

Diane Beal

B. Material Reviewed:

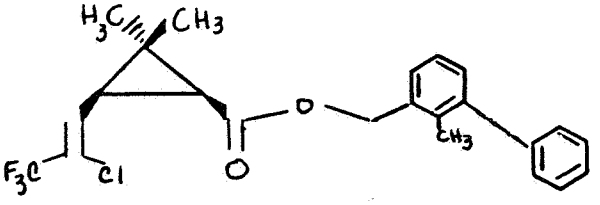
The material available for review consisted of DER's on rat and mouse Bifenthrin oncogenicity studies. company response to Toxicology Branch reviews of the rat and mouse oncogenicity studies, a paper from the open literature by Gammon and Sandar (Neurotoxicology 6(2):63-86, 1985), historical control data, Toxicology Branch "One-Liners" on Bifenthrin and part of a report entitled "Permethrin: Assessment of Chronic and Oncogenic Effects. A Summary", dated September 3, 1982.

C. Background Information:

Bifenthrin (cyclopropanecarboxylic acid, 3-(2-chloro-3,3,3-trifluro-1-propenyl)-2,2-dimethyl-(2-methyl[1,1'-biphenyl]-3-yl)methylester) is a synthetic pyrethroid. Current registrations allow application to ornamentals and other non-food crops. Temporary tolerances have been issued for apples, cottonseed, meat, fat and meat by-products of goats, sheep, cattle, horses and hogs and milk.

Bifenthrin is also referred to as FMC 54800 in this report.

Structure:




D. Evaluation of Oncogenicity Studies:

1. Mouse Oncogenicity Study:

Oncogenicity Study of FMC 54800: Lifetime feeding study in albino mice. Geiger, L. E., Barbera, J. and Ballister, E. Study No. A83-974, conducted at the FMC Toxicology Laboratory. February 3, 1986. Accession Nos. 262948-261955.

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a. Discussion of Study:

FMC 54800 (88.35% pure, with an isomer ratio of 98% cis and 2% trans) was administered in the diet to groups of 50 male and 50 female Swiss-Webster Tac(SW)fBR mice at levels of 0, 50, 200, 500 and 600 ppm. Male mice were fed the diets for a total of 87 weeks and females 92 weeks.

The incidence of relevant tumors seen in this study can be found in the following table.

*Tumor Rates+ of Mice Fed Bifenthrin

| Tumor Type | Dose (ppm) 0 | 50 | 200 | 500 | 600 |
|---|---|---|---|---|---|
| Males | | | | | |
| Urinary Bladder leiomyosarcoma | 2/46(4)** | 6/48(12) | 8/48(17) | 7/45(16) | 14/45(31)** |
| Liver adenocarcinoma | 0/24*(0) | 0/28(0) | 1/35(3) | 2/24(8) | 2/34(6) |
| adenoma | 2/41(5) | 2/43(5) | 3/43(7) | 2/39(5) | 5/40(12) |
| adenoma & adenocarcinoma | 2/41*(5) | 2/43(5) | 4/43(9) | 4/39(10) | 7/40(18) |
| Females | | | | | |
| Lung Bronchioal-veolar adenomas & adenocarcinoma | 14/49(29) | 26/47**(55) | 23/47*(49) | 19/47(40) | 23/45*(51) |

The number in parentheses is the percentage incidence.
+Tumor Bearing Animals/Animals at Risk. The number of animals that died prior to the occurrence of the first tumor for each type of tumor are removed from animals at risk.
Note - Significance of trend Analysis (Cochran-Armitage Trend Test) denoted at Control: significance of pairwise comparision with control (Fisher's Exact Test) denoted at Dose level.
* $p<0.05$ ** $p<0.01$

o On the bladder tumors:

Most of the urinary bladder leiomyosarcomas were detected microscopically. However, in at least four males these tumors were macroscopically evident, one at 500 ppm and three at 600 ppm. Although some females were reported to have urinary bladder leiomyosarcomas, there was no dose-response relationship (Control 0/50; 50 ppm, 2/50; 200 ppm, 4/50; 500 ppm, 1/50; 600 ppm 0/49).

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Historical control data on Swiss Webster mice were available from only one other study. Females were on test in this study for 93 weeks and males for 98 weeks. The incidence of leiomyosarcomas of the urinary bladder in this study was 4/49 in males and 0/49 in females.

o On the liver tumors:

Liver tumors were found in only male mice with the exception of one hepatocellular adenocarcinoma in a 500 ppm female. No predisposing hepatic changes were observed in the livers of treated animals.

Historical control data were available from only one other study as stated for the urinary bladder tumors above. The incidence of hepatocellular tumors in that study was 1/49 in males. No other historical control data on liver neoplasms were presented for review.

o On the bronchioalveolar tumors (females):

Most of the reported lung tumors were adenocarcinomas. Adenomas were seen in 0 in controls, 1 at 50 ppm, 0 at 200 ppm, 3 at 500 ppm and 1 at 600 ppm.

Historical control data were provided from the conducting laboratory on only one study in which the incidence of combined bronchioalveolar adenomas and adenocarcinomas in female mice was 18/50.

Additional data were available on female Swiss-Webster mice from the open literature and are summarized below (lung tumors only).

| Report | Strain Designation and Source | Study Duration | Incidence |
|---|---|---|---|
| Prejean, et al.[1] | SPF Swiss-Webster derived Manor Farms, Staatsburg, NY | 540 days | 21/153(13.7%) |
| Buening, et al.[2] | Swiss-Webster BLU:Ha(ICR) Spruce Farms, NY | 62-66 wks. | 12/21(57%) |
| Buening, et al.[2] | Swiss-Webster BLU:Ha(ICR) Spruce Farms, NY | 62-66 wks. | 12/30(50%) |
| Sher[3] | CFW Carworth Farms | 18 mos. | 4/100(4%) |
| Sher[3] | CFW Carworth Farms | 18 mos. | 10/203(4.9%) |
| Sher[3] | CFW Carworth Farms | 80 wks. | 19/60(31.7%) |
| Sher[3] | Swiss-Webster Carworth Farms | 2 yrs. | 28/100[a,b] |

| | | | |
|---|---|---|---|
| Sher[3] | Swiss-Webster Carworth Farms | 2 yrs. | 26/101[a,c] |
| Sher[3] | Swiss-Webster | 18 mos. | 1/46(2.2%) |
| Sher[3] | Swiss-Webster | 18 mos. | 3/34(8.8%) |

a - sex not specified
b - carcinomas only
c - presumably carcinomas only

Although it is difficult to compare the above data with the results of the Bifenthrin study, it appears that the control rate in the Bifenthrin study (28%) is within the range reported in the open literature for this strain of mouse.

b. MTD Considerations:

Body weight gain was decreased in male mice at the highest dose tested (HDT) during week 3-18 of the study. The depression was only 4-6%; however, it was statistically significant. Body weight gain in females was significantly depressed at HDT during weeks 2 and 5 only by 4 and 3 %, respectively. Tremors occurred frequently in all mice at 500 and 600 ppm during the first 60 days of the study. The incidence of retinal atrophy was significantly elevated in both males and females at the HDT. Also, incidences of bilateral testicular germinal epithelial degeneration were elevated, but no dose response relationship was evident.

A MTD was probably not reached in this study. However, based upon tremors seen at 500 and 600 ppm in both male and female mice and a slight but statistically significant depression in body weight gain in males, a MTD was probably approached at the HDT. The results of a 28-day range finding study add support to this conclusion. In this study at 750 ppm Bifenthrin, 5/10 females died by day 6 following tremors and clonic convulsions. No male mice died at this dose.

2. Rat Oncogenicity Study:

Oncogenicity Study of FMC 54800: 2-Year (734 day) Feeding Study in Albino Rats. Mc Carty, J. D., Barbera, J., Ballester, E. J. and Geiger, L. E. Study No. A83-952. Conducted by FMC Toxicology Laboratory, Somerville, NJ. January 31, 1986. Accession Nos. 261940-261947.

[1] Prejean, J. D., Pickham, J.C., Casey, A. E., Griswold, D. P., Weisburger, E. K. and Weisburger, J. H. (1973). Spontaneous Tumors in Sprague-Dawley Rats and Swiss Mice. Cancer Res. 33:2768-2773.

[2] Buening, M. K., Levin, W., Wood, A. W., Chang, R. L., Lehr, R. E., Taylor, C. W., Yagi, H., Jerina, D.,M. and Conney, A. H. (1980). Tumorigenic Activity of Benzo(e)pyrene Derivatives on Mouse Skin and in Newborn Mice. Cancer Res. 40:203-206.

[3] Sher, S. P. (1974) Tumors in Control Mice: Literature Tabulations., Toxicology and Applied Pharmacology 30:337-359.

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a. Discussion of Study:

FMC 54800 technical (88.35%; 98% cis and 2% trans isomer) was administered in the diet to groups of 50 male and 50 female Sprague-Dawley rats at levels of 0, 12, 50, 100 and 200 ppm. The duration of the study was 734 days. The incidence of various tumors possibly compound related, are outlined in the table below.

Incidence of Tumors in Sprague-Dawley Rats Fed FMC 54800

| Tumor Type | Dose (ppm) 0 | 12 | 50 | 100 | 200 |
|---|---|---|---|---|---|
| Males | | | | | |
| Fibrosarcomas | 0/50(0) | 1/50(2) | 0/50(0) | 0/50(0) | 3/50(6) |
| Pancreas islet cell adenoma | 1/47(2) | 0/25(0) | 0/27(0) | 0/31(0) | 3/50(6) |
| Females | | | | | |
| Pancreas islet cell adenoma | 0/50(0) | 0/23(0) | 0/13(0) | 0/16(0) | 1/49(2) |

The number in parentheses is the percentage incidence.

For neither tumor type was there a significantly elevated incidence at the HDT.

Historical control data was available on one other study conducted at this laboratory. Females were on study for 104 weeks and males for 100 weeks.

| | | |
|---|---|---|
| Pancreatic islet tumors | males | 0/50 |
| | females | 0/50 |
| Fibrosarcomas | males | 0/51 |

On pancreatic islet tumors, the company also referred to the Hazleton Laboratories historical control data base on Sprague-Dawley rats. For combined sexes the mean percentage incidence of this tumor was 3.5% with a range of 2.4-5.9%. The incidence of this tumor type in the Bifenthrin study was 4% for males and females combined.

The Committee did not feel that the occurrence of either tumor type was compound related, i.e. statistical significance was not achieved

for either tumor type neither in trend analysis nor in pairwise comparison and for pancreatic islet tumors, historical control data indicates that this is not a particularly rare tumor type in this strain of rat.

b. MTD Considerations:

Doses for this study were based upon the results of a 28-day range finding study. Death accompanied by tremors occurred at 300 ppm in 6/10 males by day 12 and in 1/10 females by day 20. On this basis the HDT for the two year study was chosen at 200 ppm.

In a 90 day rat feeding study tremors and decreased body weight gain were seen at 200 ppm. The technical product used in this study contained 90% cis and 10 % trans isomer (the product used in the oncogenicity studies was 98% cis and 2% trans). Use of this study for determining an MTD for a chronic feeding study may nonetheless be appropriate because the cis isomer is more biologically active than the trans.

In the two-year feeding study tremors were seen in all animals at the HDT for the first 30 days of the study. In females, body weight gain was significantly depressed 8-10% from weeks 13 through 96. Statistically significant body weight depression was not seen in the males.

Based upon the results of the 28-day range finding study where deaths occurred within 12-20 days of chemical administration at 300 ppm and upon body weight depression (8-10%) in female rats at the HDT (200 ppm) in the 2-year feeding study, 200 ppm was an appropriate dose selection to approximate a MTD in the two year feeding study.

E. Additional Toxicology Information:

1. Metabolism:

The major route of metabolism of FMC 54800 is hydrolysis at the ester linkage. Hydroxylation of the unsubstituted phenyl ring of the intact molecule also occurs.

When rats were administered a single oral dose of FMC 54800, 83% of the radioactivity was excreted in the feces (primarily parent compound) and 8% in the urine (conjugated polar metabolites) after 7 days. Fat contained the highest concentration of radioactivity. When given daily for longer periods of time, FMC 54800 was found to bioaccumulate in fat and fatty tissues.

2. Mutagenicity:

Bifenthrin was negative in the following acceptable assays: Ames Salmonella assay, chromosome aberration assay in CHO cells, and in vivo chromosomal aberration assay in rat bone marrow cells. It was also negative in the sex-linked assay in Drosophila melanogaster, the CHO assay for point mutations at the HGPRT locus and in the in vitro transformation assay in BALB/3T3 cells. These three assays were not acceptable by present Agency

guidelines.

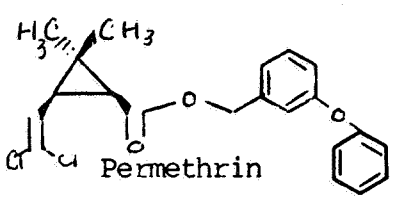
Bifenthrin was positive both with and without metabolic activation in an acceptable mouse lymphoma forward mutation assay. It was also positive for unscheduled DNA synthesis (UDS) in rat hepatocytes at 2ul/mg; however, when the assay was repeated, it was negative for UDS up to 2.5 ul/ml. Both UDS assays were acceptable.

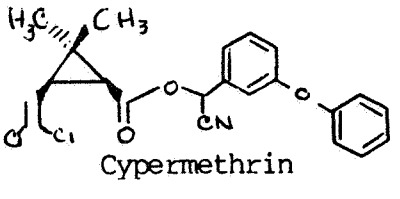
3. Reproduction and Teratology:

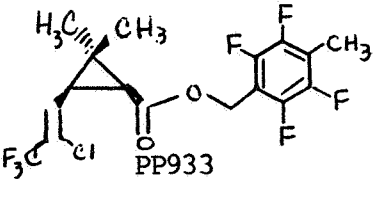
Bifenthrin was not teratogenic to either the rat or mouse but did cause fetotoxicity (hydroureter) in the rat at 2 mg/kg. In a 2-generation reproduction study, Bifenthrin administration to rats did not induce any reproductive toxicity up to 100 ppm although tremors were observed in the dams at this dosage level.

.. Structure Activity Relationship:

Bifenthrin is structurally related to the following three pyrethroids:


Permethrin


Cypermethrin


PP933

Permethrin induced hepatocellular and bronchioalveolar tumors in female mice and was negative in the rat, cypermethrin induced lung tumors in female mice, and PP993 was negative in the rat for oncogenicity and has not been tested in the mouse.

In addition, the registrant does not feel that structure activity correlations should be made between permethrin and bifenthrin since data in the open literature[3] indicates that they induce the pyrethroid syndrome by different mechanisms.

F. Weight of Evidence Considerations:

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

1. Administration of Bifenthrin to Swiss-Webster mice was associated with an increased incidence of leiomyosarcomas of the urinary bladder in male mice, an increased incidence of combined hepatocellular adenomas and adenocarcinomas also in male mice and an increased incidence of combined

[3] Gammon and Sander (1985) Neurotoxicology 6(2):63-86.

bronchioalveolar adenomas and adenocarcinomas in female mice.

2. Historical control data from the performing laboratory consisted of data from only one study. However, the incidence of leiomyosarcomas of the urinary bladder in this study indicated that the occurrence of these tumors is not a rare event, i.e. not less than 1%, on the other hand this tumor type is not commonly occurring, such as lung and liver tumors in mice.

3. The MTD was probably approached in the mouse study. Judging from the results of a 28-day range finding study at 750 ppm (5/10 females died by day 6), a dose not much higher than 600 ppm would not have been tolerated chronically by Swiss-Webster mice.

4. An increased incidence of pancreatic islet cell adenomas in combined male and female Sprague-Dawley rats and of fibrosarcomas in male rats was associated with Bifenthrin administration; however, statistical significance was not reached for either of these tumor types at the HDT.

5. A MTD was reached in the rat study at 200 ppm based upon the results of the 28-day range finding study where deaths occurred within 12-20 days of chemical administration at 300 ppm and upon body weight depression (8-10%) in female rats at the HDT (200 ppm) in the two-year feeding study.

6. When a single dose of Bifenthrin was administered to rats, 83% was excreted in the feces and 8% in the urine within 7 days. Bifenthrin bioaccumulates in fat and fatty tissue.

7. Bifenthrin was negative in several short term assays for mutagenicity but was positive for point mutations both with and without metabolic activation in the mouse lymphoma assay.

8. Bifenthrin was not teratogenic in either the rat or rabbit. It was fetotoxic in the rat causing hydroureter. In a two-generation reproduction study, it induced no reproductive toxicity at a dose that caused tremors in the dams.

9. Bifenthrin is structurally related to permethrin, cypermethrin and PP993. Permethrin induces hepatocellular and bronchioalveolar neoplasms in female mice and cypermethrin induces lung tumors in female mice. PP993 has not been tested for oncogenicity in the mouse but was negative in the rat.

G. Classification of Oncogenic Potential:

The Committee devoted considerable effort in the classification of Bifenthrin, based on the data before it, since it was readily apparent that Bifenthrin met criteria for both categories $B_2$ and C. The criteria for the $B_2$ category were met notably by malignancy of tumors, more than one tumor type in the same species, the uncommon occurrence of bladder leiomysarcomas and the degree of tumor response (31%) at 600 ppm in the mouse study. On the other hand the same information supported a Category C classification, most notably only one sex was affected, only one species was affected, mutagenicity assays provided only weak support for upgrading to $B_2$ and SAR to other pyrethroids supported a C classification. (Although the other

pyrethroids are not yet classified according to the 1986 guidelines, the previous reviews of their data sets seems to favor a C classification.) The Committee concluded that the evidence for a C classification outweighed that for a $B_2$ classification. This decision was further supported by the following facts: 1) The urinary bladder tumor response at 50, 200 and 500 ppm was about equal (12-16%) and was only elevated to 31% at 600 ppm, indicating no dose response; 2) Liver adenocarcinomas and adenomas/adenocarcinomas combined only showed a significant dose-trend but no significance in pairwise comparison; 3) The lung tumors showed no dose-related trend while the response at 50, 200 and 600 ppm but not at 500 ppm was statistically significant compared to controls; and 4) There was no indication that tumor formation occurred early in the study.

Although the Committee classified Bifenthrin as a Category C oncogen, they concluded unanimously that a quantitative estimation of the oncogenic potential for humans should be developed because of the uncommon nature of the urinary bladder tumors seen and of the limited but nonetheless supportive evidence derived from the incidence of both lung and liver neoplasms in the same study.

# FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

## SCIENTIFIC ADVISORY PANEL

## A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Bifenthrin as a Class C Oncogen

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues being considered by the Environmental Protection Agency's peer review classification of Bifenthrin as a Class C oncogen. The review was conducted in an open meeting held in Arlington, Virginia, on March 2, 1988. All Panel members, except Dr. Thomas W. Clarkson, were present for the review. In addition, Dr. Wendell W. Kilgore, University of California, Davis, served as an ad hoc member of the Panel.

Public notice of the meeting was published in the Federal Register on Thursday, February 18, 1988.

Oral statements were received from staff of the Environmental Protection Agency and from Dr. Martin Fletcher, FMC Corporation.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

## REPORT OF PANEL RECOMMENDATIONS

### Bifenthrin

The Agency requested the Panel to focus its attention upon a scientific issue relating to the Peer Review of Bifenthrin. There follows the issue and the Panel's response to the issue:

Issue:

Does the Panel have any specific comment regarding our overall assessment of the weight-of-evidence and classification of this chemical in accordance with the Agency's Guidelines for Carcinogen Risk Assessment.

Panel Response:

The Panel agrees that bifenthrin is best classified as a category C oncogen. This opinion is based on the significant occurrence only at the high dose of leiomyosarcomas in urinary bladders of male mice. However, the Panel does not believe that quantitative risk assessment is warranted. This opinion is based upon the lack of any dose response data in any animal model and the inappropriateness in applying mathematical models to data that do not show a dose response.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 3-9-88