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6

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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No.: 0053410

MEMORANDUM

DATE: May 25, 2005

SUBJECT: **RESMETHRIN:** Report of the Cancer Assessment Review Committee
PC Code: 097801

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

TO: William Dykstra, Toxicologist (RRB4)
Rebecca Daiss, Risk Assessor (RRB4)
Health Effects Division (7509C)

Katie Hall, PM
Reregistration Branch 2, Special Review & Reregistration Division (7508C)

The Cancer Assessment Review Committee met on April 13, 2005 to evaluate the carcinogenic potential of RESMETHRIN. Attached please find the Final Cancer Assessment Document.

cc: J. Pletcher
Y. Woo

JUN 14 2005

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CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
RESMETHRIN

PC CODE 097801

FINAL REPORT
May 25, 2005

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

RESMETHRIN CANCER ASSESSMENT DOCUMENT FINAL

DATA PRESENTATION: William Dykstra, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

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

Karl Baetcke

Lori Brunsman, Statistician

William Burnam, Chair

Marion Copley

Vicki Dellarco

Kit Farwell

Abdallah Khasawinah

Nancy McCarroll

Esther Rinde

Jess Rowland

Linda Taylor

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist See attached sheet

OTHER ATTENDEES: Whang Phang (HED/RRB1), Becky Daiss (HED/RRB4), Susan Hummel (HED/RRB4), Katie Hall (SRRD/RB2), Ray Kent (HED/RRB4), Dirk Helder (SRRD), Snthini Ramasamy (HED/RRB4)

RESMETHRIN CANCER ASSESSMENT DOCUMENT FINAL

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William Dykstra, Toxicologist

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EXECUTIVE SUMMARY

On April 13, 2005, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of resmethrin.

William Dykstra of Reregistration Branch 4 presented the chronic toxicity/carcinogenicity study in Sprague-Dawley rats and the carcinogenicity study in CD-1 mice. In a chronic toxicity/carcinogenicity study (MRID 43601601), technical resmethrin (85% a.i.) was administered in the diet to Sprague-Dawley rats (65/sex/dose) at dose levels of 0, 250, 1000, or 2500 ppm (0, 10.4, 41.8, and 107.2 mg/kg/day in males and 0, 12.8, 51.7, and 131.4 mg/kg/day in females, respectively) for 24 months. In a 2-year carcinogenicity study, CD-1 mice (50/sex/dose) were fed diets containing resmethrin technical (84.8% a.i.) at dose levels of 0, 0, 300, 600, or 1200 ppm for 24 months. The time-weighted average dose for these dietary levels corresponded to 0, 0, 43.4, 84.3, or 169.3 mg/kg/day for males and 0, 0, 52.9, 105.5, or 208.9 mg/kg/day for females.

The CARC concluded the following

Carcinogenicity

Rat

- In female rats, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 250, 1000, and 2500 ppm (0, 12.8, 51.7, 131.4 mg/kg/day) dose groups, respectively, were as follows:

  Adenomas: 0/56 (0%), 0/52 (0%), 1/54 (2%), 3/54 (6%)
  Carcinomas: 1/51 (2%), 0/45 (0%), 0/48 (0%), 11/45 (24%)
  Combined: 1/56 (2%), 0/52 (0%), 1/54 (2%), 14/54 (26%)

  Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for liver carcinomas, liver adenomas and/or carcinomas combined, all at $p<0.01$. There was a significant increasing trend at $p<0.01$, and a significant difference in the pair-wise comparison of the 2500 ppm dose group with the controls at $p < 0.05$, for liver adenomas. The incidences of liver adenomas (6%) and carcinomas (24%) at the high dose were outside the historical control mean (0.5% for adenomas and carcinomas) and range (0-2.2%, adenomas; 0-4%, carcinomas) for the testing laboratory. The liver tumor response was primarily carcinomas. Therefore, the CARC considered the tumors at the high dose to be treatment-related.

- There were no treatment-related increase in tumors for male rats.

▸The CARC considered the high dose of 2500 ppm to be adequate, but not excessive, to assess the carcinogenicity of resmethrin in male and female rats. In females, this was based on neurotoxic clinical signs, decreased body weight gain, non-neoplastic lesions and tumors at the high dose. In males, the dose was considered adequate based on neurotoxic clinical signs and anemia.

Mouse

▸In male mice, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 300, 600, 1200 ppm dose groups (0, 43.4, 84.3, or 169.3 mg/kg/day), respectively, were as follow:

Adenomas: 9/96 (9%), 9/45 (20%), 12/47 (26%), 15/47 (32%)
Carcinomas 2/85 (2%), 2/39 (5%), 4/35 (11%), 6/37 (16%)
Combined: 11/96 (11%), 10/45 (22%), 14/47 (30%), 18/47 (38%)

Male mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1200 ppm dose group with the controls, for liver adenomas, carcinomas and adenomas and/or carcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 600 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, both at $p<0.01$. There were also significant differences in the pair-wise comparisons of the 300 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, and of the 600 ppm dose group with the controls for liver carcinomas, all at $p<0.05$. The incidence of liver adenomas at the high dose (32%) exceeded the historical control mean for the testing lab (8%) as well as the range of the supplier (0-17%). The incidence of liver carcinomas at the high dose (16%) also exceeded the mean of the testing laboratory (6%) and the range of the supplier (1-14%). This was a robust response, with both benign and malignant tumors occurring at two non-excessive doses.

▸ No treatment-related tumors were seen in female mice.

▸ The CARC considered dosing in male mice to be adequate, but not excessive, to assess the carcinogenic potential of resmethrin based on decreased survival at 600 and 1200 ppm. Although no overt treatment-related signs of toxicity were observed in females mice at any dose in this study, the CARC considered dosing in females at the high dose of 1200 ppm to be adequate to assess the carcinogenicity potential of resmethrin based on a previously submitted mouse carcinogenicity study (MRID 00083319) where survival in both sexes at termination was significantly reduced at 1000 ppm (40% less than controls). There was only a slight decrease in survival in this newer study at 600 and 1200 ppm (19% and 14% less than the control group, respectively).

Mutagenicity

- There is no concern for mutagenicity and, overall, the data do not suggest a mutagenic mode of action for resmethrin.

Structure Activity Relationship (SAR)

- The liver appears to be a target organ for some Type 1 pyrethroids (e.g. bifenthrin, permethrin, natural pyrethrins, and tetramethrin)

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified Resmethrin as "Likely to Be Carcinogenic to Humans". This decision was based on increased incidences of benign and malignant liver tumors in female rats and male mice. There was no concern for mutagenicity.

The Committee recommended that a linear low-dose extrapolation approach for the quantification of human cancer risk be applied to the experimental animal tumor data and that quantifications of risk be estimated for liver tumors in female rats and male mice.

I. INTRODUCTION

On April 13, 2005, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of resmethrin.

II. BACKGROUND INFORMATION

Resmethrin ([5-(phenylmethyl)-3-furanyl]methyl-2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecaroxylate) or 5-benzyl-3-furyl-methyl (1RS)-cis,trans-chrysanthemate is an established pyrethroid pesticide used for flying and crawling insect control for food handling establishments, household, greenhouse, indoor landscaping, mushroom houses, industrial, stored product insects and mosquito insect control for USDA meat and poultry inspection programs and West-Nile virus. Resmethrin is also known as benzofuroline. The PC code is 097801 and the CAS Number is 10453-86-8.

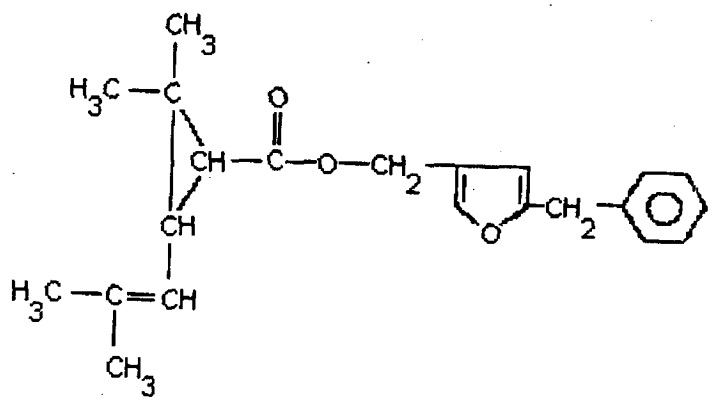

Figure 2. Resmethrin

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study with Resmethrin in Sprague-Dawley Rats

Reference Combined Chronic/Oncogenicity Study of Resmethrin Administered in Feed to Sprague-Dawley Rats for 24 Months (1994)., Hazleton Laboratory Study No. HWA 2623-104, Dated 12/28/94. **MRID 43601601**

A. Experimental Design

In a chronic toxicity/carcinogenicity study (MRID 43601601), technical resmethrin (85% a.i.) was administered in the diet to Sprague-Dawley rats (65/sex/dose) at dose levels of 0, 250, 1000, or 2500 ppm (0, 10.4, 41.8, and 107.2 mg/kg/day in males and 0, 12.8, 51.7, and 131.4 mg/kg/day in females, respectively) for 24 months.

B. Discussion of Mortality and Tumor Data

Survival Analyses

Female rats showed statistically significant differences in mortality in the pair-wise comparisons of the 250 and 1000 ppm dose groups with the controls, both at $p < 0.05$ (Table 1). There was no statistically significant increase in the trend for female rat mortality with increasing doses of Resmethrin (Memo, L. Brunsman, 4/12/05, TXR No. 0053189).

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Table 1. Resmethrin - Crl:CD BR Rat Study (MRID 43601601)

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Weeks

Dose (ppm)	1-26	27-52	53-78	79-105[f]	Total
0	0/65	1/65	10/64	22/54	33/65 (51)
250	0/65	3/65	13/62	31/49	47/65 (72)*
1000	0/65	1/65	13/64	32/51	46/65 (71)*
2500	0/65	1/65	15/64	20/49	36/65 (55)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.
[f]Final sacrifice at week 104.
( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Tumor Analyses

There were no treatment-related increase in tumors for male rats. Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for liver carcinomas, liver adenomas and/or carcinomas combined, all at $p < 0.01$. There was a significant increasing trend at $p<0.01$, and a significant difference in the pair-wise comparison of the 2500 ppm dose group with the controls at $p < 0.05$, for liver adenomas (Memo, L. Brunsman, 4/12/05, TXR No. 0053189). The statistical analyses of the female rats were based upon Peto's Prevalence Test (Table 2).

Table 2. Resmethrin - Crl:CD BR Rat Study (MRID 43601601)

Female Liver Tumor Rates+ and Peto's Prevalence Test Results

	Dose (ppm)			
	0	250	1000	2500
Adenomas (%)	0/56 (0)	0/52 (0)	1/54 (2)	3[a]/54 (6)
p =	0.00679**	-	0.09718	0.03430*
Carcinomas (%)	1/51 (2)	0/45 (0)	0/48 (0)	11[b]/45 (24)
p =	0.00000**	0.77337	0.77337	0.00047**
Combined (%)	1/56 (2)	0/52 (0)	1/54 (2)	14/54 (26)
p =	0.00000**	0.77337	0.35324	0.00008**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 75, dose 2500 ppm.
[b]First carcinoma observed at week 83, dose 2500 ppm.

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 $p < 0.01$.

Historical Controls: Historical control data from the testing laboratory was provided for this strain of rat conducted between 1989 and 1992, but not at later times For females, the range of incidence in historical controls for hepatocellular carcinomas was 0 - 4 0% (mean of 0.5%) in 12 studies of 626 animals. For hepatocellular adenomas, the range was 0 - 2.2% (mean of 0.5%). For males, the range of incidence of hepatocellular carcinomas was 0 - 8.0% (mean 3.1%) in 12 studies of 678 animals. Range of incidence of hepatocellular adenomas was 0 - 4.1% (mean of 1.0%). The incidence of hepatocellular carcinomas in females at 2500 ppm (24%) far exceeds the range of the historical controls (0-4.0%), indicating a treatment-related increase at the high dose. Similarly, the incidence of hepatocellular adenomas at 2500 ppm (6%) exceeds the range of 0-2.2% for historical controls, also indicating a treatment-related effect.

C. Non-Neoplastic Lesions in the Liver

Table 3. Non-Neoplastic Liver Lesions in Female Sprague-Dawley Rats Fed Resmethrin

Dose (ppm)	0	250	1000	2500
mg/kg/day	0	12.8	51.7	131.4
No. Examined Lesions/Sex/Dose	65	65	65	65
Eosinophilic cellular alteration				
Minimal - slight	8	7	7	5
moderate	1	0	0	3
moderately severe	0	0	1	3
Total	9	7	8	11

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The CARC considered dosing at the high dose in male and female rats to be adequate, but not excessive, to assess the carcinogenicity of resmethrin. In females, this was based on neurotoxic clinical signs, decreased body weight gain, non-neoplastic lesions and tumors at the high dose. In males, the dose was considered adequate based on neurotoxic clinical signs and anemia.

Several neurotoxic clinical signs (ataxia, hypoactivity, thin, few feces, pale eyes) were observed in more of the 2500 ppm males than controls. Ataxia occurred among more treated females than controls (13, 17, 19, and 19 in the control, low, mid, and high dose groups, respectively). Although the onset of some of the signs shortly preceded unscheduled death/moribund sacrifice rather than terminally sacrificed animals, they were considered indicative of treatment with resmethrin, which is a neurotoxic pyrethroid.

In females at 2500 ppm, mean body weight gain (up to 20% less than controls) was decreased during the last months of the study. At weeks 101 and 105, statistically significantly decreased body weight (-9% and -13% of controls, respectively) and weight gain (-20% of controls, week 105) were observed in high dose females. This correlated with a slight decrease in feed efficiency during the last weeks. Also there was a slight increase in the severity (moderate and moderate/severe) of hepatocellular eosinophilic cellular alteration in high dose females. Additional testing of resmethrin at higher doses is not required because resmethrin appears to be carcinogenic in females at the highest dose tested (2500 ppm).

Anemia (28-30% decrease in RBC parameters) was observed in males at week 104 in the high dose. Sporadic decreases in body weight in high dose males were small in magnitude (<3%), and were not considered strong evidence of adequacy of dosing.

The subchronic range-finding study (MRID 43601601) supports the doses used in the chronic study. In the subchronic study, 20/sex/dose Sprague-Dawley rats were dosed at 0, 500, 1250, 2500, 5000, or 10,000 ppm for a total of 13 weeks. Mild toxicity to the liver (hepatocyte vacuolization and hypertrophy showing a dose-related increase in severity, with clinical chemistry effects at higher doses) was observed at 2500 ppm in both sexes, with females showing more pronounced effects. At 5000 ppm, overt toxicity was observed in both sexes, including reduced weight gain and clinical signs. The range-finding study also demonstrated that thyroid is a target organ, with dose-related increased follicular cell vacuolization observed in females.

2. 2nd Rat Study

Reference: Combined Chronic/Oncogenicity Study of Resmethrin Administered in Feed to Wistar Rats for 24 Months (1980)., Food and Drug Research Laboratories No.5271, Dated 05/02/80. **MRID 00041402, 00085870, 00108828**

A. Experimental Design

In a dietary chronic toxicity/carcinogenicity study, 50 Wistar rats/sex/dose were fed SB-1382 (resmethrin tech., 90% a.i.) at concentrations of 0, 500, 2500 or 5000 ppm (corresponding to average daily intake of 0, 39.5, 193.7 or 400.9 mg/kg/day in males and 0, 47, 232.7 or 450.3 mg/kg/day in females) for 103 weeks (males) or 112 weeks (females). An additional 10 animals/sex/dose were treated and sacrificed at 12 months.

B. Tumor Data

Carcinogenic effects could not be unequivocally determined in this study due to uncertainty

regarding classification of liver hyperplastic nodules and thyroid tumors based on the lack of agreement as to histopathological interpretation of the four FDRL pathologists and lack of historical control data for Wistar rats from the laboratory. The confidence in this study is low and the quality is questionable. It was not evaluated by the CARC.

3. The 104-Week Swiss Crl:CD-1(ICR)BR Mouse Carcinogenicity Study

Reference: Oncogenicity Study of Resmethrin Administered in Feed to CD-1® Mice for 24 Months. Bio-Research Laboratories, Ltd. Senneville, Quebec, Canada; Project No. 83754. dated 1/08/92; **MRID 43052101**

A. Experimental Design

In a 2-year carcinogenicity study, CD-1 mice (50/sex/dose) were fed diets containing resmethrin technical (84.8% a.i.) at dose levels of 0, 0, 300, 600, or 1200 ppm for 24 months. The time-weighted average dose for these dietary levels corresponded to 0, 0, 43.4, 84.3, or 169.3 mg/kg/day for males and 0, 0, 52.9, 105.5, or 208.9 mg/kg/day for females. An interim sacrifice group was not included.

B. Discussion of Mortality and Tumor Data

Survival Analyses

Male mice showed a significant increasing trend in mortality with increasing doses of Resmethrin, at $p<0.01$, as well as significant differences in the pair-wise comparisons of the 600 and 1200 ppm dose groups with the controls, both at $p<0.05$ (Memo, L. Brunsman, 4/12/05, TXR No. 0053189) (Table 4).

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Table 4. Resmethrin - Swiss Crl:CD-1(ICR)BR Mouse Study (MRID 43052101)

Male Mortality Rates[a] and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-26	27-52	53-78	79-105[f]	Total
0	2/100	3/98	17/95	36/78	58/100 (58)**
300	2/50	4/48	11/44	13/33	30/50 (60)
600	1/50	2/49	17/47	15/30	35/50 (70)*
1200	0/50	5/50	14/45	18/31	37/50 (74)*

[a]Number of animals that died during interval/Number of animals alive at the beginning of the interval.
[f]Final sacrifice at week 104.
( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Tumor Analyses

Table 5. Resmethrin - Swiss Crl:CD-1(ICR)BR Mouse Study (MRID 43052101)

Male Liver Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	300	600	1200
Adenomas (%)	9[a]/96 (9)	9/45 (20)	12/47 (26)	15/47 (32)
p =	0.00001**	0.03189*	0.00075**	0.00005**
Carcinomas (%)	2/85 (2)	2[b]/39 (5)	4/35 (11)	6/37 (16)
p =	0.00231**	0.20688	0.01569*	0 00214**
Combined (%)	11/96 (11)	10/45 (22)	14/47 (30)	18/47 (38)
p =	0.00000**	0.03151*	0.00026**	0.00001**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 50, dose 0 ppm
[b]First carcinoma observed at week 69, dose 300 ppm.

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 $p < 0.01$.

Male mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1200 ppm dose group with the controls, for liver adenomas, carcinomas and adenomas and/or carcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 600 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, both at $p < 0.01$. There were also significant differences in the pair-wise comparisons of the 300 ppm dose group with the controls for liver adenomas and

adenomas and/or carcinomas combined, and of the 600 ppm dose group with the controls for liver carcinomas, all at $p < 0.05$ (Memo, L. Brunsman, 4/12/05, TXR No. 0053189). The statistical analyses of the male mice were based upon Peto's Prevalence Test (Table 5).

Historical Controls:

Laboratory historical control data were limited to one 2-year study of 50 animals; incidence of liver adenoma was 8% and carcinoma was 6% in males. Charles River historical control data for CD-1 mice for the time period of the date of the 2-year study gave a range of 0-17% for adenoma and 1-14% for carcinoma in males sacrificed between 21-24 months of age. The incidence of each tumor type (adenomas were 9-33 %, and carcinomas were 2-17%) observed in the current study exceeds the range of historical control males of this strain reported by both Bio-Research labs and the Charles River supplier laboratories.

C. Non-Neoplastic Lesions

The non-neoplastic lesions observed in the liver of both sexes of mice are presented in Table 6.

Table. 6. Non-Neoplastic Lesions of the Liver in CD-1 Mice Fed Resmethrin

Lesion/Sex/Dose	*0 ppm*	0 ppm	300 ppm	600 ppm	1200 ppm
Males - Liver No.Examined =	50	50	50	50	50
hepatocellular hypertrophy, diffuse	3	0	6	5	19
hepatocellular hypertrophy, focal	1	0	1	3	0
hepatocellular hypertrophy, centrilobular	0	0	6	9	18
focal hepatocellular hyperplasia	0	2	2	2	1
centrilobular degeneration	1	1	0	1	2
Females - Liver No.Examined =	50	50	50	49	50
hepatocellular hypertrophy, diffuse	2	0	1	5	8
hepatocellular hypertrophy, focal	1	0	0	0	2
hepatocellular hypertrophy, centrilobular	0	0	0	0	0
focal hepatocellular hyperplasia	1	2	2	3	0
centrilobular degeneration	0	0	0	2	1
focal hepatocellular vacuolization	1	1	1	0	3

D. Adequacy of Dosing for Assessment of Carcinogenicity

Adequate toxicity to evaluate carcinogenic potential was achieved in males based on statistically significant decreased survival during the last months of the study compared to the control group. Liver effects included dose-related enlargement and hypertrophy in both sexes; however, in the absence of microscopic pathology other than hypertrophy, they were considered to be metabolic adaptive responses indicating hepatic microsomes. However, it should be noted that the liver is usually the target organ for pyrethroid compounds. Animals that died or were sacrificed prior to study termination at 104 weeks had an increased incidence of agonal signs of toxicity: blue and/or distended abdomen, weak condition, tremors in females, reduced body temperature. These clinical signs were not observed in animals surviving to termination. Adequacy of dosing in males is based on decreased survival at 600 and 1200 ppm.

No overt treatment-related signs of toxicity were observed in females at any dose. Although dosing may have been inadequate in females in this study, in a previously submitted mouse carcinogenicity study (MRID 00083319), survival in both sexes at termination was significantly reduced at 1000 ppm (40% less than controls). There was only a slight decrease in survival in this newer study at 600 and 1200 ppm (19% and 14% less than the control group, respectively). Although dietary doses in this study were about 20% higher than the earlier mouse study, actual doses administered may be closer to each other because purity of the test material in this study was slightly lower (about 5%) and analyses of the test diets indicated occasional low values.

4. 2nd Mouse Study

Reference: (1979) Evaluation of Dietary Administration of SBP-1382 in CD-1 Outbred Albino Mice over an 85 Week Period: Laboratory No. 5270. Final rept. issued 8/14/79; prepared by Food and Drug Research Laboratories, Inc; **MRID 00083319.**

A. Experimental Design: In an 85-week carcinogenicity study, resmethrin technical (90% a.i.) was administered to 75 male and 75 female albino outbred CD-1 mice/dose group at dietary concentrations of 0, 250, 500, or 1000 ppm **(MRID 00083319)**. The time-weighted average dose for these dietary levels corresponded to 0, 36.3, 71.3, or 139.9 mg/kg/day for males and 0, 41.6, 82.9 or 165.8 mg/kg/day for females (based on theoretical concentration). An interim sacrifice group was not included.

B. Tumors

No treatment-related tumors were observed in male or female mice at any of the dose levels tested. There was an increase in amyloidosis at the high dose in both sexes which exacerbated the mortality in both sexes.

IV. TOXICOLOGY

1. Metabolism

C14-d-trans-resmethrin (acid and alcohol) was metabolized at single, oral low (1 mg/kg), or high (200 mg/kg) and multiple, low (1 mg/kg) oral doses essentially completely by 48-72 hours. Excretion was both fecal (single dose) and urinary (multiple doses). Fecal excretion was higher and urinary excretion was lower in males and females. Between 11-24% of the C14-alcohol but not acid label was retained in the tissues, primarily the fat and skin. Resmethrin was metabolized by cleavage of its ester bond and/or single or multiple oxidation, followed by glucuronide and other conjugates. Over 30 metabolites were found, most of which were present in low amounts and not identified. Many metabolites were unstable due largely to the instability of the furanyl ring towards oxidation. Metabolites with greater polarity tended to be excreted in higher amounts in the urine rather than the feces. Resmethrin and metabolites containing uncleaved ester were only found in feces **(MRIDs 42133801, 42136101)**.

2. Mutagenicity

All studies were acceptable and the data satisfy the pre-1991 mutagenicity guidelines. Overall, the data do not suggest a mutagenic mode of action for Resmethrin; accordingly, there is no mutagenic concern for Resmethrin. Resmethrin was not mutagenic in the Ames assay **(MRID 41068010)** or clastogenic in an in vitro chromosome aberration assay in Chinese hamster ovary cells **(MRID 41068011)**, and did not induce unscheduled DNA synthesis (UDS) in rat hepatocytes **(MRID 41068012)**.

Resmethrin technical (90.5% a.i.) was tested for reverse mutation at doses of 0, 667, 1000, 3333, 6667, and 10,000 µg/plate in Salmonella typhimurium strains TA98, TA100, TA1535, and TA1538, both with and without S-9 activation. Resmethrin did not cause an increase in revertant colonies in any strain of Salmonella tested up to the limit of solubility or limit dose (10,000 µg/plate). Cytotoxicity was not noted at any dose **(MRID 41068010)**.

Resmethrin technical (90.5% a.i.) was administered to Chinese hamster ovary cells (CGO-K1) in the absence of S-9 activation at doses of 0, 20, 40, 80, 160, and 320 µg/ml for 16 hours (sampled at 18 hours post-treatment) and in the presence of S-9 at doses of 0, 15, 30, 60 120 and 240 µg/ml for 4 hours (sampled at 12 and 24 hours post-treatment). No evidence of increased incidence of chromosomal aberrations above solvent controls were observed in cultures treated at doses up to the limit of cytotoxicity (160-320 µg/ml) without S-9 and 120-240 µg/ml with S-9 at the above sampling times **(MRID 41068011)**.

Resmethrin technical (90.5% a.i.) at doses of 0, 0.25, 2.5, 1.0, 10, 25, 100, 250, 500, and 1000

µg/ml culture media in cultured primary male rat hepatocytes. No unscheduled DNA synthesis above solvent or media control background was observed at any dose level up to 25 µg/ml in male (Fischer 344) liver primary hepatocyte cultures under the conditions of this assay. Cytotoxicity was significant above 25 µg/ml and cultures treated with higher doses could not be analyzed for UDS **(MRID 41068012)**.

3. Structure-Activity Relationship

Resmethrin is a Type I pyrethroid which is structurally related to other carcinogenic pyrethroids such as bifenthrin, tetramethrin, permethrin, and natural pyrethrins. **See Attachment 1.**

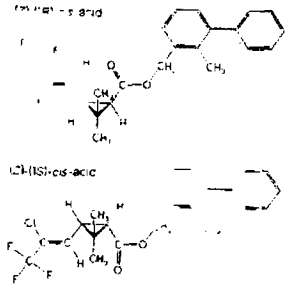

Figure 3: Bifenthrin

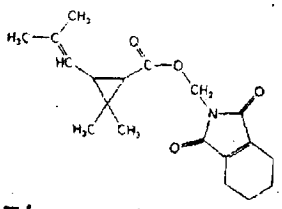

Figure 4: Tetramethrin

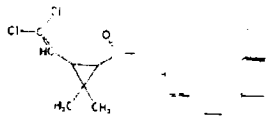

Figure 5. Permethrin

4. Subchronic and Chronic Toxicity

a) Subchronic Toxicity

EXECUTIVE SUMMARY - In a subchronic oral toxicity study (MRID 43838101), SBP-1382 (Resmethrin; 86.3% a.i., Lot #: IN-0198-B3) was administered to 20 CD®BR rats/sex/group in the diet at dose levels of 0, 500, 1250, 2500, 5000, or 10,000 ppm (equivalent to 34.8/39.7, 87.8/99.8, 178.6/196.4, 366.0/412.1, and 891.6/924.9 mg/kg/day [M/F]) for 13 weeks.

No treatment-related effects on ophthalmoscopy, hematology, or gross pathology were observed.

At 10,000 ppm, 9/20 females were found dead or sacrificed in a moribund condition between Days 4 and 76 of the study. Histopathological lesions in these animals were limited to slight to severe periportal to diffuse hypertrophy (8/9) and slight to moderate increased periportal to diffuse hepatocyte vacuolization (2/9). The cause of death in these animals was undetermined.

At ≥1250 ppm, clinical chemistry findings were limited to increased ($p \leq 0.05$) blood urea nitrogen (BUN) in the females. Relative (to body) liver weight was dose-dependently increased in the males, and dose-dependent increases ($p \leq 0.05$) in absolute, relative (to body), and relative (to brain) liver weights were observed in the females; however, relative (to body) liver weight only achieved statistical significance at ≥5000 ppm. Treatment-related histopathological findings in the liver included: minimal to severe periportal to diffuse hypertrophy, and minimal to severe periportal to diffuse hepatocyte vacuolization in the 1250-5000 ppm animals. These findings displayed a dose-related response in severity. Although the incidences of these findings were not dose-dependent, the reviewers believe that it was treatment-related. Histopathological effects noted in the thyroid were limited to minimal to moderate increased follicular cell vacuolization in the females.

At ≥2500 ppm, increases ($p <= 0.05$; not dose-dependent) in absolute and relative (to brain) liver weights were observed in the males. Clinical chemistry findings ($p \leq 0.05$) included increased BUN in the males and decreased glucose in the females.

At ≥5000 ppm, increased incidence of tremors was observed in both sexes, and frequency was dose-dependently increased, as well, in both sexes. Weekly body weights were decreased ($p \leq 0.05$) compared to controls, throughout the study in both sexes (decr 6-35%). Body weight gains were also generally decreased throughout the study in both sexes, and overall body weight gains were decreased ($p \leq 0.05$) by 13-55% in both sexes. At 5000 ppm, food consumption was transiently decreased in the males during Weeks 1-4, and was sporadically decreased in the females during Weeks 1-4, 6, 10, and 12. Terminal body weights were decreased ($p \leq 0.05$) by 10-37%. In the males, alanine aminotransferase (ALT) was increased ($p \leq 0.05$). Reducing

substances in the urine were increased compared to controls in both sexes. This finding was considered to be of equivocal toxicological significance.

Additional treatment-related effects noted at 10,000 ppm included: (i) urine stains in both sexes; (ii) thin appearance in the females; and (iii) hunched posture in the females. Decreases (no statistical analyses were performed) in weekly food consumption (g/animal/week) were observed throughout the study in the males and sporadically in the females. Total (Weeks 1-13) food consumption was decreased ($p \leq 0.05$) by 10-13% in the 10,000 ppm animals. Differences ($p \leq 0.05$) observed in clinical chemistry included increased alkaline phosphatase (ALP, males), decreased glucose (males), and increased cholesterol (females). Slight to severe increased periportal to diffuse hepatocyte vacuolization was observed in only 35% of males and 9% of females surviving to scheduled sacrifice. Although the incidence of this finding was not dose-dependent, the reviewers believe that it was treatment-related.

Effects at 500 ppm were limited to increased ($p \leq 0.05$) in absolute (incr 12%) and relative (to brain) liver weights, and minimal to moderate periportal to diffuse hepatocyte vacuolization.

The LOAEL is 1250 ppm (equivalent to 87.8/99.8 mg/kg/day [M/F]) based on increased absolute liver weight, increased BUN, and minimal to moderate thyroid follicular cell vacuolization in the females, and minimal to moderate periportal to diffuse hepatocyte hypertrophy and slight to severe periportal to diffuse hepatocyte vacuolization in both sexes. The NOAEL is 500 ppm (equivalent to 34.8/39.7 mg/kg/day [M/F]).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat.

b) Chronic Toxicity

EXECUTIVE SUMMARY: In a dietary chronic toxicity/carcinogenicity study, 50 Wistar rats/sex/dose were fed SB-1382 (resmethrin tech., 90% a.i.) at concentrations of 0, 500, 2500 or 5000 ppm (corresponding to average daily intake of 0, 39.5, 193.7 or 400.9 mg/kg/day in males and 0, 47, 232.7 or 450.3 mg/kg/day in females) for 103 weeks (males) or 112 weeks (females) **(MRIDs 00041402, 00085870, 00108828)**. An additional 10 animals/sex/dose were treated and sacrificed at 12 months.

At 2500 ppm (232.7 mg/kg/day, females), mean body weight/weight gain was slightly reduced in females during the first year of the study (statistically significantly lower mean body weight during much of the first year). Significantly higher liver weight (33%; 54% at 5000 ppm), along with increased incidence of lesions of the liver (hyperplastic nodules, nuclear hypertrophy) were observed in females. At 5000 ppm (400.9 mg/kg/day, males or 450.3 mg/kg/day, females),

slightly but statistically significantly lower mean body weights were observed in males for the first 18 weeks of the study and in females weights were reduced for much of the first 99 weeks. Mean thyroid weight was increased and increased incidence of thyroid cysts was observed in both sexes. Liver weight in males was increased (31%). (Reduced spleen weights were observed in females at all doses at terminal sacrifice but in the absence of corresponding microscopic effects was not considered a significant toxicologic effect). **The LOAEL for systemic toxicity is 2500 ppm (232.7 mg/kg/day) based on body weight and liver proliferative effects in females. The NOAEL is 500 ppm (47 mg/kg/day).**

Carcinogenic effects could not be unequivocally determined in this study due to uncertainty regarding classification of liver hyperplastic nodules and thyroid tumors and lack of historical control data for Wistar rats from the laboratory.

The chronic toxicity phase of the study **(83-1a)** is classified as **Core-minimum** and the carcinogenicity phase of the study **(83-2a)** is classified as **Core-supplementary (not upgradable)**. This study, taken together with a newer rat chronic toxicity/carcinogenicity study (MRID 43601601; reviewed in HED Doc. #011650), satisfy guideline requirements for chronic toxicity/carcinogenicity testing in rat.

EXECUTIVE SUMMARY: In an 85-week carcinogenicity study, resmethrin technical (90% a.i.) was administered to 75 male and 75 female albino outbred CD-1 mice/dose group at dietary concentrations of 0, 250, 500, or 1000 ppm **(MRID 00083319)**. The time-weighted average dose for these dietary levels corresponded to 0, 36.3, 71.3, or 139.9 mg/kg/day for males and 0, 41.6, 82.9, or 165.8 mg/kg/day for females (based on theoretical concentration). An interim sacrifice group was not included.

At 1000 ppm, survival was reduced (about 40% less than controls, both males and females). The incidence of amyloidosis as measured by increased organ involvement was slightly increased and was considered to be the primary cause of increased mortality. **The LOAEL for systemic toxicity is 1000 ppm in males (137.9 mg/kg/day) and females (165.8 mg/kg/day) based on decreased survival related to increased incidence of amyloidosis. The NOAEL is 500 ppm (71.3 mg/kg/day in males; 82.9 mg/kg/day in females).**

The study is **Core-Supplementary** and by itself doesn't satisfy the guideline requirement for a carcinogenicity study (83-2b) in mice due to several deficiencies (individual body weight and food consumption data not provided, analysis of test diets not provided, some tissues not examined microscopically). However, together with a second mouse oncogenicity study submitted by Roussel UCLAF (MRID 43052101), there is adequate information available to evaluate the carcinogenic potential of resmethrin. The two mouse carcinogenicity studies taken together therefore fulfill the guideline requirement for 83-2b.

Executive Summary: In a 52-week oral toxicity study (MRID 43062601), groups of 4/sex/dose beagle dogs were administered resmethrin (technical, 86.3% a.i.; doses not adjusted for purity) at 0, 12.5, 125, 500, or 2000 mg/kg/day in gelatin capsules (administered 2-4 times daily). When adjusted for purity of active ingredient, doses were 8.1, 108, 430, or 1720 mg/kg/day.

At 430 mg/kg/day, males had reduced body weight gain and food consumption during the first few weeks of the study (-33% during weeks 1-13), resulting in slightly lower total mean body weight gain (-18%, not statistically significant). One male had bilateral diffuse posterior capsule cataracts. Females also showed reduced body weight gain and food consumption during weeks 1-13 (-41%; not statistically significant); however, weight gain during the entire study was comparable to controls. At 1720 mg/kg/day, males and females had further decreases in mean body weight gain and pronounced liver enlargement (approx. 60%). Slightly increased severity (slight or moderate vs. minimal in controls) of vacuolization of the gall bladder mucosa epithelium were observed in males and possibly females, and 2 males had midzonal-centilobular hypertrophy of liver. Diffuse posterior capsule cataracts were observed in two males. **The LOAEL is 430 mg/kg/day based on cataract formation in males and slightly decreased body weight gain in males and females during the early weeks of the study. The NOAEL is 108 mg/kg/day.** (Actual doses received at 430 and 1720 mg/kg/day are somewhat lower than the administered dose due to excretion of pieces of unabsorbed test material in the feces).

5. Mode of Action Studies

There were no mode of action studies available.

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

The Committee's assessment of the current weight-of-the-evidence (WOE) is discussed below:

1. Carcinogenicity

Rat

- In female rats, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 250, 1000, and 2500 ppm (0, 12.8, 51.7, 131.4 mg/kg/day) dose groups, respectively, were as follows:

  Adenomas: 0/56 (0%), 0/52 (0%), 1/54 (2%), 3/54 (6%)
  Carcinomas: 1/51 (2%), 0/45 (0%), 0/48 (0%), 11/45 (24%)
  Combined: 1/56 (2%), 0/52 (0%), 1/54 (2%), 14/54 (26%)

  Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for liver carcinomas, liver adenomas and/or carcinomas combined, all at $p<0.01$. There was a significant increasing trend at $p<0.01$, and a significant difference in the pair-wise comparison of the 2500 ppm dose group with the controls at $p < 0.05$, for liver adenomas. The incidences of liver adenomas (6%) and carcinomas (24%) at the high dose were outside the historical control mean (0.5% for adenomas and carcinomas) and range (0-2.2%, adenomas; 0-4%, carcinomas) for the testing laboratory. The liver tumor response was primarily carcinomas. Therefore the CARC considered the tumors at the high dose to be treatment-related.

- There were no treatment-related increase in tumors for male rats.

- The CARC considered the high dose of 2500 ppm to be adequate, but not excessive, to assess the carcinogenicity of resmethrin in male and female rats. In females, this was based on neurotoxic clinical signs, decreased body weight gain, non-neoplastic lesions and tumors at the high dose. In males, the dose was considered adequate based on neurotoxic clinical signs and anemia.

Mouse

- In male mice, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 300, 600, 1200 ppm dose groups (0, 43.4, 84.3, or 169.3 mg/kg/day), respectively, were as follow:

  Adenomas: 9/96 (9%), 9/45 (20%), 12/47 (26%), 15/47 (32%)
  Carcinomas: 2/85 (2%), 2/39 (5%), 4/35 (11%), 6/37 (16%)
  Combined: 11/96 (11%), 10/45 (22%), 14/47 (30%), 18/47 (38%)

Male mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1200 ppm dose group with the controls, for liver adenomas, carcinomas and adenomas and/or carcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 600 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, both at $p<0.01$. There were also significant differences in the pair-wise comparisons of the 300 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, and of the 600 ppm dose group with the controls for liver carcinomas, all at $p<0.05$. The incidence of liver adenomas at the high dose (32%) exceeded the historical control mean for the testing lab (8%) as well as the range of the supplier (0-17%). The incidence of liver carcinomas at the high dose (16%) also exceeded the mean of the testing laboratory (6%) and the range of the supplier (1-14%). This was a robust response, with both benign and malignant tumors occurring at two non-excessive doses.

- No treatment-related tumors were seen in female mice.

- The CARC considered dosing in male mice to be adequate, but not excessive, to assess the carcinogenic potential of resmethrin based on decreased survival at 600 and 1200 ppm. Although no overt treatment-related signs of toxicity were observed in females mice at any dose in this study, the CARC considered dosing in females at the high dose of 1200 ppm to be adequate to assess the carcinogenicity potential of resmethrin based on a previously submitted mouse carcinogenicity study (MRID 00083319) where survival in both sexes at termination was significantly reduced at 1000 ppm (40% less than controls). There was only a slight decrease in survival in this newer study at 600 and 1200 ppm (19% and 14% less than the control group, respectively).

2. **Mutagenicity**

- There is no mutagenic concern and, overall, the data do not suggest a mutagenic mode of action for Resmethrin.

3. **Structure Activity Relationship (SAR)**

- The liver appears to be a target organ for some Type 1 pyrethroids (e.g. bifenthrin, permethrin, natural pyrethrins, and tetramethrin)

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified Resmethrin as "Likely to Be Carcinogenic to Humans". This decision was based on increased incidences of benign and malignant liver tumors in female rats and male mice. There was no concern for mutagenicity.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The Committee recommended that a linear low-dose extrapolation approach for the quantification of human cancer risk be applied to the experimental animal tumor data and that quantifications of risk be estimated for liver tumors in female rats and male mice.

VIII BIBLIOGRAPHY

MRID No.	CITATION
00028453	Machi, R.A.; Kam, C.; Gallo, M.A.; et al. (1979) Teratologic Evaluation of SBP-1382 Technical in the Albino Rat: Snell Project # 2054-066. (Unpublished study received Jan 23, 1980 under 432- 487; prepared by Booz, Allen & Hamilton, Inc., submitted by Penick Corp., Lyndhurst, N.J.; CDL:241765-A; 241766; 241768; 241769; 241770)
00029002	Becci, P.J.; Knickerbocker, M.; Parent, R.A. (1979) Teratologic Evaluation of SBP-1382 Technical in Albino Rabbits: FDRL Laboratory No. 6288. (Unpublished study including letter dated Jan 14, 1980 from R.W. Fogleman to Maarten L. deVries, received Jan 23, 1980 under 432-487; prepared by Food and Drug Research Laboratories, Inc., submitted by Penick Corp., Lyndhurst, N.J.; CDL: 241800-A)
00041402	Knickerbocker, M.; Becci, P.J.; Cox, G.E.; et al (1980) Final Re port: A Lifetime Evaluation of the Dietary Administration of SBP-1382 to Wistar Albino Rats: Laboratory No. 5271. (Unpublished study received Jul 8, 1980 under 432-487; prepared by Food and Drug Research Laboratories, Inc. and Cornell Univ., submitted by Penick Corp., Lyndhurst, N.J.; CDL:242782-A; 242786; 242785; 242783; 242784)
00081276	Schwartz, C.S.; Gephart, L.; Becci, P.J.; et al. (1979) The Evaluation of the Effects of SBP-1382 following Dietary Administration through Three Generations in Sprague-Dawley Rats: Laboratory No. 5739. (Unpublished study received Aug 30, 1979 under 432-487; prepared by Food and Drug Research Laboratories, Inc., submitted by Penick Corp., Lyndhurst, N.J.; CDL:240984-A)
00083319	Knickerbocker, M.; Cox, G.E.; Parent, R.A. (1979) Evaluation of Dietary Administration of SBP-1382 in CD-1 Outbred Albino Mice over an 85 Week Period: Laboratory No. 5270. Final rept. (Un- published study received Aug 14, 1979 under 432-487; prepared by Food and Drug Research Laboratories, Inc., submitted by Penick Corp., Lynhurst, N.J.; CDL:239853-A; 238954; 238955; 238956; 238957)
00085870	Thompson, S.W. (1981) A Lifetime Evaluation of the Dietary Administration of SBP-1382 to Wistar Albino Rats: Laboratory No. 5271. (Unpublished study, including letters dated Mar 26, 1980 from E.F. Mace to Maarten De Vries, May 13, 1981 from F.D.R. Gee to Maarten L. De Vries, Aug 17, 1981 from M.A.

Gallo to Emily F. Hedal and Nov 9, 1981 from M.L. De Vries to Franklin D.R. Gee, received Nov 10, 1981 under 432-487; prepared by Food and Drug Research Laboratories, Inc., submitted by Penick Corp., Lyndhurst, N.J.; CDL:246214-A)

00108828 Becci, P.; Hess, F.; Thompson, S (1982) A Lifetime Evaluation of the Dietary Administration of SBP-1382 to Wistar Albino Rats: FDRL Study No. 5271. (Unpublished study received May 27, 1982 under 432-487; prepared by Food and Drug Research Laboratories, Inc., submitted by Penick Corp., Lyndhurst, NJ; CDL:247579-A)

00124308 Norwood, T. (1981) A Statistical Analysis of the Effects of Dietary SBP-1382 on Three Generations of Sprague-Dawley Rats. (Unpublished study received Aug 3, 1981 under 432-487; submitted by Penick Corp., Lyndhurst, NJ; CDL:245845-A; 245846; 245847; 245848)

00157961 Gephart, L.; Johnson, W.; Becci, P.; et al. (1980) 180-Day Subchronic Oral Dosing Study with Resmethrin (SBP-1382) in Beagle Dogs: Laboratory No. 6289. Unpublished study prepared by Food and Drug Research Laboratories, Inc. 553 p.

00158476 Coombs, D.; Hardy, C.; Clark, G.; et al. (1985) 90-Day Inhalation Toxicity Study in the Rat: Resmethrin: (SBP - 1382 Technical): SBP 6/84997. Unpublished study prepared by Huntingdon Research Centre. 333 p.

41068010 Lowlier, T.; Wagner, V. (1987) Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay: Laboratory ID T5747.501014. Unpublished study prepared by Microbiological Associates, Inc. 62 p.

41068011 Putman, D. (1988) Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells: Resmethrin NDRC 104: Laboratory ID T5747.337003. Unpublished study prepared by Microbiological Associates, Inc. 30 p.

41068012 Curren, R. (1988) Unscheduled DNA Synthesis in Rat Primary Hepatocytes: Resemethrin NDRC 104: Laboratory ID T5747.380. Unpublished study prepared by Microbiological Associates, Inc. 27 p.

42066901 Meyers, L. (1991) 21-Day Percutaneous Toxicity Study of Resmethrin in Rabbits: Lab Project Number: HWA 2623-100: RBT-90-217. Un- published study prepared by Hazleton Washington, Inc. 312 p.

42076201 Catez, D. (1991) Acute oral toxicity study of Bioresmethrin (technical) in the rat. Lab Project No 90/2172/TX. Unpublished study prepared by Roussel Uclaf. 93p.

42076202 Catez, D. (1991) Acute Dermal toxicity study of Bioresmethrin (technical) in the rabbit. Lab Project No. 90/2177/TX. Unpublished study prepared by Roussel Uclaf. 42p.

42076203 Catez, D. (1991) Primary eye irritation toxicity study of Bioresmethrin (technical) in the rabbit. Lab Project No. 90/2178/TX. Unpublished study prepared by Roussel Uclaf. 33p.

42076204 Catez, D. (1991) Primary dermal irritation toxicity study of Bioresmethrin (technical) in the rabbit. Lab Project No. 90/2170/TX. Unpublished study prepared by Roussel Uclaf. 33p.

42133801 Ruzo, L.; Krautter, G.; Marsh, J.; et al. (1991) Absorption, Distribution, Elimination and Metabolism of Carbon 14-alcohol|-d- trans-Resmethrin in the Rat: Lab Project Number: 411E/239W. Unpublished study prepared by PARK.-West, Inc. and PARL.-East, Inc. 370 p.

42136101 Ruvo, L.; Crater, G.; Jiang, J. (1991) Absorption, Distribution, Elimination and Metabolism of C14-acid-d-trans-resmethrin in the rat. Project No. 410E/238W. Unpublished study prepared by PARL.-West and PARL.-East, Inc.. 371 p.

42153701 Hardy, C., Jackson, G., Suttie, A. et. al. (1989) Acute inhalation toxicity study of Bioresmethrin (technical) in the rat. 4-hour exposure. Lab Project No. 801/189712-RBT-89-137. Unpublished study prepared by Huntington Research Center, Ltd. 54p.

42153702 Khun, J.. (1990) Dermal sensitization study of Bioresmethrin (technical) in the guinea pig. Lab Project No. 6674-89 Unpublished study prepared by Stillmeadow, Inc. 17p.

43338601 Kangas, L. (1989) A 4-Week Dietary Toxicity Study of SBP-1382 in the Albino Mouse: Lab Project Number: 83753. Unpublished study prepared by Bio-Research Lab. Ltd. 241 p.

43052101 Kangas, L. (1992) A Dietary Oncogenicity Study of SBP-1382 in the Albino Mouse: Lab Project Number: RBT-92-111: 83754: F2216. Unpublished study prepared by Bio-research Labs., Ltd. 2173 p.

43062601 Dalgard, D. (1993) 52-Week oral Toxicity Study of SBP-1382 (Resmethrin) -

Technical in Dogs: Final Report: Lab Project Number: HWA 2623-105: RBT-92-100. Unpublished study prepared by Hazleton Washington, Inc. 375 p.

43189101 Hotelman, A. (1994) Reproductive Effects of SBP-1382 (Resmethrin) Technical Administered Orally via the Diet to Crl:CD BR V.F./Plus Rats for Two Generations with Two Litters per Generation: Lab Project Number: 718-004: RBT-92-102. Unpublished study prepared by Argus Research Laboratories. 1533 p.

43271701 Vandemerghe, J. (1990) Life-Span Data and Historical Data in Carcinogenicity Testing in Wistar Rats Crl: (WI)BR: Supplemental. Unpublished study prepared by Janssen Research Foundation. 210 p.

43601601 Trutter, J. (1994) Combined Chronic Toxicity and Oncogenicity Study in Rats with SBP-1382 (Resmethrin) Technical: Final Report: Lab Project Number: HWA 2623-104. Unpublished study prepared by Hazleton Washington, Inc. 2518 p.

43838101 Serabian, M. (1993) Subchronic Toxicity Study in Rats with SBP-1382 (Resmethrin) Technical: Final Report: Lab Project Number: HWA 2623-101: RBT-91-125. Unpublished study prepared by Hazleton Washington, Inc. 1221 p.

Memo Brunsman, L. 2005. Resmethrin: Qualitative Risk Assessment Based on Crl:CD BR Rat and Swiss Crl:CD-1(ICR)BR Mouse Dietary Studies. April 12, 2005. TXR No. 0053189.

ATTACHMENT 1

Carcinogenicity of Pyrethroids

Chemical	Type[1]	Species	Dose Levels Tested	Results
Bifenthrin[3]	I	Swiss Webster mice	50, 200, 500, 600 ppm	Classified as Category C (without Q*). Hemangiopericytomas of urinary bladder (♂, 600 ppm). Hepatocellular carcinomas & adenomas (♂, trend only) Combined lung adenomas & carcinomas (♀, 50-600 ppm)
		Sprague-Dawley rats	12, 50, 100, 200 ppm	Negative, adequate doses[2].
Permethrin[3]	I	CD-1 mice	20, 500, 2000 ppm	Classified as Category C with Q*. Liver adenomas/carcinomas (♂+♀, 500, 2000 & trend in ♀); adenomas (♂, all doses & trend); adenomas (♀, 500, 2000 & trend); Lung adenomas (♀, all doses & trend), carcinomas (♀, 2000 & trend); combined (♀, all doses & trend)
		CFLP mice	10, 50, 250 mg/kg (diet)	↑ in lung tumors (♀, 250 & trend). Doses inadequate.
		Alderley Park Swiss mice	250, 1000, 2500 ppm	Negative. Doses adequate.
		Wistar rats	10, 50, 250 mg/kg (diet)	Negative. Doses adequate in males but not females.
		Wistar rats	500, 1000, 2500 ppm	Negative. Doses adequate in males but not females.
		Long Evans rats	20, 100, 500 ppm	Equivocal lung tumors. Doses inadequate.
Pyrethrins[3]	I	CD-1 mice	100, 2500, 5000 ppm	Classified as "Likely" with Q*. Mouse study negative.
		CD rats	100, 1000, 3000 ppm	Thyroid follicular cell adenomas (♂, 1000, 3000 ppm) Thyroid follicular cell adenomas (♀, 3000 ppm) Liver tumors (F)
Tetramethrin[3]	I	Sprague-Dawley rats	1000, 3000, 5000 ppm	Classified as Category C (no Q*). Interstitial cell adenomas of testes (♂, 3000, 5000 ppm)
		Sprague-Dawley rats	200, 1000, 5000 ppm (started in utero)	Interstitial cell adenomas of testes (♂, 5000 ppm)
		Long Evans rats	200, 1000, 5000 ppm (started in utero)	Interstitial cell adenomas of testes (♂, 5000 ppm)
		$B_6C_3F_1$ mice	12, 60, 300, 1500 ppm	Negative. Dose levels adequate.

[1]Type of pyrethroid (I or II)
[2]Adequate doses: the animals were tested at sufficiently high dose levels for an adequate negative carcinogenicity study (i.e. overt toxicity was observed).
[3]This chemical was listed on the latest OPP List of Chemicals Evaluated for Carcinogenic Potential.