



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

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2/21/84

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#2F2623 and FAP#2H5334. Toxicology Branch Update  
on the Mouse Oncogenicity Study and Dog Chronic  
Feeding Study. *Cypermethrin.*

Tox Chem. No. 271DD

TO: T. A. Gardner, PM#17  
Registration Division (TS-767)

THRU: William L. Burnam, Branch Chief  
Toxicology Branch  
Hazard Evaluation Division (TS-769)

WLB  
2.21.84

Background:

In a previous review of this petition (see J. Doherty review for PP#2F2623 and FAP#2H5334 dated September 16, 1983) Toxicology Branch (TB) indicated that the mouse oncogenicity study showed increased incidences of benign alveologenic tumors in the females particularly in the high dose test group and that there were questions concerning the NOEL for the 1-year dog feeding study. In order to help resolve problems concerning the oncogenic potential of cypermethrin in mice, TB requested that the registrant prepare and read slides from the lung and liver of the mice which were sacrificed at the interim kill and to provide historical control data for malignant lymphoreticular tumors for the strain of mouse used. TB also requested that a study be conducted with dogs to ascertain if the signs of gastrointestinal disturbance (passing of liquid stools and vomiting) resulted from a direct local effect of the cypermethrin or from an effect mediated through the central and/or peripheral nervous system.

The registrant has provided the additional lung and liver histopathology data, additional historical control data for lung tumors, and historical control data for malignant lymphoreticular tumors. This information is reviewed below.

The registrant has not yet decided whether or not to conduct the additional dog study. For the present time and the subject petition, the registrant was prepared, however, to accept 1 mg/kg/day as the NOEL for the 1-year dog study (see comments below).

187

003647

Comments:

1. Mouse Oncogenicity Study

The pathology data provided for the lungs and liver of the mice sacrificed at the interim kill were examined. It was determined that no evidence for a decreased latency or time to tumor was demonstrated in the lungs of these interim sacrifice animals. Liver tissues showed no treatment related effects in these animals.

The mouse oncogenicity study (CTL/P/687, June 1982) may be upgraded to CORE GUIDELINES.

Toxicology Branch will prepare a summary document describing the results of the chronic feeding studies and oncogenic assessment of cypermethrin. A statistical risk assessment of cypermethrin based on the oncogenic assessment will also be prepared. These documents will be forwarded to Registration Division at a later date.

2. Dog 1-Year Feeding Study

In the letter from ICI to EPA (see R. E. Ridsdale letter dated December 9, 1983, EPA Acc. No. 072204) it was stated that ICI has not yet decided to do this study, and that "for the present time and the subject petition, we are prepared to accept 1 mg/kg/day as the NOEL for the 1-year dog study."

The letter also stated that ICI does not believe that the increased incidence of fluid feces in the 5 and 15 mg/kg/day groups is of toxicological significance, because of the absence of any histopathological changes in the alimentary tract or adverse consequences on general health. TB's position is that the increased incidences of fluid feces may be an adverse response which need not be accompanied by histopathological changes.

Thus, the NOEL for the dog study (CTL/P/703, July 6, 1982) is assigned as 1.0 mg/kg/day.

2

Review of Documents Submitted

1. Cypermethrin: Lifetime feeding study in mice, supplement to report CTL/P/687.

CTL, study no. PM0366, December 12, 1983 (date signed)  
EPA Acc. No. 072204.

The lung tissues from the mice which were sacrificed for the interim kill were palpated and 5 sections from each lung (reportedly cut in an identical manner from all mice) were prepared for microscopy and read. In addition, a single section from the liver of each mouse from groups sacrificed for the interim kill was also prepared and read.

Table 1 (xeroxed from the study report) shows the results of the neoplastic findings in the lung and liver of the mice sacrificed for the interim kill.

There were no liver tumors found in the females. There were 7 liver tumors (3 benign and 4 malignant) found in the males. The following table illustrates the revised (to include the interim sacrifice data) frequency of liver neoplasms:

	n	MALES				FEMALES			
		Benign	%	Malignant	%	Benign	%	Malignant	%
Control - 1	70**	11	15.7	12 (11)	17.1	1	1.4	2	2.9
Control - 2	70	13	18.6	10 (9)	14.3	2	2.9	5	7.1
100 ppm	70	11 (10)*	15.7	16	22.9	3	4.3	1	2.9
400 ppm	70	11 (10)	15.7	13 (12)	18.6	4	5.7	4	5.7
1600 ppm	70	5 (4)	7.1	14 (13)	20.0	1	1.4	2	2.9

\*The number in parentheses is the original finding based on all mice except those in the interim sacrifice.

\*\*Note-there were only 69 female mice examined.

The overall result including the mice in the interim sacrifice is that there is no evidence of an oncogenic response of cypermethrin in mouse liver in this study.

There were 10 additional benign alveologenic tumors found in the lungs of the mice in the interim sacrifice. Seven of these were in the male groups and 3 were in the female groups. The following table illustrates the frequency of lung tumors including the mice sacrificed for the interim kill.

003647

	n	MALES		n	FEMALES	
		Benign	Malignant		Benign	Malignant
Control - 1	70	7 (4)*	1	69	5 (4)	0
Control - 2	70	10	1	70	5 (4)	2
100 ppm	70	11 (10)	1	70	6	0
400 ppm	70	7 (6)	0	70	7	1
1600 ppm	70	9 (7)	3	70	14**(13)	0

\* The number in parentheses represents the original count, not including the mice sacrificed for the interim kill. Specifically, among the females were three additional benign neoplasms found in the lungs of the mice. These were in each of the control groups, and one in the high dose group.

\*\* The high dose test group (females) is statistically significant ( $p < .05$ , Fisher's One Tail p Statistic) when either benign tumors or benign plus malignant tumors are compared with the control groups.

The data provided in the supplement confirm that there is no oncogenic response in the male lung tissues, but that there is a statistically significant higher frequency of neoplasms in the female high dose test group. Because two of the three neoplasms found in the female groups were in the control groups, the data in the supplement do not provide a basis that there is an earlier onset of development of the tumors in the female mouse lungs.

Microscopic examination of the mice sacrificed at the interim kill also revealed that there were 8 mice which had malignant lymphoreticular tumors. Among the males, two were in the control groups and two were in the high dose test group. Among the females, there was one mouse affected in the control groups and one in the low dose group and two mice were affected in the high dose test group. Combining the results of the interim sacrifice with the results from the other mice on the study shows that there were 29(28), 25(24), 29, 17, and 26(24) males and 45(44), 35, 36(35), 33, and 37(35) females affected for the control groups, low, mid, and high dose test groups. The number in ( ) is the data not including the interim sacrifice. There is no evidence that the malignant lymphoreticular tumors were induced by the test material. Note: There were about 70 mice per group for all groups.

4

2. Incidence of malignant lymphoreticular tumors in control Swiss-derived mice.

EPA Acc. No. 072204

The registrant submitted control data from three experiments (5 groups of male and female controls). The data showed that from 6-27% of the male controls and from 18-42% of the female controls had the malignant lymphoreticular condition. By comparison, 24 to 41% of the male mice and 47 to 64% of the female mice in this oncogenicity study with cypermethrin developed this condition.

The registrant also presented graphical data which showed that mortality and bodyweights of the mice in the cypermethrin oncogenicity study were similar to other studies run at the ICI facility although the incidences of lymphoreticular tumors were lower for these studies.

TB notes that the incidences of malignant lymphoreticular tumors in the cypermethrin oncogenicity study was higher than what would be expected for this strain of mouse. There is, however, no evidence that the presence of cypermethrin induced an increase in the number of mice affected, time of onset of this condition or caused an increase in the degree of malignancy, nor was there any relationship between mice having lung tumors and malignant lymphoreticular tumors.

Because malignant lymphoreticular tumors are common in mice, the impact of this condition is not considered to be sufficient to compromise the interpretation of the study. Dr. Louis Kasza, Toxicology Branch staff pathologist, concurs with this conclusion.

Two articles from the literature were presented to further document historical control data for lung neoplasms and the malignant lymphoreticular tumor condition. These articles can be found in EPA Acc. No. 072204.

Sher, S.P.

Tumors in Control Hamsters, Rats, and Mice: Literature Tabulation.

Dated March 1982

CRC Critical Reviews in Toxicology

Sher, S.P.

Review Article: Tumors in Control Mice: Literature Tabulation.

Toxicol. Appl. Pharmacol. 30:337-359 (1974)

*John Doherty* 2/21/84  
John Doherty  
Toxicology Branch  
Hazard Evaluation Division (TS-769)

*Added*  
2/20/84  
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• CYPERMETHRIN: LIFETIME FEEDING STUDY IN MICE  
TABLE 1  
INCIDENCE OF NEOPLASTIC FINDINGS (LIVER AND LUNG ONLY) IN INTERIM KILL GROUPS AT ONE YEAR

Tissue/ Pathological Findings	Male					Female				
	Dose Cypermethrin					Dose Cypermethrin				
	Oppm Group 1 Control	Oppm Group 2 Control	100ppm Group 3	400ppm Group 4	1600ppm Group 5	Oppm Group 1 Control	Oppm Group 2 Control	100ppm Group 3	400ppm Group 4	1600ppm Group 5
ALIMENTARY SYSTEM										
<u>Liver</u> No. examined	9	10	10	10	9	8	10	9	10	10
Hepatocellular nodule (A)	0	0	1	1	1	0	0	0	0	0
- benign										
Hepatocellular nodule (B)	1	1	0	1	1	0	0	0	0	0
- malignant										
HAEMOPOIETIC AND LYMPHORETICULAR SYSTEM										
Malignant lymphoreticular tumours	1	1	0	0	2	1	0	1	0	2
RESPIRATORY SYSTEM										
<u>Lungs</u> No. examined	9	10	10	10	9	8	10	9	10	10
Alveogenic tumour	3	0	1	1	2	1	1	0	0	1
- benign										
No. of animals examined	9	10	10	10	9	8	10	9	10	10

003647

*Zeroxed from study report*  
(EPA Acc. 072204)