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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

JUN 12 1995

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Pyrethrins

FROM: John Doherty, Ph.D. 5/17/95
Review Section IV
Toxicology Branch I
Health Effects Division (7509C)
and
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Science Analysis Branch
Health Effects Division (7509C)

TO: Richard Keigwin
Product Manager #10
Insecticide-Rodenticide Branch
Registration Division (7505C)
and
Alan Dixon/Bruce Sidwell
Product Manager #53
Special Review and Reregistration Division (7508W)

THROUGH: Stephanie R. Irene Ph.D.
Acting Director, Health Effects Division (7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on February 22, 1995 to discuss and evaluate the weight-of-the-evidence on pyrethrins with particular reference to carcinogenic potential. The CPRC was unable to complete its classification of pyrethrins because of questions in the accuracy of the histopathological evaluation for several tissue types.

The CPRC, however, determined that there was sufficient evidence of carcinogenic activity based primarily on thyroid tumors in both sexes in the rat carcinogenicity study. In this study, follicular cell adenomas were determined to be statistically significantly increased by pair wise comparison in all female dose groups and in the mid and high dose male groups. On this basis, the CPRC recommends using the low dose linear extrapolation model for carcinogenic risk assessment based on follicular cell adenomas in female rats.

The use of the rat thyroid data for linear risk assessment and the classification of pyrethrins for carcinogenicity will be reconsidered pending submission by the registrants of additional data and its review by the Agency. The additional information and rereading of certain slides and preparation of new slides will be required of the registrant as follows.

1. Rat Study. In addition to thyroid tumors, there were also statistically significant increases in skin (keratoacanthomas), ovary (thecal cell), liver and parathyroid tumors. The control and high dose groups but not the low and mid dose groups were assessed microscopically for the skin and ovary. The incidence of keratoacanthomas in the control (8%) and high (23%) dose groups were much higher than the historical control data (0.4%) and this leads to questions regarding the pathology diagnostic criteria for this study.

2. Mouse lung tumors. In the mouse carcinogenicity study certain lung tumor types were determined by the CPRC consulting pathologist to far exceed any published incidence data for mouse lung neoplasms in the CD-1 strain mouse. Because the incidence of alveolar/bronchiolar carcinomas in the male mice in the 2500 and 5000 ppm groups is statistically significantly increased compared to controls, lung tumors are an important consideration in the carcinogenic classification of pyrethrins. However, because the incidence of alveolar/bronchiolar adenomas are so different from industry historical findings, the question is raised that the pathology diagnostic criteria for classification of lung tumors in this study could also be quite different from historical control.

The CPRC committee recommends that a pathology peer review for both the rat and mouse carcinogenicity studies be conducted. This peer review[1] should include:

1. Re-evaluation of the targets or potential targets in all groups. This would include at least:

In rats:	In mice:
thyroid	lung
skin	
parathyroid	
liver	
ovary	

2. Re-evaluation of all neoplasms in all dose groups.

3. Re-evaluation of all tissues in a random 10% of the males and females in the high dose and control groups.

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[1]Refer to EPA PR Notice 94-5 (8/24/94).

A. Individuals in Attendance at this meeting:

1. Peer Review Committee: [Signatures indicate concurrence with the peer review unless otherwise stated.]

Stephanie Irene

William Burnam

Karl Baetcke

Marcia Van Gemert

Kerry Dearfield

Elizabeth Doyle

Marion Copley

Hugh Pettigrew

Yin Tak Woo

2. Reviewers: [Non-committee members responsible for data presentation; signature indicates technical accuracy of the panel report.]

John Doherty[2]

Lori Brunsman

Lucas Brennecke[3] (PAI/ORNL)

3. Other Attendees:

Bernice Fisher (HED) and Amber Aranda (OGC).

[2]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

[3]Signature indicates concurrence with pathology report.

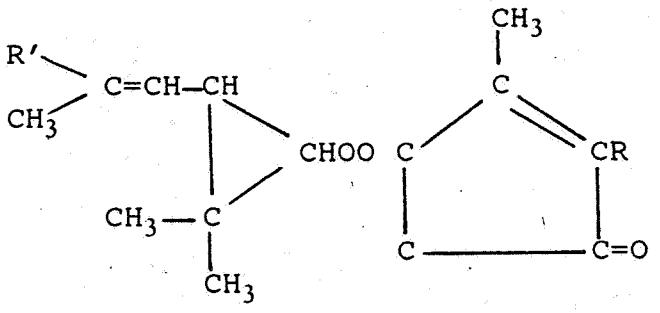
B. **Material Reviewed:**

The material available for review consisted of DER's, "one liners", data summaries prepared and/or supplied by Dr. John Doherty and tables and statistical analysis prepared by Lori Brunsman. The material is attached to the file copy of this report.

C. **Background Information:**

Pyrethrins are alkaloids extracted from chrysanthemum flowers that have been used as insecticides for hundreds of years. The concentrated extract from these flowers is called pyrethrum. As insecticides they have many uses particularly indoors and for some selected food crops. Their relative instability to light limits their use outdoors and on food crops.

The Tox Chem Number of pyrethrins is 715 and the Chemical Abstracts Registry Number (CAS No.:) is 121-21-1. The PC Code No.: 069001. Since pyrethrins are a mixture of several isomers, no structure is available in the Chemical Structure Data Bank.



Basic structure of pyrethrins[4]. R: $-CH_2CH=CHCH=CH_2$, $-CH_2CH=CHCHCH_3$ or $-CH_2CH=CHCH_3$ and R': $-CH_3$ or $-COOCH_3$

D. **Evaluation of Carcinogenicity Evidence:**

1. **Rat Carcinogenicity Study.** Reference: MRID No.: 41559501. IRDC Study No.: 556-011, July 12, 1990. , HED Document No.: 010798.

a. Experimental Design: Five groups of 60/sex Charles River CD strain rats were dosed as control (two separate groups), 100, 1000 or 3000 ppm of pyrethrum extract in their diets for a scheduled 104 weeks. These dose levels correspond to 0, 4.37,

[4]From Farm Chemicals Handbook (1985), p. C 198.

42.9 or 130 mg/kg/day for males and 0, 5.39, 55.5 or 173 mg/kg/day for females, respectively.

b. Discussion of Tumor Data: There were increases in thyroid follicular cell adenomas in females at all dose levels but only the high dose group had an increase in combined adenomas and carcinomas. In males in the mid and high dose groups, both thyroid follicular cell adenomas and adenomas and carcinomas combined were increased. At 3000 ppm there were increased hepatocellular adenomas and ovarian thecal cell tumors in females and parathyroid adenomas and keratoacanthomas in males.

Tables 1 (thyroid, males), 2 (parathyroid and skin tumors), 3 (thyroid, females), 4 (liver, females) and 5 (ovary) below illustrate the tumor incidence for these tumor types.

Keratoacanthomas were significantly increased in all dosed male groups. This analysis, however, is potentially misleading because of the few number of rats for which the skin was actually examined microscopically (note the denominators in Table 2). Usually the skin is examined microscopically in response to a macroscopic lesion and skin cancers are usually visible macroscopically.

The registrant did not provide historical control data in response to HED's request prior to the Peer Review meeting. In a later submission (MRID No.: 43567701) selected historical control information were provided for thyroid and ovary for up to 29 studies conducted between January 1981 and October 1993. These data indicated that in males thyroid follicular adenomas were infrequent occurring at a frequency of 0-4 incidents or 0-6.78% and carcinomas occurred at a rate of 0-3 incidents or 0-4.4%. Thyroid follicular hyperplasia was reported in only 5 of the 29 studies and at a incidence rate of 0-4. In females, the adenomas and carcinomas were present at a frequency of 0-2 incidents or 0-3.33%. Again thyroid follicular cell hyperplasia was infrequent being reported in only three studies (up to two incidents). Ovary "granulosa thecal cell tumor" was reported in only one study with one incident. Thus, thyroid tumors in males and females exceeded the historical control range and ovarian thecal cell tumors greatly exceed the historical control range. No historical control data were provided for liver, parathyroid or skin tumors.

Table 1 Male Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0[l]	100	1000	3000
Adenomas (%)	2[a]/118 (2)	3/59 (5)	**5/59** (8)	**5/60** (8)
p =	**0.043***	0.207	**0.042***	**0.044***
Carcinomas (%)	1/118 (1)	1[b]/59 (2)	2/59 (3)	2/60 (3)
p =	0.142	0.557	0.258	0.263
Combined (%)	3/118 (3)	4/59 (7)	**7/59** (12)	**7/60** (12)
p =	**0.020***	0.169	**0.017***	**0.018***

+ Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.
[a]First adenoma observed at week 77, dose 0 ppm.
[b]First carcinoma observed at week 101, dose 100 ppm.
[l] The two control groups were combined for this analysis.

Table 2. Male Parathyroid and Skin Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0[l]	100	1000	3000
Parathyroid Adenomas (%)	1/106 (1)	0/55 (0)	0/57 (0)	**4[a]/56** (7)
p =	**0.007****	0.658[n]	0.650[n]	**0.049***
Skin Keratoacanthomas (%)	9/118 (8)	**7[b]/24[#]** (29)	**6/14[#]** (43)	**14/60** (23)
p =	**0.016***	**0.007****	**0.001****	**0.004****

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53 for parathyroid and before week 50 for skin.
[n]Negative change from control.
[a]First parathyroid adenoma observed at week 103, dose 3000 ppm.
[b]First skin keratoacanthoma observed at week 50, dose 100 ppm.
[#]Only those animals in the 100 and 1000 ppm dose groups with macroscopic observations were examined microscopically for skin keratoacanthomas.
[l] The two control groups were combined for this analysis.

Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level. If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Female Thyroid Follicular Cell Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0[1]	100	1000	3000
Adenomas (%)	0/80 (0)	**2/41** (5)	**3[a]/45** (7)	**5/44** (11)
p =	**0.004****	**0.019***	**0.002****	**0.002****
Carcinomas (%)	3[b]/100 (3)	0/51 (0)	0/53 (0)	1/50 (2)
p =	0.572[n]	-	-	-
Combined (%)	3/100 (3)	2/51 (4)	3/53 (6)	6/50 (12)
p =	**0.014***	0.398	0.142	**0.026***

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
[n]Negative trend.
[a]First adenoma observed at week 89, dose 1000 ppm.
[b]First carcinoma observed at week 76, dose 0 ppm.
[1]The two control groups were combined for this analysis.

Table 4. Female Hepatocellular Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0[1]	100	1000	3000
Adenomas (%)	1/58 (2)	0/25 (0)	1/34 (3)	**5[a]/35** (14)
p =	**0.000****	-	0.319	**0.001****
Carcinomas (%)	1[b]/42 (2)	0/20 (0)	0/28 (0)	0/32 (0)
p =	0.799[n]	-	-	-
Combined (%)	2/58 (3)	0/25 (0)	1/34 (3)	5/35 (14)
p =	**0.001****	-	0.541	**0.006****

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
[n]Negative trend.
[a]First adenoma observed at week 99, dose 3000 ppm.
[b]First carcinoma observed at week 105, dose 0 ppm.
[1]The two control groups were combined for this analysis.

Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level. If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 5. Female Ovarian Theca Cell Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0[1]	100	1000	3000
Tumors (%)	0/42 (0)	0/2[#]	0/0[#]	4[a]/32 (12)
p =	n/a	n/a	n/a	**0.0097****

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
[a]First tumor observed at week 105, dose 3000 ppm.
[#]Only 3 animals in the 100 ppm dose group and 1 animal in the 1000 ppm dose group were examined microscopically for ovarian theca cell tumors.
[1]The two control groups were combined for this analysis.
Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level. If *, then $p < 0.05$. If **, then $p < 0.01$.

Keratoacanthomas (23%), liver adenomas in females (14%) and ovary thecal cell tumors (12%) in the high dose groups were all in excess of published historical control ranges.

c. Non-neoplastic Lesions: Accentuated lobulation of the liver (a macroscopic observation, not supported by histopathology) was increased in the male 100 (18% affected), 1000 (28% affected) and 3000 (23% affected) ppm dose groups as compared with only 10% and 13% in each of two control groups.

Hyperplasia of the thyroid was increased in both sexes with there being 3.3%, 0%, 3.3%, **8.3% ($p < 0.05$) and 11.7% ($p < 0.5$)** for males and 0%, 3.3%, 1.7%, 1.7% and **8.3%** for females for the control-1, control-2, 100, 1000 and 3000 ppm dose groups, respectively.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential: There was no effect on survival in males. Survival in females was significantly increased. Body weight decreases in the high dose group were considered minimal (maximum 6-7% in males and 7-9% in females) and were not always statistically significant. Body weight gain for the first 26 weeks was decreased 12-14% for males and 18-24% for females. Liver weight was marginally increased in the high dose groups (11-17% for both sexes). Aside from the effect noted in the liver (weight increases and accentuated lobulation, supported by large increases in plasma levels of SGPT and SGOT in the high dose but not supported by histopathology) and thyroid (limited increase in hyperplasia), there is little indication of toxicity. The dose levels are considered adequate.

2. **Mouse Carcinogenicity Study.** Reference: MRID No.: 41559401. IRDC STUDY No.: 556-013, July 5, 1990. DER Document No.: 010798.

a. Experimental Design Five groups of 60/sex CD-1 strain mice were dosed as either control (two separate groups), 100, 2500, or 5000 ppm pyrethrins in their diets for 18 months. These dose levels correspond to 0, 13.8, 346 or 686 mg/kg/day in males and 0, 16.6, 413 or 834 mg/kg/day in females, respectively.

b. Discussion of Tumor Data Increases in lung carcinomas were noted as indicated in mid and high dose male groups. Tables 6 and 7 illustrate the lung tumor data for males and females. For females, the low and mid dose groups have decreases for adenomas and combined adenomas and carcinomas.

The registrant did not provide historical control data in response to HED's request as of January 1995. Historical control data obtained from the Charles River Breeding Lab (Spontaneous Neoplastic Lesions in the Crl:CD-1®[ICR]BR Mouse, prepared by Dr. Patricia Lang) indicate that in males, bronchiolar/alveolar carcinoma has a mean of 1.4% and a range of **0-4.0%** based on examination of 8 studies with a total of 496 mice. The **5%** and **6%** frequencies obtained for the males in the 2500 and 5000 ppm dose groups are outside of the historical control range.

In females, "bronchiolar/alveolar adenoma" had a mean of 2.8% and a range from 0 to 8.8%. Thus, this study has a very high background rate of these lung tumors for females (32%). It is noted that "alveolar type II carcinoma" had a rate of 14.6% and the range was 0 to 14.3% for males; for females it was 2.0% and the range was 0-20%.

c. Non-neoplastic Lesions Pathological changes in the liver included increased incidence of "vacuolar change/fatty" in males only (1.7%, 1.7%, 3.3% 13.3% and 23.3% mice affected in the control-1, control-2, 100, 2500 and 5000 ppm dose groups, respectively). Liver weight (absolute, relative to body and brain) was also increased in males (23-26% for all three comparisons) and females (20-23%) in the 2500 ppm dose group and higher (up to 47%) for the 5000 ppm female dose group. Female liver weight was reduced (9%, $p < 0.01$, for all three comparisons) in the low dose group.

Table 6. Male Alveolar/Bronchiolar Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0[l]	100	2500	5000
Adenomas	30[a]/120	15/58	13/57	17/59
(%)	(25)	(26)	(23)	(29)
p =	0.346	0.520	0.453[n]	0.355
Carcinomas	0/110	1/55	**3[b]/55**	**3/54**
(%)	(0)	(2)	(5)	(6)
p =	**0.016***	0.333	**0.036***	**0.034***
Combined	30/120	16/58	16/57	20/59
(%)	(25)	(28)	(28)	(34)
p =	0.119	0.422	0.397	0.143

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 31 for adenomas and combined, and before week 53 for carcinomas.
[n]Negative change from control.
[a]First adenoma observed at week 31, dose 0 ppm.
[b]First carcinoma observed at week 54, dose 2500 ppm.
[l]The two control groups were combined.

Table 7. Female Alveolar/Bronchiolar Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0[l]	100	2500	5000
Adenomas	36/114	11[a]/58	5/57	22/55
(%)	(32)	(19)	(9)	(40)
p =	0.182	0.056[n]	**0.001**[n]**	0.182
Carcinomas	4[b]/118	0/59	2/58	2/56
(%)	(3)	(0)	(3)	(4)
p =	0.341	0.194[n]	0.645	0.629
Combined	40/118	11/59	7/58	24/56
(%)	(34)	(19)	(12)	(43)
p =	0.127	**0.025***[n]	**0.001**[n]**	0.164

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53 for adenomas, and before week 43 for carcinomas and combined.
[n]Negative change from control.
[a]First adenoma observed at week 59, dose 100 ppm.
[b]First carcinoma observed at week 43, dose 0 ppm.
[l]The two control groups were combined.
Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level. If *, then $p < 0.05$. If **, then $p < 0.01$.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential Survival was not affected. No effects on body weight or body weight gain were evident. Liver weight increases in the 2500 and 5000 ppm dose groups for both sexes and slight decreases (9%) in the 100 ppm female dose group were evident. Also the male 2500 and 5000 ppm dose groups had increased incidence of "vacuolar fatty change". The dose levels are considered adequate.

E. Additional Toxicology Data on Pyrethrins.

1. Metabolism Studies with pyrethrins are limited because of problems in trying to make radiolabelled isomers of the several chemicals that are the active ingredients. Available evidence indicates that the pyrethrins are readily absorbed by the gastro-intestinal tract and apparently rapidly metabolized and excreted. Their degradation or detoxification is inhibited by piperonyl butoxide and MGK-264 and other inhibitors of mixed function oxidase.

2. Mutagenicity/Genetic Toxicity Pyrethrins have been tested in each of the three major categories of mutagenicity/genetic toxicity testing of gene mutations, structural chromosomal aberrations and other genotoxic effects. No evidence of positive mutagenicity or genetic toxicity was apparent in studies deemed to be acceptable to the Agency.

a) Salmonella assay - (MRID No.: 41344701; HED Document No.: 007998). No indications of a positive response in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation at dose levels of 292, 585, 877, 2924, 5848 and 8772 ug/plate.

b) Chromosome aberration study in Chinese Hamster Ovary (CHO) cells - (MRID No.: 41344601; HED Document No.: 007998). No evidence of induced chromosome aberrations in the presence of S9 metabolic activation (concentrations tested: 0, 0.,04, 0.08, 0.16 and 0.32 ul/ml and absence of metabolic activation (concentrations tested: 0.01, 0.02, 0.04, and 0.08 ul/ml. Concentrations are uncorrected for pyrethrum and are for pyrethrin extract.

c) Unscheduled DNA synthesis in rat primary hepatocytes - (MRID No.: 41344501; HED Document No.: 008308). Not demonstrated to increase the net nuclear grain counts over the concentration range of 0, 0.3 and 1.0 ul/ml.

These studies satisfy the three categories of mutagenicity testing as per the "old" pre-1991 mutagenicity battery requirements. There is no concern for mutagenicity based on these studies.

3. Structure-Activity Correlations Pyrethrins are plant alkaloids. Pyrethroids are synthetic chemicals based on the structure of the natural pyrethrins and supposedly share the

basic vinyl cyclopropane adduct, but differ considerably in their side chains. Some pyrethroids such as permethrin and cypermethrin have been indicated to cause lung and/or liver tumors in mice. A summary table prepared by Dr. P. Hurley of HED is included with the file copy of this report which indicates the status of carcinogenicity testing of pyrethroids.

b. A factor to be considered under this category is the relationship of pyrethrins to piperonyl butoxide (PC # 067501) and MGK-264 (PC # 057001). Piperonyl butoxide (PC No.: 067501) and MGK-264 inhibit mixed function oxidases (MFO) and both produce similar non-neoplastic lesions in the liver of rats and/or mice and have been indicated as producing at least some increases in hyperplasia and/or tumors in the follicular cells of the thyroid in rats. Pyrethrins are usually formulated with PBO and/or MGK-264 and pyrethrins are metabolized by the MFO. Thus, all three chemicals interact with the same physiological system in the liver. These three chemicals also produce hyperplasia/metaplasia in the upper respiratory tract of rats in subchronic (90-day) inhalation toxicity studies. MGK-264 and pyrethrins have been presented to the HED Carcinogenicity Peer Review Committee.

4. Acute, Subchronic, and Chronic Toxicity Studies

Pyrethrins of low acute toxicity having acute LD_{50}s of 1.40 (0.87 - 2.26)g/kg orally for both sexes combined and > 2000 mg/kg for dermal. They are not regarded as dermal sensitizers in guinea pigs. The series 81-8 neurotoxicity screen study indicated NOEL and LELs of 20 and 63 mg/kg with there being fine tremors and decreases in motor activity in females. No evidence of developmental toxicity was present in rat HDT = 75 mg/kg/day) or rabbit (HDT = 250 mg/kg/day) studies.

The subchronic studies in rats and mice were submitted as range finding studies that accompanied the carcinogenicity studies. Liver weight and body weight effects were the principle findings.

Subchronic Inhalation toxicity. Piperonyl butoxide as well as pyrethrins and MGK-264 have all been indicated to cause hyperplasia and metaplasia in the larynx of rats in 90-day subchronic inhalation toxicity studies. Hyperplasia is in certain cases considered as a preneoplastic condition and that continued exposure would result in tumors in the affected region(s).

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on pyrethrins in a weight of the evidence determination of carcinogenic potential.

1. *Rat and mouse carcinogenicity studies.*

Charles River Crl CDBR strain rats (60/sex) were dosed as control (two groups), 100, 1000 or 3000 ppm of pyrethrins for a scheduled 104 weeks. Based on moderate decreases in body weight and gain and the presence of hyperplasia in the thyroid of some males (maximum 8.3% of animals affected in high dose group), the dose levels were not considered excessive.

All female dose levels were increased in thyroid follicular adenomas but only the high dose group was increased in combined adenomas and carcinomas when assessed by pair wise comparison to controls. At 1000 and 3000 ppm, thyroid follicular adenomas and combined thyroid follicular adenomas and carcinomas were increased in males. At 3000 ppm, hepatocellular adenomas and combined adenomas and carcinomas and ovarian thecal cell tumors were increased in females. Parathyroid adenomas and keratoacanthomas were increased in males.

CD-1 strain mice (60/sex) were dosed as control (2 groups), 100, 2500 or 5000 ppm of pyrethrins for 18 months. Survival and body weight were not affected. Liver weight was increased and there was "vacuolar fatty change" in this organ. The dose levels were not considered excessive. The high dose of 5000 ppm was considered adequate based on the results of the 90-day mouse study. The dose was also close to the limit dose of 7,000 ppm.

Lung alveolar/bronchiolar carcinomas in the 2500 and 5000 ppm dose male groups were increased.

2. There are limited structure activity relationship data. Some but not all pyrethroids which are synthetic chemicals based on the structure of pyrethrins have been shown to be associated with cancer in rats and/or mice but these chemical structures differ significantly from the natural pyrethrins while generally retaining the tricyclic ring and vinyl side chain. One example is that permethrin and cypermethrin are associated with lung tumors in the same strain of mice.

3. Pyrethrins did not demonstrate mutagenic or genotoxic activity in a variety of studies.

4. Several concerns about the standards used for diagnostic criteria for histopathology were raised and these issues need to be resolved in order to more completely assess the carcinogenic potential of pyrethrins.

5. Carcinogenicity in animals -- Pyrethrins

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the Committee concludes that exposure to pyrethrins resulted in increased incidences of tumors at multiple sites in Charles River rats: thyroid (adenomas) in both sexes; liver (adenomas) and ovarian theca cell tumors in females; parathyroid adenomas and skin keratoacanthomas in males. In male CD-1 mice there was also an increase in tumors of the lung (carcinomas). Structurally related chemicals (permethrin and cypermethrin) are also associated with lung tumors in CD-1 mice.

The relevance of the tumor data to an evaluation of pyrethrin potential for human carcinogenicity is discussed elsewhere in this document.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The consensus of the CPRC was that pyrethrins demonstrated carcinogenic activity at various sites in male and female rats and in male mice but that classification into a particular group should be deferred until slides in both species are re-read[5].

The CPRC felt there was enough evidence of carcinogenic potential, based on the available evidence, to conclude that a low dose linear extrapolation model based on female rat thyroid adenomas and carcinomas combined be used to estimate human risk from registered uses.

This decision was based on the following determinations by the CPRC:

1. In the rat, at doses considered minimally adequate and certainly not excessive, benign thyroid adenomas were increased in both males and females. These occurred significantly in all doses in the female and at the mid and high doses in the male. There was a compound related increase in both sexes in combined adenomas and carcinomas that was driven by the increase in adenomas.

2. In the female rat, there was an increase at the high

[5]Refer to memorandum from Lucas H. Brennecke, DVM, DACVP, Pathology Consultant, Health Effects Division Dated 30 March 1995. Copy Appended.

dose in hepatocellular adenomas and combined adenomas and carcinomas. The increase in combined tumors was driven by the increase in adenomas (considered to be an unusual tumor for females of this strain).

3. In male rats, there were increases in parathyroid adenomas and skin keratoacanthomas which were considered supportive of a positive tumor response. In female rats, there was a significant pair wise increase in ovarian theca cell tumors at the high dose when compared to controls. The low and mid doses were not analyzed for this tumor. It was believed that a reading of these slides would aid in the interpretation of these unusual tumors.

4. Pyrethrins were associated with an increase (trend and pair wise at the mid and high dose) in alveolar/ bronchiolar carcinomas in male mice.

5. The mutagenicity studies were considered adequate but negative and there is no mutagenicity concern.

6. Structure activity relationships did not add to the weight of evidence for pyrethrins *per se*.

The carcinogenicity classification of pyrethrins will be reconsidered pending CPRC review of the laboratory's pathology peer review. As indicated above, the CPRC felt there was enough evidence of carcinogenic potential to conclude that in the interim, the low dose linear extrapolation model based on female rat thyroid adenomas be used to estimate human risk due to registered uses.