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

APR 29 1992

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Third Carcinogenicity Peer Review of Bifenthrin

FROM: Byron T. Backus, Ph.D., Toxicologist Byron T. Backus 3/23/92
Toxicology Branch 2
HED (H7509C)

and
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Manager, Carcinogenicity Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: George LaRocca
Product Manager #13
Insecticide-Rodenticide Branch
Registration Division (H7505C)

The Health Effects Division Carcinogenicity Peer Review Committee (PRC) met on January 22, 1992 to discuss and evaluate the weight-of-the-evidence on bifenthrin with particular reference to its carcinogenic potential. The Peer Review Committee agreed that bifenthrin should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization, the Reference Dose (RfD) approach should be used for quantification of human risk.

**A. Individuals in Attendance:**

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

Karl Baetcke

Marcia Van Gemert

Reto Engler

Robert Beliles

Lucas Brennecke

Marion Copley

Kerry Dearfield

Hugh Pettigrew

Esther Rinde

Yin-Tak Woo

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

Byron Backus[1]

Clark Swentzel

Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope Fenner-Crisp

William L. Burnam

Julie Du

George Ghali

Richard Hill

Jean Parker

William Sette

John Quest MVG

4. Other Attendees: (Observers)

Eve Andersen (Clement) and Ann Clevenger (HED)

**B. Material Reviewed:**

The material available for review consisted of previous PRC documents, a histopathological review, and other data summaries prepared by Byron Backus and tables and statistical analysis by Bernice Fisher. The material reviewed is attached to the file copy of this report. The data reviewed are based on studies submitted to the Agency by FMC.

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[1]Also member of Committee for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

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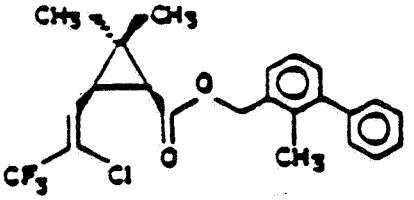
C. **Background Information:**

Bifenthrin (sometimes spelled Biphenthrin), also known as FMC 54800, [chemical name: 2-methyl[1,1'-biphenyl]-3-yl)methyl-cis, trans-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropanecarboxylate] is a synthetic pyrethroid, used as both an insecticide and acaracide. Current registered uses include application to ornamentals and some food crops. Current tolerances (permanent and temporary) include 0.5 ppm on cottonseed, 0.1 ppm in meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep, and 0.02 ppm in milk. A number of Section 18 emergency exemptions have been issued.

The Caswell (or Tox Chem) Number of bifenthrin is 463F.
The Chemical Abstracts Registry Number (CAS No.) is 82657-04-3.

The structure of bifenthrin is




D. **Evaluation of Carcinogenicity Evidence:**

1. Swiss- Webster Mouse Carcinogenicity Study

Reference: Geiger, L.E., Barbera, J., and Ballester, E.J. "Oncogenicity Study of FMC 54800: Lifetime Feeding Study in Albino Mice." February 3, 1986. MRID No. 157227 (Acc. nos. 261948, 261949, 261950, 261951, 261952, 261953, 261954, and 261955). Lab Study No. A83-974. Testing Facility: FMC Toxicology Lab. Somerville, NJ.

Reference: Butler, W.H. "Oncogenicity Lifetime Feeding Study in Albino Mice: Histopathological Review of Selected Sections of Liver, Lung and Urinary Bladder." Revised report date: June 3, 1991. In MRID 419016-01. Lab Study No. A83-974.

Reference: Butler, W.H., Cohen, S.M., and Squire, R.A. "Review of Selected Sections of Bladder from FMC Study A83-974: A 2 Year Study on FMC 54800 in the Swiss-Webster Mouse." Revised report date: June 3, 1991. In MRID 419016-01.

Reference: Butler, W.H. "Oncogenicity Lifetime Feeding Study in Albino Mice: Histopathological Review of Selected Sections of Liver, Lung and Urinary Bladder: Addendum." Report date: November 13, 1991. In MRID 420993-01.

a. Experimental Design

FMC 54800 technical (88.35%, 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 0 (control), 50, 200, 500, or 600 ppm for 87 weeks (males) and 92 weeks (females).

b. Discussion of Tumor Data

Male Swiss Webster mice showed a statistically significant increased trend for hemangiopericytomas in the urinary bladder. The incidences are shown in Table 1. The number of hemangiopericytomas was twice as high at the HDT as for the controls, although the difference was not statistically significant ($p = 0.054$). Bladder stones were not found.

The terminology used for the tumors in the male urinary bladder has been reviewed. Since the last peer review on bifenthrin, Dr. W. H. Butler has reviewed all slides prepared from the urinary bladders of the male Swiss Webster mice in the mouse carcinogenicity study on this chemical. Those slides in which tumors (or lesions) were observed by Dr. Butler were also evaluated by Dr. S. M. Cohen and Dr. R. A. Squire. This pathology panel concluded that the mouse bladder tumor observed in the bifenthrin study was not a leiomyosarcoma (as originally reported) but rather that the tumor arose in the submucosa and possibly from the vascular mesenchyme. The most apt term for this type lesion (or tumor) is hemangiopericytoma. However, these are not necessarily the same lesions that are termed hemangiopericytomas in human tissue, and hemangiopericytomas have not been reported from human urinary bladders.

In the reevaluation of the male urinary bladders, an additional 6 lesions (or tumors) were identified in the controls, bringing the incidence in this group to 7/47. No additional hemangiopericytomas of the urinary bladder were observed in any of the other groups. Even with the increased incidence of this tumor type in the controls, there still remains a statistically significant increased trend for hemangiopericytomas in the urinary bladder for males. Historical control data on Swiss Webster mice were available from only one other study from FMC in which the incidence of this tumor type was 4/49 in males and 0/49 in females.

Male mice also had a significant dose-related increasing trend in hepatocellular carcinomas and in combined hepatocellular adenomas and/or carcinomas. There was no significant dose-related trend for lung tumors in females, but the 50, 200, and 600 ppm dose groups had significantly higher incidences than their controls (14/49, 26/47, 23/47, 19/47, and 23/45 for 0, 50, 200, 500, and 600 ppm, respectively).

c. Non-neoplastic Lesions

There were slight increases in incidences of glandular hyperplasias of the stomach (not significant by Fisher's Exact Test) and retinal atrophy (significant by Fisher's Exact Test) in males and females of the highest (600 ppm) dose group. The males of this group also showed an increased incidence of cortical atrophy of the adrenal gland. Incidences of bilateral germinal epithelial degeneration of the testes were significantly elevated in males.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dosing was considered to be adequate in both sexes for assessing the carcinogenic potential of bifenthrin. Dietary exposure levels were selected on the basis of results from two 28-day studies. In the first, no effects were noted at 0, 50, 100, 200, or 300 ppm. In the second, the concentrations were 0, 500, 600, 750, and 1000 ppm. At 1000 ppm all female mice died by day 12 and 7/10 males by day 7. At 750 ppm, 5/10 females died by day 6 (with clonic convulsions) but there were no mortalities among males. In the chronic study, tremors were observed in all males and females of the 500 and 600 ppm exposure groups during the first 3 months of the study.

Table 1.

Bifenthrin - Swiss-Webster Male Mice, Urinary Bladder Tumor Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

| | Dose (ppm) | | | | |
|---|---|---|---|---|---|
| | 0 | 50 | 200 | 500 | 600 |
| Tumors | | | | | |
| Submucosal | 7/47 | 6[a]/48 | 8/48 | 7/45 | 14/45 |
| (%) | (15) | (12) | (17) | (16) | (31) |
| p= | 0.025* | 0.484 | 0.518 | 0.579 | 0.054 |

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a] First tumor observed at week 39, dose 50 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

2. Sprague-Dawley Rat Carcinogenicity Study

Reference: McCarty, J.D., Barbera, J., Ballester, E.J., and Geiger, L.E. "Oncogenicity Study of FMC 54800: 2 Year (734 Day) Feeding Study in Albino Rats." January 31, 1986. MRID No. 157226 (Acc. nos. 261940, 261941, 261942, 261943, 261944, 261945, 261946, and 261947). Lab Study No. A83-952. Testing Facility: FMC Toxicology Laboratory, Somerville, NJ.

a. Experimental Design

FMC 54800 technical (88.35%, with an isomer ratio of 98% cis and 2% trans) was administered in the diet for 734 days to groups of 50 male and 50 female Sprague-Dawley rats at 0 (control), 12, 50, 100, or 200 ppm.

b. Discussion of Tumor Data

For the most common tumors (pituitary adenoma, adrenal cortical adenoma, adrenal medullary neoplasm - benign and malignant) there were no indications of a dose-response relationship. No statistical increase was found for pancreatic islet tumors. Incidences of pancreatic cell adenoma in males were 1/47, 0/25, 0/27, 0/31, and 3/50 for the 0, 12, 50, 100, and 200 ppm groups respectively. Incidences of fibrosarcoma in males were 0/50, 1/50, 0/50, 0/50, 3/50 for the 0, 12, 50, 100, and 200 ppm groups respectively.

The second PRC did not believe that the occurrence of either tumor type was compound-related. Statistical significance was not achieved for either tumor type, either in trend analysis or in pairwise comparison. Historical control data indicate that this is not a particularly rare tumor type in this strain of rat.

c. Non-neoplastic Lesions

Pituitary congestion was observed in 3/36 females at 200 ppm (vs. 0/44 controls), but was not observed in females at any other dose level. Nonglandular gastritis was observed in 3/48 males and 2/49 females at 200 ppm (controls: 1/40 and 0/49), while retinal degeneration was observed in 3/28 females at 200 ppm (0/42 controls).

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dosing was considered to be adequate in both sexes for assessing the carcinogenic potential of bifenthrin. Dose levels were selected on the basis of a 28-day range-finding study in which all rats at 400 ppm died by day 15, and 6/10 males and 1/10 females at 300 ppm died by day 20. In the chronic study, tremors were observed in all 200 ppm males in the period from day 4 to day 28, and in all 200 ppm females in the period from day 4 to day 30.

**E. Additional Toxicology Data on Bifenthrin:**

1. Reference Dose

The Reference Dose (RfD) is 0.015 mg/kg body weight/day, based on a NOEL of 1.5 mg/kg bwt/day and an uncertainty factor of 100. The NOEL value was derived from a one year dog feeding study in which tremors resulted and has been approved by both the HED (11/6/87) and Agency (7/20/88) Reference Dose committees.

2. Metabolism

In oral dosing studies using C14-labeled bifenthrin, most (about 70%) of the radioactivity was recovered in the feces, and was found to be due to the parent compound and its hydroxylated metabolites. Some (20%) radioactivity was excreted in the urine; compounds present were hydrolytic and hydrolytic/oxidative degradation products of the parent compound. The major metabolic route in plasma appears to be hydrolysis of the ester linkage with oxidation of the resulting alcohol to the acid. Significant bioaccumulation of the parent compound can occur in tissues (including skin) with high fat content, with half-lives in these tissues of about 50 days.

3. Mutagenicity

The test substance was negative in 5 different tests for mutagenicity, but it was marginally active in a forward mutation test in mouse lymphoma cells. Overall, based on the available information, there is a low concern for bifenthrin mutagenicity.

a. Salmonella (Ames) assay: In an acceptable study, bifenthrin technical was negative both with and without S9 activation in strains TA98, TA100, TA1535, TA1537, and TA1538. In addition, FMC has submitted acceptable Ames studies - all with **negative** findings - for three impurities (FMC 102032, FMC 78162, FMC 78161) present in technical bifenthrin. MRID # 00132524

b. Chromosomal aberrations in Chinese Hamster Ovary (CHO) cells: In an acceptable study, bifenthrin (FMC 54800) doses ranging from 100 to 10000 μg/ml with and without S9 activation did **not** cause an increased incidence of chromosomal aberrations in CHO cells. It is noted that the reviewers think that it is odd that so high a level could be tested in this assay when it is way above the reported solubility limit in another assay (see d.) and way above a cytotoxic level reported in other assays (e. and f. below) MRID # 00141195

c. Chromosomal aberrations in rat bone marrow cells: In an acceptable study, bifenthrin, administered orally to rats at 3, 10, or 30 mg/kg/day over a 5 day period, did **not** cause an increase in severity or incidence of chromosomal aberrations in bone marrow cells. MRID # 00138111

d. HGPRT locus mutation in mouse lymphoma cells: In an acceptable study, bifenthrin was tested at 15.8, 50, 158, and 500 μg/ml (1st assay) and

50, 150, and 200 μg/ml (second assay) with and without concurrent exposure to rat S9. Solubility limit of the test material was 200 μg/ml. Under the assay conditions there was no indication that the test material elicited a mutagenic response. MRID # 40630001

e. Unscheduled DNA synthesis in rat hepatocytes: Two studies have been submitted. In the first study, bifenthrin was considered to be weakly mutagenic at 2 μl/ml as there was an average net grain count of 9.3/nucleus as compared with 2.5-3.8 for different controls. There was no indication of any increases in average mean net nuclear grain counts at lower dosage levels (0.1 to 1.0 μl/ml), but the standard deviations associated with these counts were unacceptably high. In the second assay, there was no evidence of UDS at doses ranging from 1.0 to 2.5 μl/ml using several criteria (increase in average net nuclear grains/nucleus, number of nuclei/exposure level with 5 and/or 20 or more net nuclear grains) for evaluation. Overall, bifenthrin does not appear to be active in this assay. MRID #s 00138109, 00138110, 00157560

f. Forward mutation at the TK locus in mouse lymphoma cells: In an acceptable study, doses of 0.042 to 0.24 μl/ml without S9 resulted in a 1.8 to 4.2x dose-dependent increase in mutation frequency at the TK locus. The 4.2x increase was at the top of the concentration with a cytotoxic level of 5% relative growth. (The response was 250 x $10^{-6}$ vs. 60 x $10^{-6}$ control.) The next highest concentration was just above doubling of background. Doses of 0.024 to 0.1 μl/ml caused a 1.3 to 2.0x dose-dependent increase in mutation frequency. The test material was considered to be marginally mutagenic in this assay.

4. Developmental Toxicity

In a study in which bifenthrin was administered by gavage to female rats at 0, 0.5, 1.0 or 2.0 mg/kg/day, the maternal and fetal NOELs were 1.0 mg/kg/day; the maternal LEL was 2 mg/kg/day (tremors occurred); this was also considered to be the fetal LEL, as there was an increased incidence of hydroureter without hydronephrosis.

In a rabbit developmental toxicity study, doses administered by gavage were 0, 2.67, 4 and 8 mg/kg/day. The maternal LEL was 4 mg/kg/day (head and forelimb twitching); at 8 mg/kg/day almost all dams showed twitching and tremors, and two aborted, one after having had clonic convulsions. No developmental toxicity was observed at 8 mg/kg/day (HDT).

5. Structure-Activity Correlations

Bifenthrin has some structural similarities to tetramethrin, permethrin, and cypermethrin, shown in Figure 1.

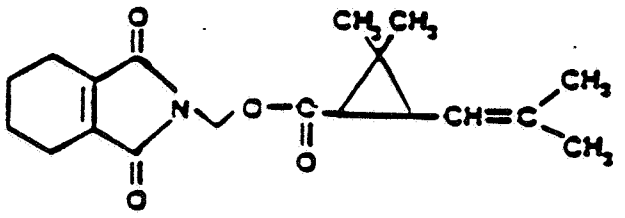
Tetramethrin is currently classified as a Group C carcinogen without risk assessment quantitation (memorandum of December 11, 1989) on the basis of a statistically significant dose-related increase in the incidence of interstitial cell adenomas in the testes of rats at dietary exposure levels of 1000 ppm and above ppm) dietary exposure levels.

Permethrin is currently classified as a Group C carcinogen with a risk assessment quantitation (memorandum of September 18, 1989). The quantitative risk assessment was based on data from a CD-1 mouse study involving a dose-related increase in combined lung adenomas and/or carcinomas observed in females (the same tumor type found with bifenthrin).

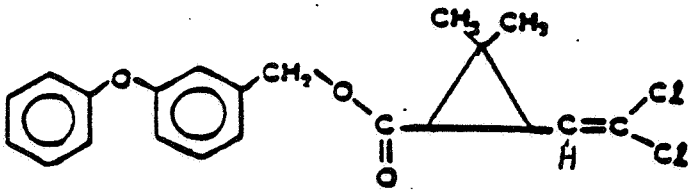
Cypermethrin is classified as a "weak" Group C carcinogen (memorandum dated February 17, 1988), based on the finding of statistically significant positive dose-related trends for lung adenomas/carcinomas combined and for lung adenomas alone in female SPF mice (101 week study; dietary exposure levels 0, 100, 400 and 1600 ppm) (the same tumor type found with bifenthrin). From the memorandum of February 17, 1988: "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."

**Figure 1.**

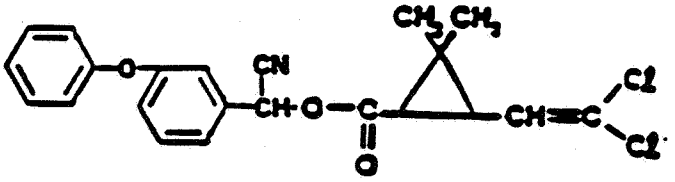
**Structural Analogs of Bifenthrin**



Tetramethrin



Permethrin



Cypermethrin

**F. Weight of Evidence Considerations:**

The Committee considered the following facts regarding the toxicology data on bifenthrin in a weight-of-the-evidence determination of carcinogenic potential.

1. In a chronic study of Swiss Webster mice, fed with 0, 50, 200, 500 or 600 ppm of bifenthrin in the diet, hemangiopericytomas in the urinary bladder of the males were found with a statistically significant increasing trend. Incidences were 7/47, 6/48, 8/48, 7/45 and 14/45 for the controls and tested groups, respectively. The number of hemangiopericytomas was twice as high at the HDT as for the controls, although the difference was not statistically significant ($p = 0.054$) by pair-wise comparison.

2. The registrant originally designated these lesions as leiomyosarcomas, but a panel of three well-known pathologists (WH Butler, SM Cohen and RA Squire) reevaluated the slides and designated these lesions as hemangiopericytomas (most appropriate term). The original pathologist was not asked whether he agreed with the new panel of pathologists regarding the revised classification of the tumors.

3. The registrant reevaluated the slides since the last PRC meeting, and found an additional 6 lesions in the control animals. Historical control data for this type of lesion are minimal, since the registrant has only performed one other chronic study in Swiss Webster mice. Furthermore, the type of section used in the present study (longitudinal through the bladder trigone) is unusual; the usual section for this area is transverse. This type of tumor is frequently small and therefore often difficult to find; it may not be as uncommon as originally believed.

4. The PRC is concerned that, with the reevaluation, only the number of tumors in the controls was reported as increased, and that no increases were reported in the treated animals.

5. The PRC believes that it is unlikely that the hemangiopericytomas are malignant.

6. Male mice also had a significant dose related increasing trend in hepatocellular carcinomas and in the combined hepatocellular adenomas and/or carcinomas. Female mice had significantly higher incidences of combined lung adenomas and carcinomas in the 50, 200, and 600 ppm groups although there was no significant dose-related trend.

7. No compound-related increases in tumors were found in a chronic study in rats which used doses adequate for assessing the carcinogenic potential of bifenthrin.

8. The mutagenicity data present a low concern for bifenthrin. The test substance was negative in 5 different tests of mutagenicity, but it was marginally active in a forward mutation test in mouse lymphoma cells at the tk locus.

9. Structural analogs (other synthetic pyrethroids) have been shown to cause testicular tumors in rats and lung tumors in female mice.

G. **Classification of Carcinogenic Potential:**

Criteria contained in the EPA Guidelines [FR51: 33992-34003, 1986] for classifying a carcinogen were considered.

The Peer Review Committee agreed that bifenthrin should be classified as Group C - Possible Human carcinogen and recommended that for the purpose of risk characterization, the Reference Dose (RfD) approach should be used for quantification of human risk.

This decision was based in part on the statistically significant increased trend for hemangiopericytomas in the urinary bladders of male Swiss Webster mice. The incidence of these lesions was double at the HDT (600 ppm) as compared to controls, but there was only borderline statistical significance in pair-wise analysis at the HDT ($p = 0.054$). However, the PRC noted that hemangiopericytomas in the mouse are not likely to be malignant and may not be uncommon in this strain. The male mice also had significant dose-related trends with respect to hepatocellular carcinomas and combined hepatocellular adenomas and carcinomas; and female mice at 50, 200, and 600 ppm had significantly higher incidences than their controls with respect to combined lung adenomas and carcinomas although there was no significant dose-related trend. No compound-related tumors were noted in rats. The mutagenicity evidence presents low concern for bifenthrin. Structurally related pyrethroids (permethrin and cypermethrin) have caused increased incidences of lung tumors in female mice in feeding studies. These substances were classified as Group C carcinogens by the HED PRC.

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