UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

12/12/1988

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Permethrin. Revised summary of the oncogenicity data base.

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Background

Permethrin is a pyrethroid insecticide which is currently considered by the Agency to be oncogenic based on observations of dose related increased incidence of lung and liver tumors in female mice. Permethrin has not been peer reviewed by the Health Effects Division Peer Review Committee (or its predecessor in the former Toxicology Branch of Hazard Evaluation Division). In this regard, it is requested that permethrin be peer reviewed and a recommendation made for its classification for oncogenicity category and as to whether or not quantitative risk assessments need to be made for the various uses and tolerances associated with this pesticide.

The following information is being provided in this package.

Part A. Summary of Neoplastic Findings and Overview of the Chronic Feeding and Oncogenicity Studies.

Part B. Topical discussions of the mutagenicity, metabolism, developmental toxicity and structure activity relationships of permethrin.

Attachment: Memo dated Sept. 9, 1988 from Bernice Fisher entitled: "Permethrin-Qualitative Risk Assessment, Two Year Chronic/Oncogenicity Mouse Study".

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Part A. Summary of the Neoplastic Findings and Overview of the Chronic Feeding and Oncogenicity Studies.

3 Rat chronic feeding/oncogenicity studies
1 Invalid mouse oncogenicity study
3 Valid mouse oncogenicity studies
1 Shimkin mouse lung bioassay study

Rat Studies

1. Burroughs-Wellcome Study (Wellcome Foundation, July, 1980)

In this study Wistar rats were dosed with either 0, 10, 50 or 250 mg/kg/day of permethrin (25% cis/75% trans) for two years. The NOEL for the study was set at 10 mg/kg/day. At 50 mg/kg/day and above there was evidence of hepatocyte hypertrophy. At the highest test dose level there was also increased liver weight. The MTD was considered to be reached based on slightly increased mortality in the males and occasionally tremors in both sexes in the high dose group. TB determined that there were no indications that permethrin was oncogenic in this study. The study was assigned CORE GUIDELINES classification.

2. ICI Study (ICI Laboratory, England, November, 1977).

In this study Wistar rats were dosed with either 0, 500, 1000, or 2500 ppm (125 mg/kg/day) of permethrin (40% cis/60% trans) for two years. No firm NOEL was established for this study. At 500 ppm and above there was increased liver and kidney weight, at 1000 ppm and above there was increased liver enzyme activity and hepatocyte vacuolation and hypertrophy. The MTD was considered to be reached based on increased mortality in the males in the high dose group. TB determined that there were no indications that permethrin was oncogenic in this study. The study was assigned CORE MINIMUM classification.

3. FMC Study (BioDynamics, November, 1977)

In this study Long-Evans rats were dosed with either 0, 20, 100 or 500 ppm (25 mg/kg/day) of permethrin (40% cis/60% trans) for two years. The NOEL for this study was set at 100 ppm although at this level there were slight increases in liver weight. At 500 ppm there were more definite increases in liver weight but a MTD may not have been reached in this study. Evaluation of the oncogenic findings for this study, and particularly the lung tumor data, was at one time the subject of considerable scrutiny. Because of inconsistencies in the histological methodologies used to prepare the lung tissue for analysis it was eventually determined that making a scientifically acceptable evaluation of the results for this organ was

precluded. A summary table illustrating the neoplastic findings in the lungs of the males as determined by several assessments is as follows.

Table 1. Lung tumors in the FMC Rat Study.

Dose Level (ppm)	Original Analysis	Reassess-ment	After Step Sectioning (250 u intervals)	Area Adjusted Original Analysis	All Slides
0	1/59	1/60	8/60	1/60	8/60
20	3/57	3/57	6/57	2/57	8/57
100	6/57	8/60*	10/60	5/60	15/60[b]
500	5/56	6/60*	10/60	4/60	14/60[b]

Data are incidence of tumors/number of animals examined.
*Statistically significant $p < 0.05$.
[b] borderline statistical significance, p approximately 0.10

This study was eventually assigned CORE MINIMUM classification. No other organ was considered to demonstrate an oncogenic response to permethrin.

Mouse Studies

1. FMC Mouse I Study (BioDynamics Laboratory, 1978)

This study was determined to be INVALID by TB based on reports that there were test diet feeding errors for a significant portion of the study and because of misplacing the animals and failure to positively identify the misplaced animals.

2. FMC Mouse II Study (BioDynamics Laboratory, October, 1979)

This study was conducted to replace the Mouse I study. In this study, male CD-1 strain mice were dosed with permethrin for two years with either 0, 20, 500 or 2000 ppm (300 mg/kg/day). Females were dosed with either 0, 20, 2500 or 5000 ppm (750 mg/kg/day). The important non-neoplastic findings related to permethrin treatment included increased mortality in males dosed with 2000 ppm; increased liver weights in females dosed with 2500 and 5000 ppm and increased lung weights in females dosed with 5000 ppm. Other findings included a dose related increase in "multifocal alveolar cell proliferation" in the mid and high dose group females and the incidence of multifocal hepatocytomegaly was also observed to be increased in the livers of both males and

females. In the high dose groups which were the groups most severely affected, the liver lesion did not exceed 18.7% (in males) and the lung lesion did not exceed 17.3% of the mice in these groups.

Review of the oncogenicity aspects of this study revealed dose related increased incidence of both lung and liver neoplasms in females in the two highest test dose groups. TB did not consider that there were indications of definite oncogenic effects in other organs/tissues in this study. The oncogenic findings (based on a rereading of the slides by Dr. L.K. Ackerman of Environmental Pathology Laboratories) are presented in the following tables.

Table 2. Liver Tumor Data in the FMC Mouse II Study

Dose Group (ppm)	Adenoma/Hepatoma[1] Incidence	Adenoma/Hepatoma[1] Percent	Carcinoma Incidence	Carcinoma Percent	Combined[3] Incidence	Combined[3] Percent
Females						
0	3/74^{t}	4.1%^{t}	4/74	5.4%	6/74^{t}	8.1%^{t}
20	4/76	5.3%	3/76	3.9%	7/76	9.2%
2500	23/76^{ss}	30.3%^{ss}	3/76	3.9%	25/76^{ss}	32.9%^{ss}
5000	29/75^{ss}	38.7%^{ss}	2/75	2.7%	30/75^{ss}	40.0%^{ss}
Hist. Control[2]	3.0(0-7.8)% (9 studies)		1.3(0-4.9)%		4.3(1.1-11)%	
Males						
0	8/75^{t}	10.7%^{t}	16/75	21.3%	22/73	30.1%
20	19/75^{ss}	25.3%^{ss}	12/75	16.0%	29/73	39.7%
500	17/75^{ss}	22.7%^{ss}	19/75	25.3%	34/70^{ss}	48.6%^{ss}
2000	19/75^{ss}	25.3%^{ss}	8/75	10.7%	25/69^{ss}	36.2%^{ss}
Hist. Control[2]	6.1(0-11.7)% (9 studies)		7.9(1.7-12.8)%		14.0(5.3-20.0)%	

See next page for footnotes.

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Table 3. Lung Tumor Data in the FMC Mouse II Study.

Dose Group (ppm)	Adenoma Incidence	Adenoma Percent	Carcinoma Incidence	Carcinoma Percent	Combined Incidence	Combined Percent
Females						
0	10/75[t]	13.3%[t]	6/75[t]	8.0%[t]	15/75[t]	20.0%[t]
20	18/76[ss]	23.7%[ss]	7/76	9.2%	24/76[ss]	31.6%[ss]
2500	26/75[ss]	34.7%[ss]	11/75	14.7%	35/75[ss]	46.7%[ss]
5000	37/75[ss]	49.3%[ss]	15/75[ss]	20.0%[ss]	44/75[ss]	58.7%[ss]
Hist. Control[2]	5.0(0-20.4)% (9 studies)		8.5(2.0-16.0)%		13.5(6.5-22.4)%	
Males						
0	16/75	21.3%	7/75	9.3%	23/75	30.7%
20	17/75	22.7%	5/75	6.7%	20/75	26.7%
500	20/74	27.0%	13/74	17.7%	28/74	37.8%
2000	17/75	22.7%	4/75	5.3%	21/75	28.0%
Hist. Control[2]	4.0(0-10.4)% (9 studies)		7.7(4.0-14.3)%		13.5(6.5-22.4)%	

[1]Hepatoma is considered as an adenoma.

[2]Historical control data are presented as the mean and the range from nine studies as submitted by the BioDynamics Laboratory in the fall of 1988.

[3]Mice having hepatoma (in liver) and adenoma (in lung) and carcinoma in the same organ in the Mouse II study were counted only once for the combined category. Otherwise the hepatomas, adenomas and carcinomas were all considered separately.

Footnotes continued next page.

[t]A dose dependent trend was demonstrated statistically.

[ss]Group demonstrated to be statistically significantly different in pairwise comparison with the control group.

Refer to the memo from Bernice Fisher dated September 9, 1988 for inquiries concerning the statistical analysis of the Mouse II study.

N.B.: The denominators and also the numerators for hepatomas and lung adenomas presented above differ from the denominators and numerators used by Ms. Fisher because in the statistical analysis the denominators were adjusted to include only mice at risk following development of the first lung tumor. In the tables above, the total number of mice on the study were used as the denominator in order to more appropriately compare the results of the Mouse II study with the historical control data provided by the BioDynamics Co..

The above tables (together with the statistical analysis of the study prepared by Ms. Fisher attached) indicate that permethrin is oncogenic in the female mouse lung and liver. Even the lowest dose level of 20 ppm can be shown to be statistically significant (p=0.0495) for lung tumors. The livers of females show marked increases in tumors in dose dependent manner for the two high dose test groups. The incidence of tumors in the male livers also can be shown to be statistically significantly greater than the control. There is, however, no dose response for increased incidence of liver tumors among the male groups. This study was classified as CORE GUIDELINES.

3. Burroughs-Wellcome Study (Wellcome Foundation, Dec, 1980)

In this study CFLP (Swiss derived) mice were dosed with either 0, 10, 50 or 250 mg/kg/day of permethrin (25% cis/75% trans) for 92 weeks. Systemic effects were noted at the high dose groups only which included slightly increased liver and kidney weight, and cuboidal/columnar metaplasia of alveolar epithelium in lungs. An MTD may not have been reached in this study. With the exception of the lung, there were no indications that permethrin was oncogenic in this study. The following table summarizes the lung tumor data. [This study was classified as CORE GUIDELINES.]

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Table 4. Mice with One or More Adenomatous Tumors in the Lungs in the Burroughs-Wellcome Mouse Study.

Dose Group (mg/kg/day)	Males Incidence	Males Percent	Females Incidence	Females Percent
0	26/99	26.3	3/96	3.1
10	14/75	18.7	5/71	7.0
50	17/73	23.3	7/74	9.5
250	16/74	21.6	15/74*	20.3*
Hist. Control[1]			20.4(7.5-30.0%)	

* statistically significantly different from control group, $p < 0.05$.
[1]Historical control data (mean and percentage range) derived from 9 studies containing 807 female CPLP control mice and include mice affected with lung adenomas and carcinomas.

4. ICI Mouse Study (ICI Laboratory, January, 1978).

In this study Alderly Park strain (Swiss derived) mice were dosed with either 0, 250, 1000 or 2500 ppm (375 mg/kg/day) of permethrin (40% cis/60% trans) for 98 weeks. Non-neoplastic systemic effects were noted at 1000 ppm and above. At 1000 ppm and above there were minimal changes in liver enzyme activity, increases in liver weight and histopathological changes in the liver (eosinophilia of hepatocytes). At the highest dose level there was an increase in mortality for both males and females assuring that the MTD dose was achieved. TB review determined that there was no evidence that permethrin was oncogenic in this study. The following table presents the findings for adenomas in the lung. For male mice, no lung carcinomas were observed. For female mice, one carcinoma was observed in the low, mid and high dose groups. It was apparent that there was a slight increase in lung adenomas in the high dose group males but this increase was not determined to be statistically significant. [This study was classsified as CORE MINIMUN.]

Table 5. Adenomas in Mouse Lungs in the ICI Mouse Study

Dose Level (ppm)	Males		Females	
	Incidence	Percent	Incidence	Percent
0	11/70	15.7	11/70	15.7
250	6/70	8.6	8/70	11.4
1000	13/70	18.6	10/70	14.3
2500	17/70[a]	24.3	15/70	21.4

[a]Fisher's Exact Test p = 0.145 (not significant).

5. Shimkin Mouse Lung Bioassay (Biocon, Rockville, Md., 1985)

In this study groups of 16 male and 16 female strain A/J mice were dosed with either 285, 475 (females only), 713.5 and 1425 mg/kg of permethrin (40% cis/60% trans) for three days a week for eight weeks. After 24 weeks the mice were sacrificed and their lungs examined for tumors. A separate positive control group was dosed with urethane (1000 mg/kg). These mice were evaluated for development of lung tumors. The frequency of tumors in the permethrin treated mice was equivalent to the corn oil and untreated control groups. Urethane produced the expected positive response. No evidence that permethrin promoted lung tumors in this study was generated.

SUMMARY

In summary, the rat oncogenicity data do not provide evidence that permethrin is oncogenic in this species. Two of the three rat studies presented were considered to have achieved the MTD and with certain exceptions as indicated above met the Agency's criteria for acceptable studies.

One study with mice (the FMC Mouse II study) clearly demonstrated increased incidence of both lung and liver tumors in females associated with dietary permethrin. Although statistically significant increases in male mouse liver tumors (hepatomas only) and female lung tumors at 20 ppm were demonstrated, it is not conclusive that these increases are related to dietary permethrin. Since the mice affected with lung

and liver tumors were mostly in the survivors or died in the later months of the study, no evidence that permethrin decreased the latency of tumor development was provided. The lung and liver tumors which were increased in response to permethrin in the diet are commonly occurring tumors. Thus permethrin did not cause rare of unusual tumors.

One other mouse study (the Burroughs-Wellcome study) apparently corroborated the finding that permethrin may be oncogenic to mouse lungs since the high dose group in this study was also statistically significant for lung tumors. However, the observed lung tumor incidence in all treatment groups fell within the historical control range and even below the mean for the mean for the historical control data. A third study (the ICI study) with mice did not indicate that permethrin was oncogenic, although there was noted a slight but not statistically significant increase in male lung tumors at the highest dose level tested.

A Shimkin Mouse Lung Bioassay was also presented. This study did not confirm that the lung was a target organ for an oncogenic effect of permethrin in mice that are especially susceptible to lung tumors.

Part B. Topical Discussions

1. Metabolism.

The Agency has several studies which indicate that permethrin is rapidly absorbed from the gastrointestinal tract, metabolizes primarily by attack at the ester site, after which the metabolites are conjugated and excreted in the urine. Only trace amounts of radiolabelled material remain in the tissues.

2. Developmental Toxicity.

The Agency has several teratology and multi-generation reproduction studies none of which have demonstrated specific developmental toxicity resulting from permethrin treatment.

3. Mutagenicity.

The mutagenicity studies thus far reviewed by TB have not demonstrated permethrin to possess any evidence of mutagenicity. The following table summarizes the studies available

Table 6. Summary of Mutagenicity Studies with Permethrin.

Category I, Gene Mutation.

Ames Test Litton Bionetics #2575, Dec. 1975	S.typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and S. cerevisiae strain D4 were tested over the range of 0.001 to 5.0 ul/plate.	Not mutagenic with and without metabolic activation.
Ames Test SRI #LSC4768, Jan, 1976.	S.typhimurium strains TA1535, TA1537, TA1538 TA98 and TA100 and E. coli strain WP2 were tested over the range of 1 to 1000 ug/plate.	Not mutagenic with and without metabolic activation.
Mouse lymphoma Assay. Wellcome Foundation #TTEP/77/0007, Jan. 19, 1977.	Cultures of L578Y/TK+/- mouse lymphoma cells were tested over the range of 31-125 ug/ml.	Not mutagenic with and without metabolic activation. 47 ug/ml highest working concentration.

Category II, Chromosome Aberration.

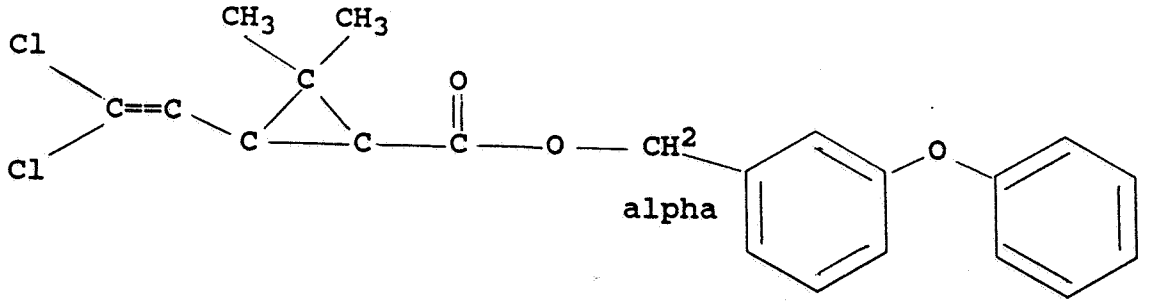
Dominant Lethal Wellcome Research Laboratories. HEFG 75-10, Nov. 27, 1975 and HEFG 76-2 Feb. 17, 1976.	Permethrin tested at 285 and 452 mg/kg /day.	No evidence of any dominant lethal mutation. (Considered questionable by I. Mauer).
Dominant Lethal Omni Research # Daad 05-84-M-L186 June-July 1988.	Permethrin tested at 26, 130 and 260 mg/kg/day.	No evidence of any dominant lethal mutation. (Considered unacceptable by I. Mauer).

Category III, Other Mechanism of Mutagenicity.

No studies available. Additional studies are required especially studies to complete categories II (chromosome aberration) and Category III (other mechanism of mutagenicity). Dr. Mauer has recommended that one or more cell transformation assays with permethrin be conducted and submitted.

4. Structure Activity Relationships.

Permethrin is a pyrethroid represented by the following chemical structure:



Cypermethrin, the alpha cyano analog of permethrin, has previously been peer reviewed by TB. Cypermethrin was concluded to be a type C oncogen based on increased incidence of lung tumors (alveologenic adenoma and alveologenic carcinomas combined). The Peer Review Committee concluded that quantitative risk assessments need not be determined for the individual registrations and tolerances for cypermethrin.

Bifenthrin is another pyrethroid which has been peer reviewed by TB. Bifenthrin has a trifluoro methyl group in place of a chlorine on the vinyl moiety and the alcohol side chain is a dibenzyl methyl rather than a phenoxy benzyl group. Bifenthrin was determined to be associated with increased incidence of liver (in males), lung (in females) and urinary bladder tumors (in males) in mice. The Peer Review Committee recommended that quantitative risk assessments be developed for the uses of bifenthrin based largely on the association with bladder tumors.

	Mouse			Rat		
	F	M		M	F	
CD-1	Clear Liver + Lung	Some Liver (no Lung)	(No Study)	No	No	Written
				No	No	Written
Swiss	~~Some~~ Lung (equivocal)	(equivocal)	No Evidence	(No NTP)	equivocal	No	Only Evid
Alday Park	No liver	No liver				

C = without Risk assessment