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PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

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MEMORANDUM

DATE: 0ctober 23, 2002

SUBJECT: Permethrin: Report of the Cancer Assessment Review Committee (Third Evaluation)

FROM: Jessica Kidwell Jessica Kidwell
Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)

TO: Yung Yang, Toxicologist
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The Cancer Assessment Review Committee met on August 21, 2002 to re-evaluate the carcinogenic potential of Permethrin. Attached please find the Final Cancer Assessment Document.

cc: K. Dearfield
R. Hill
J. Pletcher
Y. Woo

CANCER ASSESSMENT DOCUMENT

THIRD EVALUATION OF THE CARCINOGENIC POTENTIAL OF PERMETHRIN

PC Code 109701

FINAL REPORT

October 23, 2002

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

PERMETHRIN CANCER ASSESSMENT DOCUMENT FINAL

DATA PRESENTATION: Yung G. Yang
Yung Yang, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell
Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

Karl Baetcke	Karl R. Baetcke
William Burnam	
Marion Copley	Marion Copley
Kerry Dearfield	Kerry Dearfield
Virginia Dobozy	Virginia Dobozy
Esther Rinde	Esther Rinde
Joycelyn Stewart	Joycelyn E Stewart
K. Clark Swentzel	K. Clark Swentzel
Linda Taylor	Linda Lee Taylor
Yin-Tak Woo	See attached sheet

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report and statistical analysis of data, respectively)

John Pletcher, Consulting Pathologist	See attached sheet
Lori Brunsman, Statistical Analysis	Lori L. Brunsman

OTHER ATTENDEES: Virginia Fornillo, HED/SIMB

TOTAL P.02

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Yin-Tak Woo Yin Tak Woo

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** TX CONFIRMATION REPORT ** AS OF OCT 15 2002 10:02 PAGE.1

PATHOLOGY ASSOC

COMMAND #117

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EXECUTIVE SUMMARY

Previously, permethrin has been reviewed by the Health Effects Division's Carcinogenicity Peer Review Committee (CPRC) and classified as a Category C carcinogen based on lung and liver tumors in female mice. The CPRC also recommended that a low dose linear extrapolation model with a Q_1* of 1.84×10^{-2} $(mg/kg/day)^{-1}$ be applied to the animal data for the quantitative risk assessment based on the female mouse lung (adenoma and/or carcinoma) tumors.

On August 21, 2002, the Cancer Assessment Review Committee (CARC) of the Health Effects Division met to re-evaluate the carcinogenic potential of permethrin with new data submitted by the FMC Corporation.

The CARC concluded that permethrin showed evidence of carcinogenicity based on the following:

- Permethrin induced reproducible benign lung tumors in female mice and liver tumors in both male and female CD-1 mice. The new carcinogenicity/reversibility study confirms the permethrin-induced benign lung and liver tumors in female mice seen in the FMC Mouse II study. The CARC also reconsidered the 1995 Pathology Work Group (PWG) report on a reassessment of the lung tumor slides from the FMC mouse II study and determined it to be acceptable. The PWG report indicated that permethrin induced benign lung tumors. The CARC also confirmed a previous CPRC report that there were statistically significant increases in liver adenomas in male mice at all doses (and outside historical control range at all doses) with a significant dose-related trend in the FMC Mouse II study (Memo, E. Rinde, April 7, 1989, "Peer Review of Permethrin").

- No statistically significant increase in malignant lung or liver tumors were seen in male or female mice in either of the above mentioned studies.

- There was no evidence of carcinogenicity in male or female Wistar rats. However, the CPRC (1989) questioned the adequacy of the permethrin doses to assess carcinogenic potential in female rats. The CARC revisited the adequacy of dosing issue and determined that the dosing was adequate to assess carcinogenicity in both sexes.

- The evidence of carcinogenicity in the Long-Evans rat study was equivocal. The CPRC (1989) also stated that rats (both sexes) did not receive adequate doses. The CARC concluded that the adequacy of the dose can not be resolved at this time for the Long-Evans rats.

- The acceptable genetic toxicology studies on permethrin indicate that the compound is not mutagenic in the *Salmonella typhimurium*/mammalian activation gene mutation and the mouse lymphoma assays. Permethrin is also negative for clastogenicity in a mouse bone

marrow micronucleus assay and does not cause unscheduled DNA synthesis in primary rat hepatocytes. There is no evidence of increased dominant lethal mutations in the germinal cells of mice. Although the submitted mutagenicity studies do not indicate mutagenic activity, the CARC acknowledged that two published studies from Barrueco *et al.* (1992, 1994) suggested that permethrin has clastogenic activity (e.g., micronuclei and aberrations inductions) in cultured human lymphocytes and Chinese hamster ovary cells, but only in the absence of S9 activation and at cytotoxic levels.

- Structure activity relationship (SAR) indicated that Cypermethrin is a close structural analogue to permethrin. Cypermethrin is classified as a Category "C" carcinogen (possible human carcinogen) based on female mice lung tumors (adenomas and combined) with no Q_1*. The evidence (common tumor, one species (mouse), one sex (female), 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 (Cancer Peer Review Committee, 1988).

- There are no mode of action studies available at this time.

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the CARC, by majority vote, classified permethrin as **"Likely to be Carcinogenic to Humans"** by the oral route. The Committee also recommended using a linear low-dose extrapolation approach for the quantification of human cancer risk based on female mouse lung tumors (combined adenomas and carcinomas) using the data from the PWG assessment.

I. INTRODUCTION

On August 21, 2002, the Cancer Assessment Review Committee (CARC) of the Health Effects Division met to re-evaluate the carcinogenic potential of permethrin.

II. BACKGROUND

In December 1988, the Carcinogenicity Peer Review Committee (CPRC) met to evaluate the database of permethrin for its carcinogenicity potential. The CPRC concluded that permethrin should be classified as a Category C (possible human carcinogen) based on evidences of lung and liver tumors in female mice (Memo, Rinde 1989). The CPRC also recommended that a low dose linear extrapolation model with a Q_1* of 1.84×10^{-2} $(mg/kg/day)^{-1}$ be applied to the animal data for the quantitative risk assessment based on the female mouse lung (adenoma and/or carcinoma) tumors (Memo, Fisher 1988).

In May 1989, the FIFRA Scientific Advisory Panel (SAP) met and commented on the CPRC's assessment on carcinogenicity of permethrin. The SAP recommended that permethrin be classified as a Category C oncogen and did not recommend any quantitative risk assessment because of the relative weak tumorigenicity and the lack of mutagenicity data (Memo, Jaeger 1989).

Subsequently, the CPRC met again in June 1989 to consider comments and recommendations made by the SAP. The CPRC reaffirmed its prior classification of permethrin as a Group C (possible human carcinogen) and again recommended that a quantitative risk assessment be performed (Memo, Budd, 1989).

In December 1995, the FMC Corporation submitted a study entitled "Permethrin Oncogenicity Reclassification" and requested that the carcinogenicity classification of permethrin be changed. The study was a reassessment of the lung tumor slides from the FMC "mouse II" study (MRID 00062806) as conducted by a Pathology Work Group (PWG) (Butler et al. 1995). However, the study was determined to be unacceptable due to the absence of acceptable pathology peer reviews of both the lung and liver tissues (Memo, John Doherty, 1996, HED Doc #011927).

In January 2002, the Health Effects Division revised the process for re-evaluating pesticides classified as Group C carcinogens with a Q_1* for quantification of human cancer risk.
Under this new policy, permethrin is a candidate for potential reclassifying Group C carcinogens to "Suggestive" or "Likely"(HOT sheet, January 18, 2002).

In February 2002, the FMC Corporation submitted a new study entitled "Permethrin technical: 100-week carcinogenicity/reversibility study in mice with administration by the diet." (MRID 45597105). A document entitled "Rationale for Downgrading the Carcinogenicity Classification of Permethrin" also was submitted (MRID 45597101). Again, the FMC Corporation asked that the classification of carcinogenicity for permethrin be changed.

III. DISCUSSION

The following issues were discussed at the 8/21/02 CARC meeting. The "*CARC's Response*" is noted directly after each issue. The discussion of lung tumors is presented first, followed by the discussion of liver tumors.

A. LUNG TUMORS

1. The acceptability of the Pathology Work Group (PWG) report on the FMC "Mouse II" lung pathology.

Previously, the Agency has determined that the "peer review" of the lung tissue from FMC Mouse II study is unacceptable because only 9-15% of the available animals per dose group were assessed by the peer review work group. In addition, the PWG did not review liver tissue which is also a target organ for carcinogenicity (Memo, J. Doherty, 1996, HED Doc. 011927).

The FMC argued that "A reassessment of all animals by the peer review panel is not required by the procedures outlined in the PR Notice 94-5." A further review of the PWG report suggested that the report may be acceptable. The PWG report stated that "Sections of lung from all mice were retrieved from the archive of FMC. These sections were reviewed by Dr. W. H. Butler. Sections of lung from all female animals where there was a difference in diagnosis between the EPL review (by Dr. Ackerman at the request of EPA) and Dr. Butler were blinded and placed in random order. All the blinded slides were examined by the group and the individual diagnoses recorded. The consensus opinion was then recorded. When the consensus was not unanimous the blinded slides were examined on a multiheaded microscope and the consensus was confirmed. The results of the consensus were then compared with the EPL diagnoses." The protocol has met the Agency's procedural requirement (PR Notice 94-5, August 24, 1994).

The results of the PWG report indicated that there were fewer animals diagnosed with carcinoma by the PWG than were used in the HED's CPRC of permethrin (EPL's review). However, there were also more animals diagnosed with adenoma in the PWG report. Therefore, the PWG reported approximately the same number of total tumors as were indicated by the EPL assessment (Table 1).

Table 1. Comparison of the readings of permethrin-induced lung tumors in female CD-1 mice in the FMC "mouse II" from the EPL and the PWG assessments.

Dose Level	Adenomas		Carcinoma	
	EPL	PWG	EPL	PWG
Control	9/71 (13%)	11/74 (15%)	6/66 (9%)	5/74 (7%)
20 ppm	17/68* (25%)	20/76 (26%)	7/62 (11%)	3/76 (4%)
2500 ppm	24/68** (35%)	27/76** (36%)	11/59 (19%)	7/76 (9%)
5000 ppm	29/69** (42%)	34/75** (45%)	15/62* (24%)	8/75 (11%)

Significance of pairwise comparison with control. (* P <0.05; ** P<0.01)
Data extracted from pages 4 and 7 of the PWG report.

CARC RESPONSE: The CARC accepts the findings of the Pathology Working Group. The PWG review showed an increase in benign adenomas for the 2500 and 5000 ppm females and no significant increase in the incidence of pulmonary carcinomas in female mice in the FMC Mouse II study.

2. Review of lung tumors in the new study submitted by the FMC Corporation entitled "Permethrin technical:100-week carcinogenicity/reversibility study in CD-1 mice with administration by the diet. (MRID 45597105)".

In the 100-week feeding mouse study (MRID 45597105), female mice were exposed to permethrin at a dose of 5000 ppm in the diet for various lengths of time followed by removal of treatment of permethrin (recovery). Significantly increased incidences of lung adenomas were observed in female mice treated for 52, 65, or 78 weeks and sacrificed immediately; however, no increased incidence of lung carcinomas was observed (Table 2). During the recovery period, the incidences of lung adenoma continued to increase compared to the control; however, there was no increase in lung carcinomas in treated mice (Table 3). The results of the new study support the findings of the PWG that more adenomas than carcinomas were developed following permethrin exposure (Table 4). It is to be noted that the exposure time frames in these studies were different (104 weeks in the FMC mouse II study and 78 weeks in the new study).

TABLE 2: Incidences of neoplastic microscopic findings in the lung of female CD-1 mice after various weeks of treatment with 5000 ppm Permethrin in the diet [a]

Organ/Finding	Control 39 wks.	Treated 39 wks.	Control 52 wks.	Treated 52 wks	Control 65 wks.	Treated 65 wks.	Control 78 wks.	Treated 78 wks.
Bronchiolo-alveolar adenoma	4/50 (8%)	9/50 (18%)	5/49 (10%)	14/43** (33%)	4/50 (8%)	17/56** (30%)	7/67 (10%)	30/71** (42%)
Bronchiolo-alveolar carcinoma	0/50	0/50	0/49	0/43	0/50	0/56	1/67	0/71

[a] Data obtained from Table 9, page 18 of the DER, MRID 45597105.
[b] Number of mice with lesion/total number of mice examined in the study group including those that died prior to the scheduled study termination.
* Significantly different (p<0.05) from the control, Fisher's exact test by the reviewer.
** Significantly different (p<0.01) from the control, Fisher's exact test by the reviewer.

TABLE 3: Incidences of neoplastic microscopic findings in the lung of female CD-1 mice after various weeks of treatment with 5000 ppm Permethrin in the diet followed by various recovery periods [a]

Organ/ Finding	Control 78 wks.	Treated 39 wks. Recover to 78 wks.	Treated 52 wks. Recover to 78 wks.	Treated 65 wks. Recover to 78 wks.	Control 101 wks.	Treated 39 wks. Recover to 101 wks.	Treated 52 wks. Recover to 101 wks.	Treated 65 wks. Recover to 101 wks.	Treated 78 wks. Recover to 101 wks.
Bronchiolo-alveolar adenoma	7/67 (10%)	22/72** (31%)	28/66** (42%)	37/74** (50%)	15/107 (14%)	44/103** (43%)	50/107** (47%)	46/94** (49%)	50/103** (49%)
Lung/ carcinoma	1/67	1/72	1/66	3/74	1/107	4/103	2/107	2/94	2/103

[a] Data obtained from Table 10, page 19 of the DER, MRID 45597105.
[b] Number of mice with lesion/total number of mice examined in the study group including those that died prior to the scheduled study termination.
* Significantly increased (p<0.05) compared to the corresponding control group at week 78 or 101, 2x2 chi square test by the reviewer.
** Significantly increased (p<0.01) compared to the corresponding control group at week 78 or 101, 2x2 chi square test by the reviewer.

Table 4. Comparison of the readings of permethrin-induced lung tumors in female CD-1 mice in the FMC "mouse II" from the EPL and the PWG assessments vs new 78-week feeding study

Dose Level	Adenomas			Carcinoma			Combined		
	EPL	PWG	78-week	EPL	PWG	78-week	EPL	PWG	78-week
Control	9/71 (13%)	11/71 (15%)	7/66 (11%)	6/66 (9%)	5/65 (8%)	1/65 (2%)	15/71 (21%)	16/71 (23%)	8/66 (12)
5000 ppm	29/69** (42%)	34/69** (49%)	30/67** (45%)	15/62* (24%)	8/63 (13%)	0/65 (0%)	44/69** (64%)	42/69** (61%)	30/67** (45%)

Revised data (animals dying before first tumor not included) are provided by the FMC, May 20, 2002.
Significance of pairwise comparison with control. * P <0.05; ** P<0.01

CARC RESPONSE: In the reversibility study, the increased incidence of lung adenomas in female mice confirmed the results of the FMC Mouse II study and the PWG findings. No increased incidence of lung carcinomas was observed in the reversibility study. In the reversibility study, lung adenomas first appeared at 39 weeks with the incidence of lung adenomas continuing to increase during the recovery period; however, there was no increase in lung carcinomas in treated mice (e.g., the pulmonary adenomas did not progress to malignancies).

B. LIVER TUMORS

1. Status of the PWG report on the liver tumors in the FMC mouse II study.

The PWG did not review the slides from the liver. The FMC argued that "a peer review of liver tissue in both female and male mice is not essential in order to reconsider the removal of a q* designation." However, the CPRC report (1989) stated that "Statistically significant increases in liver adenomas in male mice at all doses, and outside historical control range at all doses, with a significant dose-related trend; statistically significant increases in combined liver adenoma/carcinoma at mid- and high-dose in males. Statistically significant increase in liver adenomas in female mice at the mid- and high-dose, both were outside historical control range, with a significant dose-related trend; statistically significant increases in combined liver adenoma/carcinoma at mid- and high-dose, with a significant dose-related trend."

CARC RESPONSE: The CARC accepts the findings of the Pathology Working Group which addressed lung tumors only.

2. Review of liver tumors in the new study submitted by the FMC Corporation entitled "Permethrin technical:100-week carcinogenicity/reversibility study in mice with administration by the diet. (MRID 45597105)".

In this study, there were no significant increases of liver tumors in female mice administered 5000 ppm in the diet immediately after exposure to permethrin for 39, 52, or 65 weeks (Table 5). Eosinophilic adenomas were increased after 78 weeks of treatment and after the recovery period. There were significant increases in the incidences of basophilic and eosinophilic hepatocellular adenomas in female mice administered 5000 ppm in the diet for 39, 52, or 78 weeks followed by recovery to week 101 (Table 6). No increases in hepatocellular carcinoma incidences were seen and the time to tumor onset for the adenomas was not different in treated animals compared to the controls.

TABLE 5: Incidences of neoplastic microscopic findings in the liver after various weeks of treatment with 5000 ppm Permethrin in the diet [a]

Organ/Finding	Control 39 wks.	Treated 39 wks.	Control 52 wks.	Treated 52 wks	Control 65 wks.	Treated 65 wks.	Control 78 wks.	Treated 78 wks.
Basophilic hepatocellular adenoma	1/44[b]	0/44	0/49	0/43	1/49	1/56	1/67 (1%)	3/72 (4%)
Eosinophilic hepatocellular adenoma	0/44	0/44	0/49	2/43	0/49	2/56	1/67 (1%)	7/72* (10%)
Hepatocellular carcinoma	0/44	0/42	0/49	0/43	0/49	0/56	1/67	2/72

[a] Data extracted from Table 9, page 18 of the DER, MRID 45597105.
[b] Number of mice with lesion/total number of mice examined in the study group including those that died prior to the scheduled study termination.
* Significantly different ($p<0.05$) from the control, Fisher's exact test by the reviewer.
** Significantly different ($p<0.01$) from the control, Fisher's exact test by the reviewer.

TABLE 6: Incidences of neoplastic microscopic findings in the liver after various weeks of treatment with 5000 ppm Permethrin in the diet followed by various recovery periods [a]

Organ/ Finding	Control 78 wks.	Treated 39 wks. Recover to 78 wks.	Treated 52 wks. Recover to 78 wks.	Treated 65 wks. Recover to 78 wks.	Control 101 wks.	Treated 39 wks. Recover to 101 wks.	Treated 52 wks. Recover to 101 wks.	Treated 65 wks. Recover to 101 wks.	Treated 78 wks. Recover to 101 wks.
Basophilic hepatocellular adenoma	1/67 (1%)	1/72 (1%)	3/66 (5%)	4/74 (5%)	1/106 (1%)	10/101** (10%)	7/106* (7%)	0/94 (0%)	9/104** (9%)
Eosinophilic hepatocellular adenoma	1/67	0/72	1/66	1/74	2/106 (2%)	3/101 (3%)	5/106 (5%)	4/94 (4%)	10/104* (10%)
Hepatocellular carcinoma	1/67	0/72	0/66	0/74	0/106	1/101	0/106	0/94	0/104

[a] Data extracted from Table 10,page 19 of the study report, MRID 45597105.
[b] Number of mice with lesion/total number of mice examined in the study group including those that died prior to the scheduled study termination.
* Significantly increased ($p<0.05$) compared to the corresponding control group at week 78 or 101, 2x2 chi square test by the reviewer.
** Significantly increased ($p<0.01$) compared to the corresponding control group at week 78 or 101, 2x2 chi square test by the reviewer.

Increased liver weights and liver adenomas development following permethrin exposure has been suggested to be an adaptive effect caused by enzyme induction. In this 100-week mouse study, the total enzyme activities of cytochrome P450 (CYP) mixed function oxidases (CYP, CYP1A, CYP2B, CYP2E1, and CYP3A) in the livers of animals treated for 52 weeks were increased by 142-283%, and the activity of CYP4A was increased by 829% compared to the control values. A literature study (Butler, W. H., 1996) submitted by the Registrant suggested that hepatic eosinophilic lesions developed from centrilobular hypertrophy resulted from enzyme induction and should not be considered as tumors at all. However, the CARC concluded that no data were provided to support Butler's opinion.

CARC RESPONSE: In the reversibility study, the increased incidence of liver adenomas in female mice confirmed the results of the FMC Mouse II study. Consistent with the Mouse II study, no increased incidence of liver carcinomas was observed in the reversibility study.

IV. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

1. Carcinogenicity

The CARC concluded that permethrin showed evidence of carcinogenicity due to the following:

- Evidence of carcinogenicity was seen in the lung of CD-1 female mice and the liver of both male and female CD-1 mice. These two tumors types were benign and reproducible in two CD-1 mouse studies (1979 FMC Mouse II study and 2000 Carcinogenicity/Reversibility study). The reversibility study (using female mice only) confirmed the permethrin-induced increase in benign lung and liver tumors that were seen in the FMC Mouse II study and the PWG report (for lung only). Also, no increased incidence of liver carcinomas was observed in the reversibility study.

MOUSE - Female

- In the carcinogenicity/reversibility study (MRID 45597105), significantly increased incidences of lung adenomas were observed in female CD-1 mice that were treated for 52, 65, or 78 weeks and sacrificed immediately; however, no increased incidence of lung carcinomas was observed. The incidence of lung adenomas at 52, 65, and 78 weeks, respectively, was 14/43 (8%), 17/56 (30%), and 30/71 (42%) at 5000 ppm versus 5/49 (10%), 4/50 (8%), and 7/67 (10%) for the controls.

- In the carcinogenicity/reversibility study with the recovery period, lung adenomas first appeared at 39 weeks (early onset) (statistically significant) in female CD-1 mice with the incidence of lung adenomas continuing to increase during the recovery period (not reversible); however, there was still no increase in lung carcinomas in treated mice.

- The results of the carcinogenicity/reversibility study confirmed the results of the FMC Mouse II and the findings of the PWG that showed more adenomas than carcinomas were developed following permethrin exposure. A comparison of the readings of permethrin-induced lung tumors in female mice in the FMC Mouse II using the PWG assessment and the reversibility study showed a statistically significant increase in lung adenomas at 5000 ppm for both the PWG [34/69 (49%) at 5000 ppm compared to 11/71 (15%) for controls] and the reversibility study [30/67 (45%) at 5000 ppm compared to 7/66 (11%) for controls] and in combined lung adenomas/carcinomas for the PWG [42/69 (61%) at 5000 ppm compared to 16/71 (23%) for controls] and the reversibility study [30/67(45%) at 5000 ppm compared to 8/66 (12%) for controls]. No statistically significant increase in lung carcinomas was seen in either the PWG assessment or the reversibility study.

- In the carcinogenicity/reversibility study, there were significant increases in hepatocellular adenomas (both basophilic and eosinophilic combined) in female mice after 78 weeks of treatment and after the recovery period. The incidence of hepatocellular adenomas (basophilic + eosinophilic) at 78 weeks was 10/72 (14%) at 5000 ppm vs. 2/67 (3%) for the controls. There were also significant increases in the incidences of hepatocellular adenomas (basophilic + eosinophilic) in female mice administered 5000 ppm in the diet for 39, 52, or 78 weeks followed by recovery to week 101. No increases in hepatocellular carcinomas were seen.

MOUSE-Male

- The CARC concurred with the CPRC report (1989) that there were statistically significant increases in liver adenomas in male CD-1 mice at all doses (and outside historical control range at all doses) with a significant dose-related trend in the FMC Mouse II study. The new carcinogenicity/reversibility study did not test male mice.

RAT

- There was no evidence of carcinogenicity in male or female Wistar rats. Previously, the CPRC questioned that female rats did not receive adequate doses of permethrin to assess carcinogenic potential. The CARC revisited the adequacy of dosing issue and determined that the dosing was adequate to assess carcinogenicity in both sexes for Wistar rats. This was based on liver effects and tremors and hypersensitivity observed in both sexes at 2500 ppm in a chronic toxicity/carcinogenicity study in Wistar rats (MRID 92142123). In addition, a 28-day range-finding study showed 100% mortality in both sexes at 10,000 ppm and 50% mortality in males fed 5000 ppm (MRID 00120267). The maximum dose in the chronic toxicity/carcinogenicity study was chosen to be 50% of the dietary LD_{50} for males. A 14-day oral neurotoxicity study (MRID 00071952) in male Wistar rats given doses ranging from 2500 to 7500 ppm showed mortality at 5000 and 7500 ppm, decreased body weight gain at doses ≥2500 ppm, and tremors up to 7500 ppm. Tremors were transient up to 3000 ppm; tremors persisted at doses ≥3750 ppm during the study.

- The carcinogenicity evidence in the Long-Evans rat study was equivocal. The CPRC also questioned that rats (both sexes) did not receive adequate doses. The CARC determined that the adequacy of the dose can not be resolved at this time for the Long-Evans rat.

2. Mutagenicity

- The acceptable genetic toxicology studies on permethrin indicate that the compound is not mutagenic in the *Salmonella typhimurium*/mammalian activation gene mutation and the mouse lymphoma assays. Permethrin is also negative for clastogenicity in a mouse bone marrow micronucleus assay and does not cause unscheduled DNA synthesis in primary rat hepatocytes. There is no evidence of increased dominant lethal mutations in the germinal cells of male mice. Although the submitted mutagenicity studies do not indicate mutagenic activity, the CARC acknowledged that two published studies from Barrueco *et al.* (1992, 1994) suggested that permethrin has clastogenic activity (e.g., micronuclei and aberrations inductions) in cultured human lymphocytes and Chinese hamster ovary cells, but only in the absence of S9 activation and at cytotoxic doses.

3. Structure Activity Relationship

- Cypermethrin is a close structural analogue to permethrin. Cypermethrin is classified as a Category "C" carcinogen (possible human carcinogen) based on female mice lung tumors (adenomas and combined) with no Q_1*. The evidence (common tumor, one species (mouse), one sex (female), 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 (Cancer Peer Review Committee, 1988)

4. Mode of Action Studies

- There are no mode of action studies available at this time.

V. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the CARC, by majority vote, classified permethrin as **"Likely to be Carcinogenic to Humans"** by the oral route. There was considerable discussion among the CARC about the merits of a "Suggestive", instead of a "Likely", classification. Some members felt that since only benign lung and liver tumors were observed in only one species (i.e., mouse), no carcinomas were observed (i.e, no progression to malignancy), and since permethrin is not mutagenic, the classification of "Suggestive" was supported. However, in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the majority of the CARC classified permethrin as "Likely to be Carcinogenic to Humans" by the oral route based on the following weight-of-the-evidence considerations:

1. Two tumor types were seen in one species. Lung adenomas were seen in female CD-1 mice and hepatocellular adenomas were seen in both male and female CD-1 mice. These two tumors types were reproducible in two mouse studies (1979 FMC Mouse II study and 2000 Carcinogenicity/Reversibility study).

2. The lung tumors in female mice had an early onset (39 weeks) and were not reversible up to 104 weeks recovery period in the reversibility study. The liver tumors also were not reversible in this study.

3. The tumor findings in the Long-Evans rat were considered equivocal.

4. Structure activity relationship indicated that Cypermethrin is a structural analogue of permethrin. Cypermethrin is classified as a Category "C" carcinogen (possible human carcinogen) with no Q_1* based on female mice lung tumors (adenomas and combined).

VI. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The Committee recommended using a linear low-dose extrapolation approach for the quantification of human cancer risk based on female mouse lung tumors (combined adenomas and carcinomas) using the data from the PWG assessment.

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