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

MAY 24 1989

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Permethrin: Peer Review Meeting II. Discussion of the Science Advisory Panel's recommendations regarding oncogenicity classification and appropriateness of quantitative oncogenic risk assessment to support tolerances and registrations. Scheduled for June 1, 1989.

FROM: John Doherty
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

TO: Esther Rinde
Oncogencity Peer Review Manager
Science Analysis and Coordination Branch
Health Effects DIvision (H7509C)

THROUGH: Robert Zendzian
Acting Section Head
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

THROUGH Edwin Budd
Acting Branch Chief
Toxicology Branch I
Health Effects Division (H7509C)

Health Effects Division Peer Review Committee met on December 12, 1988 to discuss the oncogenicity data base for permethrin and to classify permethrin according to the EPA Oncogenicity Guidelines (FR5A 1: 33992-34003). The conclusion of this meeting as quoted from the Committee report (refer to Memorandum from Esther Rinde, Ph.D., dated April 7, 1989) is as follows;

"The Peer Review Committee classified Permethin as a Category C (possible human carcinogen), based on evidence in one species (mouse). The evidence in the second species (Long-Evans rat) was considered to be equivocal, but suggestive. The Committee also called for a quantitative risk assessment for Permethrin, based on: 2 tumor types (liver and lung) of which one (lung) was

malignant, the dose-related response seen in the mouse, suggestive evidence in the Long-Evans rat, and supportive SAR information."

Since the Agency's ongoing policy with regard to permethrin did not include quantitative oncogenic risk assessments to support tolerances and registrations, the issue of the oncogenicity classification and the need for quantitative oncogenic risk assessments was referred to the Science Advisory Panel for recommendations.

The Science Advisory Panel met on May 9, 1989 to discuss these issues. The recommendations of this panel are as quoted below:

"The Science Advisory Panel has reviewed the data base on the oncogenicity of Permethrin which consists of 3 rat and 3 mouse bioassays. In only one mouse study was any dose response manifested in lung tumors in the female (both adenomas and carcinomas). The compound was not mutagenic in a battery of bioassays. Accordingly, the Panel recommends that Permethrin be classified as a Category C oncogen. However, because of the relatively weak tumorigenicity and the lack of mutagenicity data, the Panel does not recommend any quantitative risk assessment."

It is requested that The HED Peer Review Committee be reconvened to consider the following topics:

1. Classification of permethrin as a category C oncogen. Both the Science Advisory Panel and the Peer Review Committee concur that permethrin is a category C oncogen.

2. Need for quantitative oncogenic risk assessments to support registrations and tolerances for permethrin.

3. Final conclusions regarding the Oncogenic Peer Review of permethrin.

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MEMORANDUM

SUBJECT: Permethrin Peer Review Meeting II: Comments on the Need for Quantitative Oncogenic risk Assessment for Tolerances and Registrations for Permethrin.

TOX CHEM No.: 652BB

FROM: John D. Doherty, Ph.D., D.A.B.T. 4/1/89
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

TO: Participants
Peer Review Committee for Permethrin
Health Effects Division (H7509C)

The conclusion of the Peer Review Meeting I held on December 12, 1988 for the pyrethroid insecticide permethrin is quoted as follows:

"The Peer Review Committee classified Permethrin as a Category C (possible human carcinogen), based on evidence in one species (mouse). The evidence in the second species (Long-Evans rat) was considered to be equivocal, but suggestive. The committee also called for a quantitative risk assessment for Permethrin, based on: 2 tumor types (liver and lung) of which one (lung) was malignant, the dose-related response seen in the mouse, suggestive evidence in the Long-Evans rat, and supportive SAR information."

The Science Advisory Panel met an May 9, 1989 to discuss the oncogenic classification of permethrin and to advise the Agency on the need for quantitative oncogenic risk assessment. The recommendations made by this panel are quoted as follows:

"The Science Advisory Panel has reviewed the data base on the oncogenicity of Permethrin which consists of 3 rat and 3 mouse bioassays. In only one mouse study was any dose response manifested in lung tumors in the female (both adenomas and carcinomas). The compound was not mutagenic in a battery of bioassays. Accordingly, the Panel recommends that Permethrin be classified as a Category C oncogen. However, because of the relatively weak tumorigenicity and the lack of mutagenicity data, the Panel does not recommend any quantitative risk assessment."

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The HED Peer Review Committee and the Science Advisory Panel both agree that permethrin should be classified as category C with regard to oncogenicity classification. There is no agreement, however, on the need for quantitative oncogenic risk assessment. The advice of the SAP can be accepted and permethrin can be regulated on the basis of its systemic effects without quantitative oncogenic risk assessments as it is currently being regulated. Alternatively the Peer Review Panel may decide not to accept the advice of the SAP committee and recommend that quantitative oncogenic risk assessments <u>are</u> appropriate for the tolerances and registrations of permethrin.

The following is a rediscussion of the rational that the Peer Review Committee used to determine that quantitative oncogenic risk assessments are appropriate for permethrin.

1. <u>Two tumor types: lung and liver</u>.

The lung and liver data from the FMC Mouse II study confirm that this basic observation is correct. These tumor types, however, were present in aged mice, they are commonly occurring tumor types and there was no evidence of decreased latency in their onset. Only one of the three mouse studies had dose related liver tumors. A second mouse study (the Burroughs-Wellcome study) demonstrated an increase in the incidence of lung tumors of the same type seen in the FMC Mouse II study, but the incidence reported was still within the range of historical control for the strain of mice tested.

The summary table showing the total neoplastic findings in the lung and liver from <u>both</u> FMC Mouse I and Mouse II studies is attached. There was no indication that permethrin increased the incidence of lung and liver tumors in the FMC Mouse I study. Although this study is considered INVALID because of misplacing certain animals and because the dose levels were changed after the study began, the misplaced animals were reported as being accounted for and the mice received the high dose group level for 82 weeks. If permethrin were indeed oncogenic in this strain of mouse, there should have been at least some indications of increased lung and liver tumors noted in the FMC Mouse I study. See item 4 below for discussion of using data determined to be INVALID for regulatory purposes.

2. <u>Malignant Tumors in the Lung</u>

The lung tumor data from the FMC Mouse II study for the female mice are illustrated in the following table:

	Adenoma	Carcinoma
Control	9/71(13)	6/66(9)
20 ppm	17/68(25)*[1]	7/62(11)
2500 ppm	24/68(35)**	11/59(19)
5000 ppm	29/69(42)**	15/62(24)*[2]
Range for historical control	0-20.4%	2.0-16.0%
Significant Trend	**	**

Data are number of mice with tumor/number of mice at risk(percentage). These data are from the Table prepared by Bernice Fisher and presented in the Peer Review I Committee Report.

*P < 0.05, **P < 0.01

[1] P= 0.0495, just barely statistically significant.
[2] P= 0.0187

Only the high dose group females (P=0.0187) are statistically significantly positive for incidences of malignant tumors and this group (24% incidence) is higher than the historical control upper limit (16% incidence). A word of caution regarding the comparison with the historical control data is that the Table above uses mice at risk for the denominator, whereas the historical control data uses total mice available in the test group. Using mice at risk results in a higher percentage than when total mice available are used for the denominator. The frequency of carcinomas in the FMC Mouse II study would be 20% if the total available mice (75) were used as the denominator and would be closer to the range for the historical controls.

Overall the evidence that permethrin induces malignant tumors in the FMC Mouse II study can be regarded as borderline and is not corroborated by other studies with permethrin.

3. Dose response seen in the mouse for lung and liver tumors.

The basic observation is correct, the dose response is clearly evident for female mouse lung and liver tumors in the FMC Mouse

II study.

The significance of this dose response in lung and liver tumors may be lessened with regard to permethrin causing a specific tumor response. Liver weight in the females was elevated 26% and 42% for the mid and high dose groups respectively. Liver microsomal oxidase system is also elevated by permethrin at dose levels lower than the 2500 and 5000 ppm dose levels at which permethrin was demonstrated in the Mouse II study to be associated with increased incidence of lung and liver tumors. Thus, the tumors may occur at a dose level that is in excess of what some consider as the Maximum Tolerated Dose.

4. Suggestive evidence in the Long-Evans rat.

The Long-Evans rat study was previously determined by TB to not be useful in evaluating for an oncogenic effect in the lung. There are two other rat studies which did not support the suggestion indicated by the Long-Evans rat study and these studies assessed equivalent and higher dose levels of permethrin.

In using this study, which the Agency considers as equivocal, to support its call for quantitative oncogenic risk assessment the Agency is elevating a suggestion to the level of regulatory significance even though the suggestion could not be corroborated in two other rat studies.

The FMC Mouse I study does not corroborate the FMC Mouse II study with regard to demonstrating increases in lung or liver tumors but the Agency is not using this information. Clearly this is a case of selectively using data that the Agency considers flawed to support its position but disregarding similarly categorized data that does not support its position.

5. Supportive SAR information.

Although the closely related pyrethroid cypermethrin, which differs from permethrin by the presence of an alpha cyano group, was also demonstrated to be associated with increased lung tumors, the Peer Review Committee did not call for quantitative risk assessment. Cypermethrin did not demonstrate increases in liver tumors.

The pyrethroid bifenthrin differs from permethrin in both the alcoholic side chain and substitutes on the vinyl group and resulted in tumors at other locations than did permethrin.

At the SAP meeting, the registrants presented a list containing seven other pyrethroids some of which are similar to permethrin in structure that were not demonstrated to be oncogenic in the

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rat or mouse. The registrants state that the Agency is being selective in its use of SAR information.

6. Liver adenomas in male mice in the FMC Mouse II study.

The Peer Review Committee report indicated that there were "statistically significant increases in liver adenomas at all doses (and outside historical control range at all doses) with a significant dose-related trend." The following Table illustrates the liver adenoma data from the FMC Mouse II study:

	Male liver (adenoma) data		
Control	6/66	(9%)	
20 ppm	17/63	(27%)	0.0052
500 ppm	15/63	(24%)	0.0157
2000 ppm	17/57	(30%)	0.0001

Data are in incidences of adenomas/mice at risk and in () the percentage. The last column is the P statistic from the Peto Prevalence test (provided by Bernice Fisher).

The historical control information provided by the testing laboratory indicate that the range of adenomas in males in 0-11.7%.

Although the data are clearly statistically significant for each dose level when compared to the study control, there is no dose response over the broad range from 20 to 2000 ppm. The Science Advisory Panel did not regard these data an being as indication of an oncogenic effect of permethrin.

7. Totality of the studies.

When all mouse and rat bioassays are considered there are eight studies. Five mouse (FMC Mouse I and II, ICI, Burroughs-Wellcome and the Shimkin studies) and three rat (FMC, ICI and Burroughs-Wellcome). Only one of these is actually regarded as being positive (Mouse II, lung and liver tumors in females). A second mouse study (Burroughs-Wellcome study) also demonstrated a slight increase in lung tumors (in the high dose group) that were within the historical control range for that strain but apparently is not regarded as being a positive oncogenic finding by the Science Advisory Panel. None of the rat studies are actually regarded as demonstrating a positive oncogenic response to permethrin.

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8. Summary

There is no explanation as to why the Mouse II study appears to be so obviously oncogenic with regard to dose related increases in lung and liver tumors when conclusive evidence of oncogenicity in as many as seven other studies with permethrin is not apparent. There is thus limited evidence of oncogenicity in laboratory animals (category C). Because of the equivocal nature of the total picture (all rat and mouse bioassays, mutagenicity and metabolism data) regarding the oncogenicity of permethrin, the advice of the Science Advisory Panel which did not recommend for quantitative oncogenic risk assessment may be considered appropriate.

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Reviewer's Peer Review Package for 1st Meeting

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 Permethrin as a Class C Oncogen

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 in connection with the peer review classification of permethrin as a Class C oncogen. The review was conducted in an open meeting held in Arlington, Virginia, on May 9, 1989. All Panel members, except Dr. Robert Anthony and Dr. James Swenberg, were present for the review.

Public notice of the meeting was published in the Federal Register on April 17, 1989.

Oral statements were received from staff of the Environmental Protection Agency and from Dr. Robert C. Ridsdale (ICI, Americas), and Dr. John Ishmael (ICI, United Kingdom).

Written comments were received from Dr. James Swenberg (FIFRA SAP) and read into the record for consideration by the Panel.

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

Permethrin

Issue:

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

Panel Comments on Permethrin

The Scientific Advisory Panel has reviewed the data base on the oncogenicity of Permethrin which consists of 3 rat and 3 mouse bioassays. In only one mouse study was any dose response manifested in lung tumors in the female (both adenomas and carcinomas). The compound was not mutagenic in a battery of

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bioassays. Accordingly, the Panel recommends that Permethrin be classified as a Category C Oncogen. However, because of the relatively weak tumorigenicity and the lack of mutagenicity data, the Panel does not recommend any quantitative risk assessment.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Robert B. Taegg
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 5/16/89