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CYPERMETHRIN:

ASSESSMENT OF CHRONIC AND ONCOGENIC EFFECTS

A SUMMARY

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by

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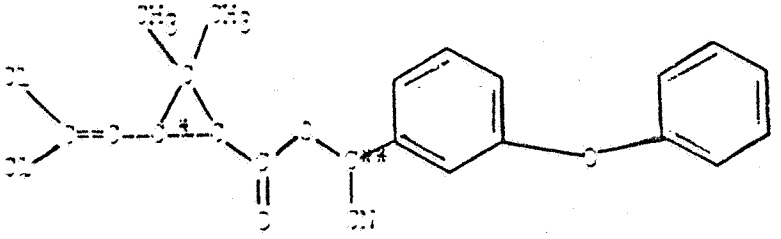
I. Introduction

Cypermethrin is the common name for (+/-) alpha-cyano-(3-phenoxyphenyl)-methyl (+/-) cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate. Cypermethrin is one of several synthetic pyrethroids which have been introduced over the past decade for a variety of insecticidal uses including both agricultural and domestic applications. Both ICI Americas Inc. and the FMC Corporation have requested establishment of tolerances for cypermethrin in/on raw agricultural commodities and as a food additive as well as registrations for their respective formulations. Cypermethrin is proposed to be marketed under the trade names CYMBUSH® and DEMON® (both ICI) and AMMO® (FMC). Technical cypermethrin is also known by the code names PP383, NRDC 149 and WL 43467. The basic toxicity data have been submitted chiefly by ICI Americas Inc. but is reportedly jointly owned with the FMC Corporation. The Shell Oil Company also has conducted many of the toxicity studies but it has not applied for tolerances or registrations. Many of the toxicity studies on the technical material were generated in European laboratories.

Review of the studies submitted to support the various uses of cypermethrin have indicated that this chemical is of moderate acute oral toxicity to rats (LD_{50} = 112-309 mg/kg) and that it is not teratogenic in rats or rabbits. The mouse oncogenicity study revealed increased incidences of benign neoplasms in the lungs of females in the high dose test group only. A similar neoplastic response was noted for permethrin, a synthetic pyrethroid which differs from cypermethrin only in the absence of the cyano group in the alpha carbon position.

This document is an overview of the long term feeding and oncogenicity studies on cypermethrin and is intended to assist in the making of regulatory decisions regarding the use of cypermethrin.



(+/-) alpha-cyano-(3-phenoxyphenyl)methyl (+/-) cis/trans-3-(2,2-dichloroethenyl) 2,2-dimethylcyclopropanecarboxylate.
*cis/trans position
**alpha carbon position

II. Availability and Usefulness of Long Term Feeding and Oncogenicity Studies

Three rodent long term chronic feeding and/or oncogenicity studies and a dog chronic feeding study have been submitted to EPA in support of requests to register products containing cypermethrin and establish tolerances for cypermethrin on various crops. These studies are listed in Table 1 below.

Table 1. List of chronic feeding and/or oncogenicity studies with cypermethrin.

Study Lab-year	Animals (No./sex/group)	Duration (weeks)	Dosage Levels
A. Rat studies			
Shell-1979	96 controls 48 each test group (including 48 controls and 24 test group rats scheduled for interim sacrifice)	104	0, 1, 10, 100, and 1,000 ppm
ICI-1982	64 (including 12 from each group scheduled for interim sacrifice)	104	0, 0*, 20, 150, and 1,500 ppm
B. Mouse Study			
ICI-1982	70 (including 9-10 from each group scheduled for interim sacrifice)	97(males) 101(females)	0, 0*, 100, 400, and 1,600 ppm
C. Dog Study			
ICI-1982	6	52	0, 1, 5, and 15 mg/kg/day (by gavage)

*For the ICI-1982 rat and mouse studies there were two separate sets of control groups run concurrently.

For these studies, the cypermethrin used ranged in purity from 88% to 98% and the ratio of the cis to trans isomers ranged from 55% cis and 45% trans to 50% cis and 50% trans. The differences in the percentage of purity for the different lots used and the small differences in the cis/trans ratio were not considered to be of sufficient magnitude to compromise interstudy comparisions. Each study was considered to have been conducted with essentially the same test substance.

Of these four studies, the ICI rat, mouse and dog chronic feeding studies were determined to be most useful for assessing the chronic feeding and oncogenic effects of cypermethrin in rodents and dogs.

The other rat study, Shell-1979, was determined to be of limited usefulness as both a chronic feeding and oncogenicity study because an insufficient number of test animals were actually dosed for the two year period.

III. Synopses of the Long-Term Feeding and Oncogenicity Studies

Shell-1979-Rat Study — Shell Toxicology Laboratory, # TLGR.1089.78, Feb. 1979. Refer to EPA Acc. No. 070564.

Five groups of male and female Wistar rats (SPF, obtained from the Shell Breeding Labs) were fed diets containing either 0, 1, 10, 100 or 1000 ppm of cypermethrin (cis/trans ratio of 1:1 from batch #30 with a purity of 98%). There were 96 males and females for the controls and 48 males and females for each test dose group. Interim sacrifices of 12 male and female controls and 6 males and females from each of the dose groups were made at 6 and 12 months. 24 control rats and 12 rats from each sex from each of the dosed groups were sacrificed at 18 months. Thus, there were 48 controls of each sex and 24 test group rats of each sex for each dose level scheduled to receive the control or test diets for the full 104 week feeding period.

At termination there were 12-17 males and 8-12 females surviving in the test groups receiving cypermethrin. The only test chemical related effects noted in this study were depressions in body weight (<10% at 1000 ppm). There was also some evidence of lower food consumption during the early weeks of the study. There were no consistent dose related effects noted on the several hematology and clinical chemistry parameters investigated. No urinalyses were performed. There were also no changes in organ weights and, in particular, the liver weights were not reported to be elevated.

Microscopic examination of a comprehensive set of tissues/organs was made for all surviving rats. Only the control, 100 and 1000 ppm dose groups were examined microscopically for the interim sacrificed animals.

No single tumor type or organ showed evidence of a positive neoplastic response to treatment. In particular, there were 5 incidences of lung adenocarcinoma, two among the controls (one male and one female), two in the groups receiving 100 ppm (one male and one female), and one in the male high dose test group. There were no adenomas reported in the lung tissue. There were no indications of dose related increases in nonneoplastic or possibly preneoplastic (hyperplastic) lesions.

ICI-1982-Rat Study — ICI Central Toxicology Laboratory, #CTL/P/669, June, 1982. Refer to EPA Acc. No. 071070 and 071071.

The test animals used were Wistar derived rats (SPF, obtained from the colony maintained at the Alderley Park facility in Cheshire, England). Five groups of 52 male and 52 female rats were given diets containing either 0 (two groups of 52 of each sex), 20, 150, or 1500 ppm of cypermethrin. Satellite groups of 12 male and 12 female rats per group were also maintained and designated for an interim sacrifice at 52 weeks. For the first six weeks of the study the rats in the high dose test group received 1000 ppm. The cypermethrin used for this study had a cis:trans ratio of 55:45 (nominal) and the purity was between 88% and 93%.

At termination of the study (after 104 weeks of dosing), there were 21-28 male rats and 22-27 female rats surviving per dosage group. Evaluation of the chronic feeding aspects of this study resulted in assigning a NOEL of 150 ppm. At 150 ppm, there were slight changes in body weight and slightly increased smooth endoplasmic reticulum in liver hepatocytes. These changes were considered to be an adaptive response rather than a toxic response. The LEL was determined to be 1500 ppm. At this level, there was body weight loss, increased liver weights and increased smooth endoplasmic reticulum in hepatocytes and some hematological and other clinical changes of a small magnitude. Although liver weight was increased 21% for females in the 1500 ppm group at 52 weeks (interim sacrifice), there was no significant increase in liver weight in this test group at termination.

All of the rats on the study were scheduled to receive a complete histopathologic evaluation which routinely included some 42 tissue/organ types.

There were no dose-related or treatment related nonneoplastic lesions noted.

No single tumor type or tissue/organ showed evidence of a positive neoplastic response to treatment. In particular, there was only a single incidence of an adenoma in the lungs (in a female control group).

ICI-1982-Mouse Study — ICI Central Toxicology Laboratories, CTL/P/687, June 1982. Refer to EPA Acc. No. 071072, 071073, 0711570 and 072204.

The test animals were Swiss strain mice (SPF, from the Alderley Park stock). Five groups of 70 male and 70 female mice were given either 0 control (2 groups) or 100, 400 or 1600 ppm of cypermethrin in their diets. Of these, 9-10 males and females per group were selected for an interim sacrifice at 52 weeks. The test material used for this study came from two lots which had purities of 91.5% and 94.2% and the cis:trans ratio was either 53:47 or 54:46.

No test chemical effect was noted on survival, but at termination (97 weeks for males and 101 weeks for females) there were only 9-15 males and 7-14 females per group indicating that overall survival to termination was poor. However, 50% of the mice (30 or more of males or females in each group) survived through about weeks 80-84.

Evaluation of the chronic feeding aspects of this study led to the conclusion that the NOEL was 400 ppm. There was noted a slight gain in liver weight at this level but this was considered to be an adaptive response and not a toxic response. At 1600 ppm (LEL) there were noted decreases in body weight (both males and females) that were most noticeable during the early phases of the study, increases in liver weight and generalized changes in blood elements. No clinical chemistries or urinalyses were performed.

A series of approximately 45 tissues/organs from each mouse were examined histologically from all mice dying during the study and the survivors, but not the mice sacrificed at the interim kill. Lung and liver tissues from the interim kill groups were later examined in response to Toxicology Branch's request.

There were no increases in nonneoplastic lesions which were considered to be related to the test material. In particular, there was no evidence that possible preneoplastic lesions in the lungs were related to the presence of cypermethrin in the diet.

There was noted an increase in the number of benign neoplasms in the lungs of females, but not in males, as indicated in the table below:

Table 2. Lung tumors in Swiss mice fed cypermethrin for their lifetime

	Lung Neoplasms						
	Males				Females		
Group	n	Benign[1]	Malignant[1]	Total	n	Benign[1]	Malignant[1]	Total
Control-1	70	7	1	8	69	5	0	5
Control-2	70	10	1	11	70	5	2	7
Low (100 ppm)	70	11	1	12	70	6	0	6
Mid (400 ppm)	70	7	0	7	70	7	1	8
High (1600 ppm)	70	9	3	12	70	14*	0	14*

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

1 Benign=adenoma, Malignant=carcinoma.

There was no treatment related increase in benign neoplasms among the male groups. The high dose male group had 3 incidences of mice with malignant neoplasms whereas there were only single incidences in each of the two control groups and one in the low dose group. The data for the slight increase in incidences of malignant neoplasms in the high dose male group are not statistically significant (using Fisher's One Tailed p Statistic, p=0.310) when compared with the controls. Moreover, chemically induced increased incidences of malignant lung neoplasms would be expected to be accompanied by increases in benign neoplasms (lung adenomas). In this study, the lung adenomas were uniformly distributed among the male test and control groups. It is the conclusion of Toxicology Branch that there is no evidence that cypermethrin was associated with induction of a neoplastic effect in the male mice.

As indicated in the above table, there is a statistically significant increase in the incidences of benign adenomas in the lungs of the females in the high dose test group. There were only a total of three mice affected with malignant neoplasms among the five female groups. Two of the mice affected with malignant neoplasms were in the control group. The third mouse affected with a malignant neoplasm was in the mid dose (400 ppm) group. Thus, there is no evidence that the presence of cypermethrin in the diet induced an increased degree of malignancy for lung tumors.

Most of the female mice affected with lung adenomas were in the terminal sacrifice groups. One female mouse in each of the two control groups and one female mouse in the high (1600 ppm) dose group among the mice sacrificed for the interim kill had a benign neoplasm (adenoma) in the lung. There is no evidence that cypermethrin in the diet decreased the latency for the onset of lung neoplasms in the females.

Many mice in both the male and female control and test groups developed malignant lymphoreticular tumors but there was no evidence that the frequency or time of onset was related to the presence of cypermethrin in the diet. No correlation was found between the mice having lymphoreticular tumors and lung tumors.

In this study, the high dose female test group was shown to be associated with a statistically significant increase in lung adenomas. No evidence was presented which suggested that cypermethrin decreased the latency period for the occurrence of this tumor type or increased the degree of malignancy.

ICI-1982-Dog Study ICI Central Toxicology Laboratory, #CTL/P/103, July 6, 1982. Refer to EPA Acc. No. 071069.

Cypermethrin was administered to four groups of 6 beagle dogs of each sex at dose levels of 0, 1, 5, and 15 mg/kg/day for a period of 52 weeks. The cypermethrin was dissolved in corn oil and the solution was administered to the dogs by capsule. The cypermethrin used was of 90.6% purity and the cis:trans ratio was 53.9:46.1.

No deaths or changes in body weight resulted. The dogs in the high dose group exhibited a loss in appetite, tremors, gait changes, incoordination, disorientation and hypersensitivity. There were no indications that nonneoplastic microscopic l[illegible] ions were induced by cypermethrin. No consistent dose-related or toxicologically meaningful changes in clinical blood chemistries, hematology, urinalyses or organ weights were noted.

The dogs dosed with 5 mg/kg/day of cypermethrin showed a five fold (males) and ten fold (females) increase in the reported incidences of passing of liquid stools. At 15 mg/kg/day there was about a thirty fold increase in the incidences of this symptom for both sexes. Thus, the NOEL for this study was determined to be 1.0 mg/kg/day.

IV. Mutagenicity and Metabolism Studies.

A battery of mutagenicity studies were submitted all of which were negative. The mutagenesis studies submitted and reviewed (see Table 3) included bacterial (Ames test) and yeast point mutation studies, a dominant lethal study in mice and an in vivo chromosomal abberration test (Chinese hamster bone marrow cells).

Metabolism studies in rats, mice and dogs were also submitted. The results of each of these studies indicated that cypermethrin is rapidly metabolized and excreted in the urine and that little if any residue remains behind in the body. Additional metabolism studies with cows and g[illegible]ted and reviewed by Residue Chemistry Branch.

The metabolic pathway for the degradation of cypermethr[illegible] in mamma[illegible] primarily through hydrolysis at the esteratic site to yield [illegible] cyclopropane carboxylate and 3-phenoxyphenyl benzyl alcohol, [illegible] acid. Conjugated forms of the parent compound and the 3-phenoxy [illegible]e also found. The major metabolites of cypermethrin are essentially similar to those of permethrin. During metabolism of cypermethrin the cyano group is eliminated from the molecule but there is no evidence that cyanide toxicity results from cypermethrin ingestion.

V. NOEL for Nononcogenic Effects.

The nononcogenic effects noted for each of the four long term studies are summarized in Table 4.

The first rat study (Shell-1979) is included although not as many parameters for hematology, blood chemistry or urinalysis were determined. This study shows no effects due to the test material except for slight weight loss at 1000 ppm (50 mg/kg/day). The second rat study (ICI-1982) also used the Wistar strain rat but more parameters were investigated and more rats were available at termination. Thus, the ICI-1982 rat study is considered as the best available chronic feeding study in rodents. The mouse study was designed as an oncogenicity study and not enough parameters were investigated to qualify this study as a chronic feeding study. The NOEL for the ICI-1982 rat study is 150 ppm (7.5 mg/kg/day).

The NOEL for the dog study was set at 1.0 mg/kg/day. At higher doses (5 and 15 mg/kg/day) there was clear evidence of gastrointestinal disturbance and in addition at 15 mg/kg/day the dogs exhibited tremors, gait changes, incoordination, disorientation, hypersensitivity and appetite loss.

The NOEL which Toxicology Branch recommends for determining the Acceptable Daily Intake (ADI) is 1.0 mg/kg/day based on the dog 1-year study. Customarily Toxicology Branch uses the most sensitive species in setting the ADI.

VI. Assessment of Oncogenic Effects

Review of the rat and mouse oncogenicity studies indicated an increased (statistically significant) incidence of benign lung adenomas in the high dose test group female mice. No other indications of a possible oncogenic effect in the rat and mouse oncogenicity studies were recognized by Toxicology Branch.

The definition of chemical carcinogenesis currently used by the International Agency for Research on Cancer (IARC)[1] is "the widely accepted meaning of the term 'chemical carcinogenesis' --- is the induction by chemicals of neoplasms that are not usually observed, the earlier induction by chemicals of neoplasms that are usually observed, and/or the induction by chemicals of more neoplasms than are usually found".

Cypermethrin has been demonstrated to increase the frequency of neoplasms that are usually found.

In addition to or supplemental to the criteria in the above definition, the following seven criteria are discussed separately with respect to the potential of cypermethrin to induce oncogenic effects in experimental animals.

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(1) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans , Volume 22, WHO, Lyon, France, March 1980, p. 14.

Table 3. Mutagenicity Studies with Cypermethrin

Study	Reference	Results	Conclusion
acterial Reverse utation Assay Ames Test)	ICI Study #CTL/P/595 Nov. 13, 1980 (EPA Acc. No. 070564)	No evidence of mutagenicity with or without metabolic activation (S9) in S. typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100.	Cypermethrin is not a mutagen under the conditions of this assay.
acterial Reverse utation Assay Ames Test)	Shell Toxicology Lab. Study #TLGR.80.059 June 1980 (EPA Acc. No. 070564)	No evidence of mutagenicity with or without metabolic activation (S9) in S. typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100 or in E. coli strains WP_2 and WP_2 uvrA.	Cypermethrin is not a mutagen under the conditions of this assay.
east Mutation ssay in vitro	"	No evidence of mutagenicity with or without metabolic activation (S9) in Saccharomyces cerevisiae JD1.	Cypermethrin is not a mutagen under the conditions of this assay.
ost Mediated ssay in vivo	"	No evidence of mutagenicity in Saccharomyces cerevisiae inoculated into mice pretreated with cypermethrin.	Cypermethrin is not a mutagen under the conditions of this assay.
hromosome Abberation Study Chinese Hamster one Marrow Cells)	Shell Research Ltd. TLGR.0136.77, Dec. 1977. (EPA Acc. No. 070564)	No evidence of chromosome abberrations after dosing with 40 mg/kg for two days (HDT)	Cypermethrin is not a mutagen under the conditions of this asay
ominant Lethal ssay in vivo (mice)	Shell Toxicology Lab. Study #TLGR.0042.77 December 1977 (EPA Acc. No. 070564)	No evidence of a dominant lethal mutagenic effect at 10 mg/kg for 5 days (highest dose tested).	Cypermethrin is not a mutagen under the conditions of this assay.

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Table 4 . Summary of selected nononcogenic effects of cypermethrin.

est Dose Level (1)	Rat Shell-1979	Rat ICI-1982	Mouse ICI-1982	Dog ICI-1982
0	No Effects	No Effects	No Effects	No Effects
).05 mg/kg/ day	No Effects	NT*	NT*	NT*
).50 mg/kg/ day	No Effects	NT*	NT*	NT*
.0 mg/kg/ day	NT*	No Effects	NT*	No Effects
.0 mg/kg/ day	No Effects	NT*	NT*	-gastrointestinal disturbances (liquid stools)
.5 mg/kg/ day	NT*	-slight decreases in body weight -slightly increased smooth endoplasmic reticulum in hepatocytes** (See next highest dose level for LEL for this study).	NT*	NT*
.5 mg/kg/ day	NT*	NT*	No Effects	-gastrointestinal disturbances (liquid stools) -tremors, gait changes, incoordination, disorientation, hypersensitivity, appetitte loss.
50 mg/kg/ day	-slight depressions in body weight gain (< 10%).	NT*	NT*	NT*

BLE 4 (continued).

st Dose evel (1)	Rat Shell-1979	Rat ICI-1982	Mouse ICI-1982	Dog ICI-1982
) mg/kg/ y	NT*	NT*	No Effects (except minor liver weight gain)	NT*
) mg/kg/ y	NT*	-increased smooth endoplasmic reticulum in hepatocytes -decreased body weight gain and food consumption -slight effects on several hematological parameters, minor changes in cholesterol, triglycerides, urea, and glucose -slight changes in urine volume, pH, S.G. -minor liver (increase) and kidney (decrease) weight changes.	NT*	NT*
) mg/kg/	NT*	NT*	-decreased body weight gain -slight effects in several hematological parameters -liver weight increases	NT*

*-Not tested at this level for this study.
This increase in smooth endoplasmic reticulum is considered to be an adaptive response rather than a toxicological response to cypermethrin treatment.
) Dosage levels for rats and mice in ppm were converted to dosage levels in mg/kg/day based on the following conversion factors:
rats-1 ppm = 0.05 mg/kg/day
mice-1 ppm = 0.15 mg/kg/day

1. Oncogenicity in different a) species, b) strains, c) sexes and d) organs.

As indicated above, a statistically significant increased incidence of neoplasms was observed in a single species (mouse), strain (Swiss), sex (female) and in only one organ (lung).

Additional support for determining that cypermethrin has the potential to induce neoplasms in lungs of female mice is provided by a comparision of the cypermethrin data with that of permethrin, a closely related structural congener. Refer to the EPA (Toxicology Branch) document entitled "Permethrin, Assessment of Chronic and Oncogenic Effects, A Summary" by O.E. Paynter, E.R. Budd, and B.D. Litt, dated September 3, 1982. This document describes a statistically significant increased incidence of lung and liver tumors in female Charles River CD-1 (Swiss derived) mice in one study and a "suggestive" increase in lung tumors in female CFLP (Swiss derived) mice in another study. In a third study performed with ICI Alderley Park (Swiss derived) mice, the same mice used in the cypermethrin study, slightly increased incidences of lung adenomas and/or adenocarcinomas were observed in female mice, but it could not be concluded that this increase was related to treatment with permethrin. Females of the Charles River CD-1 strain, however, showed clear evidence of lung and liver oncogenicity due to exposure.

2. Presence of rare neoplasms and number of different types of neoplasms in one or more species.

Neither the two rat nor the mouse oncogenicity studies showed evidence that neoplasms, considered to be rare neoplasms, were induced by the presence of cypermethrin in the diet.

The overall net production of tumors for each of the rat studies indicated a uniform distribution of tumors among the dosed groups and the control groups. When all of the lung tumors are eliminated from the count, the overall net production of tumors in the mouse study also indicated a uniform distribution of tumors among the dosed groups and the controls.

Thus, cypermethrin was not shown to be related to the induction of rare neoplasms or to a general increase in various types of tumors.

3. Increased incidence of malignant neoplasms.

There was no evidence that the degree of malignancy for the various neoplasms observed in either of the rat oncogenicity studies was affected by the presence of cypermethrin in the diet.

In the mouse study, the type of lung tumor which showed an increased frequency at the high dosage level (only) and in females (only) were adenomas, which are benign and not malignant. There were three females with malignant lung tumors. Of these, 2 were in one control group and the third was in the group receiving 400 ppm of cypermethrin in the diet. Thus, there was no indication that cypermethrin increased the degree of malignancy of neoplasms in the female mouse lungs.

Many of the mice in the cypermethrin mouse study developed malignant lymphoreticular tumors. However, there was no correlation between the presence of cypermethrin in the diet and the incidence of the mice affected.

4. Decreased latency (time to tumor discovery).

In the mouse oncogenicity study with cypermethrin, most mice affected with lung tumors were in the terminal sacrifice group and there was no evidence that cypermethrin induced an earlier onset of lung or other neoplasms.

There was no evidence of decreased latency for development of tumors in either of the rat studies.

5. Dose response relationship.

The evidence of a positive oncogenic response in the mouse study was present only in the high dose female test group.

6. Mutagenicity tests.

Neither the bacterial and yeast point mutation studies, the dominant lethal study, nor the chromosomal abberration study (with Chinese hamsters) resulted in a positive mutagenic response. Thus, there is no evidence that cypermethrin is mutagenic. Similar negative results were obtained when permethrin was tested in a battery of mutagenesis studies.

On this basis, it is apparent that the induction of lung tumors by cypermethrin is not related to mechanisms directly involving the genetic apparatus of the cell.

7. Spontaneous tumor incidence in untreated mice (for lung tissue).

Toxicology Branch has available data from other oncogenicity studies using the same strain and source of Swiss mouse as was used for the oncogenicity study with cypermethrin. The spontaneous tumor incidence in the lungs for the controls in these studies and for the cypermethrin study are as follows:

Table 5. Spontaneous lung tumor incidence in mice at the ICI Central Toxicology Laboratory (Alderley Park stock).

Study	Number of Tumor Bearing Animals* Males	Females
ICI-Permethrin Study (See Paynter, Budd, and Litt Assessment dated Sept. 3, 1982)	11/70 (15.7%)	11/70 (15.7%)
ICI-Study (data submitted to EPA Feb. 13, 1981 by the ICI and FMC Corporations in support of permethrin)	Group 1 9/59 (15.2%)	9/59 (15.2%)
	Group 2 8/60 (13.3%)	4/59 (6.8%)
ICI- Cypermethrin Study (See synopsis in this document)	Group 1 8/70 (11.4%)	5/69 (7.2%)
	Group 2 11/70 (15.7%)	7/70 (10.0%)

*Both lung adenomas and carcinomas are included for the cypermethrin and permethrin studies. The numbers provided for the third study did not indicate whether or not both benign and malignant tumors were included.

The above table indicates that the range for males is 11.4 to 15.7% and the range for females is 6.8 to 15.7%. The incidence of tumors in the high dose female test group in the oncogenicity study with cypermethrin was 20.0%. 20.0% is in excess of the available historical control data for the spontaneous incidence of tumors in the lungs of the female Swiss mouse used for the cypermethrin assay.

Current Toxicology Branch policy regarding the use of historical control data is that it should not substitute entirely for the concurrent control data. In the case with cypermethrin, there were two concurrent control groups of 70 mice and each of these gave nearly the same low spontaneous rate of lung tumor development. Use of the concurrent control data supports a conclusion that cypermethrin in the diet was related to the increased incidence of lung tumors in the high dose female test group mice.

The Task Force of Past Presidents of the Society of Toxicology has discussed the use of historical control data as follows:

"The following propositions may be taken as scientifically useful in the evaluation of a chemical carcinogenic response, with distincitions drawn between the use of concurrent control and historical control data. (1) If the incidence rate in the concurrent control group is lower than in the historical control groups, but the incidences rates in the treated groups are within the historical control range, the differences between the treated and control groups are not biologically significant. (2) If the incidence rates in the treated groups are higher than the historical control range but not statistically significantly greater than the concurrent control incidence, the conclusion would be that there is no relation to treatment, but with the reservation that this result could be a false negative resulting from some flaw. (3) If the incidence rates in the treated groups are significantly greater than in the concurrent controls, and greater than the historical control range, a treatment effect may be present which is unlikely to be a false positive test".

(Task Force of Past Presidents, Animal data in hazard evaluation: Paths and pitfalls. Fundam. and Appl. Toxicol., 2:101-107,1982)

In the case of cypermethrin, the incidence rate in the high dose female test group is greater than both the concurrent control groups and the available historical control groups. Thus, consistent with the criteria of the Task Force of Past Presidents, it is unlikely that the effect noted with cypermethrin is a false positive.

VII. Conclusions

On the basis of all available toxicological data, Toxicology Branch has determined that there is sufficient evidence to conclude that, at a dosage level of 1600 ppm in the diet for a lifetime, cypermethrin exhibits a low oncogenic potential in female mice.

The available data support nononcogenic NOEL's of 1.0 mg/kg/day in the dog (one year study) and 150 ppm in the rat.