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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
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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 12/14/87

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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 tne discussion; signatures indicate concurrence with overall conclusions of the Committee.)

Anne Barton

Robert Beliles

B. Material Reviewed:

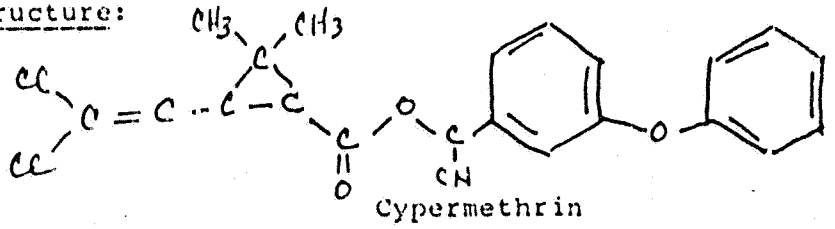
The material reviewed consisted of: (1) a background summary of available toxicology information on Cypermethrin; (2) various memoranda related to risk assessments and tolerance requests on Cypermethrin; (3) DER's of rat and mouse oncogenicity studies, a chronic dog study, and two 3-generation reproduction 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-dichlorovinyl)-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

Alveologenic Tumor Type	Sex	Dose Level (ppm) 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 wit' Cypermethrin administration in this study were a depression in body weight gain (<10%) and lower fc 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.

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 permethrin 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 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.

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