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SEP 27 1989

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 8H5559-Sumithrin (d-phenothrin) - Review of Range Finding Studies (13-Week Rat; 5-Week Mouse) Submitted By Sumitomo Chemical Company.

HED Project No.: 9-1372
Record No.: 244326
Tox Chem No.: 652B
MRID No.: 409982-01,-02

FROM: Carolyn A. Gregorio, Toxicologist *CAG 9-18-89*
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Toxicology Branch I, Insecticide, Rodenticide Support
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TO: Joseph M. Tavano, PM Team 17
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THRU: Edwin R. Budd, Section Head
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The registrant has submitted two range-finding studies in response to the Agency's request for additional information regarding the sumithrin combined chronic feeding/oncogenicity studies for the rat² and mouse³. The doses selected in these studies (0, 300, 1000, 3000 ppm) have been questioned as to whether the highest dose tested was sufficiently high in order to

¹Memo, E. Budd to J. Tavano, March 16, 1989. Sumithrin (d-phenothrin) - Review of Toxicity Studies Submitted by Sumitomo Chemical Company In Support of FAP #1H5233 and EPA Registration No. 10308-6.

²Sumithrin: Combined Chronic Feeding/Oncogenicity Study in Rats (LSR #85/SUM003/886; January 1987).

³Sumithrin: Combined Chronic Feeding/Oncogenicity Study in Mice (LSR #86/SUM007/166; April 1987).

satisfy the Agency's requirement for establishing a "maximum tolerated dose" (MTD). Detailed reviews of the two range-finding studies are attached.

Summaries of the pertinent information are presented below.

1. Sumithrin: Toxicity in Dietary Administration To Rats Over 13 Weeks (LSR #82/SUM002/222; February 23, 1983).

Test Material - Sumithrin, technical grade

Conclusion - This 13-week study is classified as Core Minimum. The limited evidence of compound related liver effects observed at the 3000 and 10000 ppm dose levels in this study indicate that the highest dose tested in the chronic feeding/onco study (3000 ppm) was not sufficiently high to adequately characterize the oncogenic potential of sumithrin. The chronic feeding/oncogenicity study will remain classified as Core Supplementary and is not acceptable in fulfillment of an oncogenicity study in rats.

A. Male Rat

NOEL = 1000 ppm (70 mg/kg/day)
LOEL = 3000 ppm (216 mg/kg/day). Increased liver weights, increased lactase dehydrogenase, decreased cholesterol.

At 10000 ppm (706 mg/kg/day) increased liver weights, increased biliary hyperplasia, decreased cholesterol, increased alkaline phosphatase, increased lactase dehydrogenase, decreased glucose, increased lymphocytes.

B. Female Rat

NOEL = 1000 ppm (75 mg/kg/day)
LOEL = 3000 ppm (227 mg/kg/day). Increased liver weights, decreased cholesterol, increased lactase dehydrogenase.

At 10000 ppm (714 mg/kg/day) increased liver weights, decreased cholesterol, increased lactase dehydrogenase, increased albumin, decreased glucose, increased lymphocytes, increased hydrometra of the uterus.

2. Sumithrin: Five Week Range-Finding Toxicity Study In Mice (LSR #83/SUM006/024; June 1, 1983).

Test Material - Sumithrin, technical grade

Conclusion - This 5-week study is classified as Core Supplementary pending submission and review of the complete

individual animal histopathology data. In the interim, the limited evidence of compound related liver effects observed at the 3000 and 10000 ppm dose levels in this study indicate that the highest dose tested in the chronic feeding/onco study (3000 ppm) was not sufficiently high to adequately characterize the oncogenic potential of sumithrin. The chronic feeding/oncogenicity study will remain classified as Core Supplementary and is not acceptable in fulfillment of an oncogenicity study in mice.

A. Male Mice

NOEL = 1000 ppm (190 mg/kg/day)
LOEL = 3000 ppm (565 mg/kg/day). Increased liver weights, increased periacinar hepatocytic hypertrophy.

At 10000 ppm (1958 mg/kg/day) increased alkaline phosphatase, increased liver weights, decreased kidney weights, increased periacinar hepatocytic hypertrophy.

B. Female Mice

NOEL = 1000 ppm (230 mg/kg/day)
LOEL = 3000 ppm (710 mg/kg/day). Increased liver weight.

At 10000 ppm (2339 mg/kg/day) increased liver weights, increased periacinar hypertrophy, increased alkaline phosphatase.

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Reviewed By: Carolyn A. Gregorio *CAg 7-21-89*
Section I, Toxicology Branch I - IRS (TS-769C)
Secondary Reviewer: Robert P. Zendzian, Acting Section Head
Toxicology Branch I - IRS (TS-769C) *R.P.Z. 7/24/89*

DATA EVALUATION REPORT

Study Type: 82-1 13-Week Oral Range-Finding In Rats
Tox Chem No.: 652B
Accession No.: None
MRID No.: 409982-02
Test Material: Sumithrin, technical grade (Purity 92.6%)
Synonyms: d-phenothrin
Sponsor: Sumitomo Chemical Company Limited
Testing Facility: Life Science Research (Suffolk, England)
Study No.: 82/SUM002/222
Title: Sumithrin: Toxicity In Dietary Administration To Rats Over 13 Weeks.
Author: V.M. Yappup, R. Ashby, J.C. Whitney
Report Issued: February 23, 1983

Conclusion: Possible treatment related effects were observed in the liver of both high dose males and females (10000 ppm) when compared to respective concurrent control animals as evidenced by increased lymphocytes, increased liver enzyme activity (males only), decreased cholesterol, increased lactase dehydrogenase, increased plasma albumin, decreased glucose (females only), increased liver weights (absolute and relative to body weight) and increased biliary hyperplasia (males only). In addition, increased hydrometra was also observed in high dose females. All other examined parameters were similar to those reported for control animals.

Very limited evidence of minor liver toxicity was observed in the 3000 ppm males and females. The noted effects were decreased cholesterol, increased lactase dehydrogenase (females only), decreased glucose and increased liver weights (both absolute and relative to bodyweight). All other examined parameters were similar to those reported for respective control animals.

Decreased mean glucose was reported in all treated female groups

(300, 1000, 3000, and 10000 ppm) when compared to concurrent control values. However, the inter-group differences were very small and there was no apparent dose-related trend.

This study is classified as Core Minimum as follows:

1. Male Rat

NOEL = 1000 ppm (70 mg/kg/day)
LOEL = 3000 ppm (216 mg/kg/day) Increased liver weights, increased lactase dehydrogenase, decreased cholesterol.
At 10000 ppm (706 mg/kg/day) increased liver enzymes, increased liver weights, increased biliary hyperplasia, decreased cholesterol, increased alkaline phosphatase, increased lactase dehydrogenase, decreased glucose, increased lymphocytes.

2. Female Rat

NOEL = 1000 ppm (75 mg/kg/day)
LOEL = 3000 ppm (227 mg/kg/day) Increased liver weights, decreased cholesterol, increased lactase dehydrogenase.
At 10000 ppm (714 mg/kg/day) increased liver weights, decreased cholesterol, increased lactase dehydrogenase, increased albumin, decreased glucose, increased lymphocytes, increased hydrometra of the uterus.

Classification (Core-Grade): Core-Minimum

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

A quality assurance statement, dated Feb. 22, 1983 and signed by D.J. Ford (Head Quality Assurance Unit, LSR) was present.

A. MATERIALS

1. Test Compound: Sumithrin, technical grade, Lot No.: 10102, Purity: 92.6%, pale yellow liquid, stored at 4° C.
2. Test Animals: Fischer F 344 rats, Supplier: Charles River (Kent, England), four to six weeks old upon arrival; body weights: males, 95-125 g and females, 87-109 g; acclimation period: 7 days; Housing: one animal/polypropylene cage.
3. Diet: Spratts Laboratory Animal Diet No. 2, powdered; Supplier: Spratt's Patent Limited (Essex, England).

B. STUDY DESIGN

1. Animal Assignment: Animals were assigned using a set of computer-generated random numbers to the following test groups:

<u>Test Group</u>	<u>Dietary Dose (ppm)</u>	<u>Males</u>	<u>Females</u>
1	0	15	15
2	300	15	15
3	1000	15	15
4	3000	15	15
5	10000	15	15

All animals were given food and water ad libitum for the duration of the study.

2. Dosage Levels: 0, 300, 1000, 3000, 10000 ppm
3. Diet Preparation: Diets were prepared weekly and stored at room temperature in the animal room within light-proof plastic storage bins. The stability of the test diets were determined after one and two weeks of storage at room temperature and found to be stable. Homogeneity of the test compound for Group 2 (300 ppm) and Group 5 (10000 ppm) was checked prior to commencement of treatment and was found to be acceptable.

Concentration of test material in the diet was analytically determined at weeks 1 and 13 of the study. The range of percentages of intended values for groups 2, 3, 4 and 5 were 89-92%, 91-102%, 96-104% and 98-87%, respectively.

C. METHODS:

1. Observations: Animals were observed twice each day for mortality and signs of toxicity and were palpated weekly for swellings. Severely debilitated and moribund animals were sacrificed.
2. Body Weights: All animals were weighed weekly.

3. Food Consumption, Water Consumption, Food Conversion Ratio and Compound Intake: Food consumption, food conversion and compound intake were determined for individual animals on a weekly basis. Water consumption was checked daily by visual inspection of water bottles and over a 3 day period in weeks 5, 6, 10, 11.

4. Blood Collection: Although no pre-test blood sampling was performed, after five and eleven weeks of treatment, blood from 10 males and 10 females from each group was collected from the retro-orbital sinus. The report did not state whether the animals were deprived of water or food prior to collection of blood samples.

The following hematological parameters were examined:

- Packed Cell Volume (PCV)
- Hemoglobin (HCB)
- Leukocyte Count (WBC)
- Leukocyte Count, differential (lymphocytes, eosinophils, basophils, monocytes)
- Erythrocyte Count (RBC)
- Mean Cell Hemoglobin (MCHC)
- Mean Cell Volume (MCV)
- Mean Cell Hemoglobin (MCH)
- Platelet Count

"Due to lower haemoglobin concentrations in females receiving 10000 ppm, the samples obtained after five weeks of treatment were examined" for reticulocyte counts.

The following blood chemistries were examined:

- Alanine amino-transferase (ALT)
- Aspartate amino-transferase (AST)
- Alkaline phosphatase (AP)
- Urea
- Glucose
- Total Protein
- Electrophoretic protein fractions
- Calcium
- Sodium
- Potassium
- Chloride concentration
- Total cholesterol
- Bilirubin Concentration, total, direct
- Lactate dehydrogenase

5. Urinalysis: After five and eleven weeks of treatment, urine from 10 males and 10 females from each group was collected. Drinking water was removed "at approximately 12.30 hours and urine samples were collected for approximately 14-16 hours with food and water removed." The samples were examined for:

Appearance	Protein
Volume	Ketones
pH	Blood
Glucose	Bilirubin
Specific Gravity	Urobilin
Nitrite	Microscopy
Total Reducing Substance	

6. Gross Necropsy: All animals were subjected to a standardized gross necropsy procedure which included:

- a) preparation of femoral bone marrow smear,
- b) examination of the external surfaces, the contents of the cranial, thoracic and abdominal cavities and the residual carcass,
- c) weighing of selected organs (described below) and,
- d) removal and fixation of organs and/or tissues for histopathological examination (described below).

7. Organ Weights: Absolute and relative to body weights were determined for the following selected organs: adrenal glands, brain, epididymides, heart, kidneys, liver, lung, ovaries, pituitary, prostate gland, spleen, testes, thymus, thyroids (with parathyroids) and uterus for all groups at termination of the study.

8. Histology: Histological examination of the following tissues for treatment groups 1 (control) and 5 (10000 ppm): abnormalities, adrenals, brain, cecum, colon, duodenum, epididymides, Hardarian glands, heart, ileum, jejunum, kidneys, esophagus, ovaries, pancreas, pituitary, prostate, salivary, sciatic nerve, skeletal muscle. spinal cord (thoracic and lumbar), spleen, liver, lungs (with main stem bronchi), lymph nodes (cervical and mesenteric), mammary glands (caudal), stomach (pylorus and fundus), testes, thymus, thyroids (with parathyroids), trachea, urinary bladder, uterine cervix and uterus.

D. RESULTS

1. Observations: Signs of toxicity, appearance and behavior observed in this study were typical of rats of the strain and age employed. No deaths and no palpable swellings were reported in any treatment group.

2. Body Weights:

2.1 Group Mean Body Weights - A slight decrease (4-6%) in the mean body weights of Group 5 males (10000 ppm) was observed when compared to control animals over the 13 weeks on test (Registrant submitted Table 2, attached). No differences were noted in any of the female treatment groups when compared to controls.

These data do not suggest any obvious effect of the test compound for male or female treatment groups.

2.2 Group Mean Body Weight Changes - A slightly slower (7%) rate of increase in mean body weights for high dose males (10000 ppm) was observed when compared to controls through 13 weeks on treatment. The body weight increment at 13 weeks was 191 grams for controls versus 178 grams for the 10000 ppm animals. In analyzing the weekly group mean body weight changes, the average weekly gain for the high dose males was slightly slower (varying from 1 to 6 grams) than concurrent controls throughout the study (Registrant Table 2, attached). These data are not considered to be an indication of a sustained or meaningful response.

No appreciable differences between control and treated female rats were observed.

3. Food Consumption, Water Consumption, Food Conversion Ratio and Compound Intake:

3.1 Food Consumption - "Throughout the treatment period the food consumption of rats receiving 10,000 ppm was lower than that of controls." Group mean food consumption values (g/rat/week) after 13 weeks of treatment were as follows (taken from registrant submitted Table 1):

<u>Food Consumption (13 weeks)</u>					
<u>Dose (ppm)</u>	<u>0</u>	<u>300</u>	<u>1000</u>	<u>3000</u>	<u>10000</u>
<u>-Male</u>					
(g/rat/wk)	1455	1414	1426	1465	1396
% Control	-----	-3%	-2%	-1%	-4%
<u>-Female</u>					
(g/rat/wk)	1022	1002	1013	1019	953
% Control	-----	-2%	-----	-----	-5%

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Since the animals were not affected with respect to altered growth patterns, this finding is not considered to be toxicologically significant.

3.2 Water Consumption - Water consumption was similar in all groups throughout the study.

3.3 Food Conversion Ratios - The food conversion ratios (amount of food consumed per unit gain in body weight) were similar for all groups throughout the study.

3.4 Compound Intake - Compound intake calculated as group mean values in units of mg/kg/day, is reported as follows:

Group	Dietary Dose (ppm)	Compound Intake (mg/kg/day)	
		Males	Females
		-----	-----
1	0		
2	300	21	23
3	1000	70	75
4	3000	216	227
5	10000	706	714

4. Blood Collection:

4.1 Hematological Examination: Statistically significant (Student's t-test) increases in lymphocytes in both the 10000 ppm treated male and female rats were observed at the 5 and 11 week examination intervals. Sporadic changes were observed in various parameters at the 5 and 11 week examination periods but are not considered to be evidence of a toxic response to treatment.

Dose (ppm)	Lymphocytes ^a			
	Males		Females	
	5-Wk	11-Wk	5-Wk	11-Wk
0	7.2	5.6	6.5	5.7
300	7.8	5.3	7.3	5.9
1000	8.5**	6.2	7.1	5.3
3000	7.7	5.6	7.2	5.7
10000	8.0	6.4*	7.7*	6.6*

* P<0.05

** P<0.01

^aTaken from registrant submitted Table 6A and B

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4.2 Clinical Chemistries: Several examined parameters revealed statistically significant changes (Student's t-test) between treated groups and respective controls and are considered to be possible evidence of treatment related toxicity (taken from registrant submitted Tables 7A and 7B). These parameters are discussed below.

Group mean values for total cholesterol was decreased in the 3000 and 10000 ppm males (both at the 5 and 11 week examinations) and in the 10000 ppm treatment female groups (at 11 weeks only) when compared to concurrent control animals.

Total Cholesterol (mg %)

Dose (ppm)	Males		Females	
	5-Wk	11-Wk	5-Wk	11-Wk
0	44	59	55	61
300	45	59	72***	59
1000	42	58	55	70**
3000	34***	46***	63**	52**
10000	22***	34***	31***	41***

* P<0.05
 ** P<0.01
 *** P<0.001

Likewise, increased plasma albumin was reported in females treated with 3000 and 10000 ppm (at 11 week examination) when compared to concurrent control animals. Similar increases were observed in the 3000 ppm males (11 weeks examination) and the 10000 ppm males (5 and 11 week examination).

Albumin (g %)

Dose (ppm)	Males		Females	
	5-Wk	11-Wk	5-Wk	11-Wk
0	3.3	3.5	3.3	3.5
300	3.2	3.9*	3.2	3.9**
1000	3.5	3.5	3.5	3.5
3000	3.4	4.0**	3.6**	3.8**
10000	3.6**	4.2***	3.3	4.4***

* P<0.05
 ** P<0.01
 *** P<0.001

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Group mean alkaline phosphatase values were significantly increased in the 3000 and 10000 ppm males at the 5 week examination and in the 10000 ppm group only at the 11 week evaluation when compared to concurrent control males. No significant alterations were reported in any female treated group when compared to controls.

Alkaline Phosphatase (iu/L)

<u>Dose (ppm)</u>	<u>Males</u>	
	<u>5-Wk</u>	<u>11-Wk</u>
0	246	175
300	237	166
1000	228*	160*
3000	261*	174
10000	271*	196*

* P<0.05
 ** P<0.01
 *** P<0.001

Mean group glucose was significantly decreased in the 10000 ppm treatment female group at the 5 week examination period and in all female treatment groups at 11 weeks when compared to controls. All male treatment groups were similar to controls at both examination times.

Glucose (mg %)

<u>Dose (ppm)</u>	<u>Females</u>	
	<u>5-Wk</u>	<u>11-Wk</u>
0	145	148
300	145	137**
1000	139	137**
3000	144	138**
10000	138*	129***

* P<0.05
 ** P<0.01
 *** P<0.001

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Group mean lactase dehydrogenase values were significantly increased in the 10000 ppm females after 5 weeks of treatment and only slightly (not statistically significant) at the 11 week examination. Group means for the 10000 ppm male group were significantly increased at 11 weeks only.

Dose (ppm)	<u>Lactase Dehydrogenase (iu/L)</u>			
	Males		Females	
	5-Wk	11-Wk	5-Wk	11-Wk
0	793	430	691	619
300	815	491	610*	616
1000	600*	483	759	692
3000	649	413	544***	775*
10000	785	638**	832***	640***

* P<0.05
 ** P<0.01
 *** P<0.001

5. Gross Necropsy: Gross pathological examination did not reveal any lesions or effects related to the test material. Findings were consistent with what would be expected in this strain and age of rats used in this study.

Femoral bone marrow smears taken after 13 weeks of treatment were not altered (based on cellularity and composition) in any animal in any group.

6. Organ Weights: Group mean values for liver weights are presented below. For male rats, absolute and relative (to body weight) were significantly increased for the 10000 ppm (Group 5) treatment animals when compared to controls (Student's t-test). Similar increases were reported for the 3000 (Group 4) and 10000 ppm (Group 5) females. These findings establish the liver as a possible target organ and are considered to be related to treatment.

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Organ Weights: Group Mean Values^a For Liver (G)

<u>Dose (ppm)</u>	<u>0</u>	<u>300</u>	<u>1000</u>	<u>3000</u>	<u>10000</u>
<u>Male</u>					
<u>-Absolute</u> 13-wks	13.1	12.6	13.3	13.3	15.3***
<u>-Relative to Bodyweight</u> 13-wks	4.4	4.2	4.4	4.4	5.3***
<u>Female</u>					
<u>-Absolute</u> 13-wks	6.9	6.6	7.7	7.6**	9.4***
<u>-Relative to Bodyweight</u> 13-wks	3.8	3.7	4.0	4.2**	5.3***

** P<0.01

*** P<0.001

^aTable 8 and 9, Registrant submitted text.

Group mean values for spleen and thymus weights for males and thymus for females are presented below. A statistically significant decrease in the thymus was reported for the 10000 ppm female (absolute and relative to bodyweight) and male (absolute weight only) when compared to concurrent control animals. The relevance of this finding is questionable since correlation to other examined indices, such as hematology and histopathology, was not evident. Group mean spleen weights (absolute) were lower in the 3000 and 10000 ppm males. However, as noted by the registrant, "the inter-group differences were small, lack dosage-relationship and therefore considered to be equivocal toxicological significance."

No other absolute or relative (to body weight) organ weight suggested a compound related effect.

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Organ Weights: Group Mean Values^a For Spleen and Thymus (G)

<u>Dose (ppm)</u>	<u>0</u>	<u>300</u>	<u>1000</u>	<u>3000</u>	<u>10000</u>
<u>Male - SPLEEN</u>					
<u>-Absolute</u> 13-wks	0.60	0.57*	0.58	0.56**	0.55**
<u>-Relative to Body weight</u> 13-wks	0.20	0.19*	0.19	0.19*	0.19

<u>Male - THYMUS</u>					
<u>-Absolute</u> 13-wks	0.33	0.30	0.26*	0.33	0.28*
<u>-Relative to Body weight</u> 13-wks	10.9	10.2	8.8**	11.1	9.8
<u>Female - THYMUS</u>					
<u>-Absolute</u> 13-wks	0.27	0.26	0.26	0.24	0.22*
<u>-Relative to Body weight</u> 13-wks	14.7	14.5	14.4	13.4	12.6*

* P<0.05

** P<0.01

^aTable 8 and 9, Registrant submitted text.7. Histopathology Examination:

7.1 Non-Neoplastic: Most non-neoplastic lesions observed in this study were of a type and incidence that normally be expected to be seen in rats of this strain and age. The most common findings were: nephrocalcinosis of the kidney, peri-acinar hepatocytic vacuolation, congestion of the thymus (registrant submitted summary Table attached). These findings occurred equally in both the control and 10000 ppm treated groups and are not considered to be related to the test material.

In the liver, an increased incidence of biliary hyperplasia was reported in the 10000 ppm males (4/15 animals observed) when compared to concurrent control males (0/15 animals observed). These observations and additional supporting evidence, such as statistically significant increase in liver weights (absolute and relative to body weight), decreased cholesterol, increased alkaline phosphatase and increased lactate dehydrogenase, that suggest that the liver is a target organ.

Additionally, there was an increase in incidence of hydrometra of

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the uterus in high dose females (3/15 animals examined) when compared to control (0/15 examined). The toxicological significance of this finding is of minimal concern even if it is treatment related.

7.2 Neoplastic: No neoplastic changes were reported in any test group.

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Reviewed By: Carolyn A. Gregorio *AG 7-21-89*
Section I, Toxicology Branch I - IRS (TS-769C)
Secondary Reviewer: Robert P. Zendzian, Acting Section Head
Toxicology Branch I - IRS (TS-769C) *2/15/89*

DATA EVALUATION REPORT

Study Type: 82-1 5-Week Oral Range-Finding In Mice

Tox Chem No.: 652B

Accession No.: None

MRID No.: ~~402764-02~~ 404961-01

Test Material: Sumithrin, technical grade (Purity 92.6%)

Synonyms: d-phenothrin

Sponsor: Sumitomo Chemical Company Limited

Testing Facility: Life Science Research (Suffolk, England)

Study No.: 83/SUM006/024

Title: Sumithrin: Five Week Range-Finding Toxicity Study In Mice.

Author: S.J. Ames, S.M. Macrae, J.C. Whitney

Report Issued: June 1, 1983

Conclusion: Possible treatment related effects were observed in the liver of both high dose males and females (10000 ppm) as evidenced by increases in liver enzyme activity, liver weights (absolute and relative to body weight) and periacinar hepatocytic hypertrophy when compared to control animals. In addition, decreased kidney weights (absolute and relative to body weight) were also observed in high dose males and may be indicative of a toxic response. All other examined parameters were similar to those reported for control animals.

An increase in liver weights (both absolute and relative to body weight) and periacinar hepatocytic hypertrophy was observed in the next highest dose (3000 ppm) males while an increase in liver weights only was reported in females of this group when compared to respective control animals; no differences in other examined parameters were noted.

This study is classified as Core Supplementary pending the submission and review of the individual animal histopathological data. In the interim, the tentative conclusions for this study

are as follows:

1. Male Mice

NOEL = 1000 ppm (190 mg/kg/day)

LOEL = 3000 ppm (565 mg/kg/day) Increased liver weights,
increased periacinar hepatocytic hypertrophy.

At 10000 ppm (1958 mg/kg/day) increased alkaline
phosphatase, increased liver weights, decreased kidney
weights, increased periacinar hepatocytic hypertrophy.

2. Female Mice

NOEL = 1000 ppm (230 mg/kg/day)

LOEL = 3000 ppm (710 mg/kg/day) Increased liver weights.

At 10000 ppm (2339 mg/kg/day) increased liver weights and
increased periacinar hepatocytic hypertrophy. increased
alkaline phosphatase.

Classification (Core-Grade):

Core-Supplementary pending submission of additional information.

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

A quality assurance statement, dated May 10, 1983 and signed
by D.J. Ford (Head Quality Assurance Unit, LSR) was present.

A. MATERIALS

1. Test Compound: Sumithrin, technical grade, Lot No.: 10102, Purity: 92.6%, pale yellow liquid, stored at 4 C.

2. Test Animals: B6C3F1 hybrid mice, Supplier: Charles River (Kent, England), "under five weeks of age upon arrival"; body weights (2 days after arrival): males, 13-17 g and females, 12-20 g; acclimation period: 7 days; Housing: one animal/polypropylene cage.

3. Diet: Laboratory Animal Diet No. 2, powdered: Supplier: Labsure, K and K Greeff Chemicals, Ltd. (Surrey, England).

B. STUDY DESIGN

1. Animal Assignment: Animals were assigned using a set of computer-generated random numbers to the following test groups:

<u>Test Group</u>	<u>Dietary Dose (ppm)</u>	<u>Males</u>	<u>Females</u>
1	0	12	12
2	300	12	12
3	1000.	12	12
4	3000	12	12
5	10000	12	12

All animals were given food and water ad libitum for the duration of the study.

2. Dosage Levels: "The dietary concentrations for this study were selected by the Sponsor."

3. Diet Preparation: Diets were prepared weekly and stored at room temperature in the animal room within light-proof plastic storage bins. The stability and homogeneity were reported to be "identical to those used in a preliminary study conducted with Sumithrin in the rat (see LSR Report No. 82/SUM002/222) evidence was available prior to the commencement of this study that stability and homogeneity of admixed Sumithrin was satisfactory; these assays were therefore not repeated."

Concentration of test material in the diet was analytically determined at weeks 1 and 5. The mean percentage of intended values for groups 1, 2, 3, 4 and 5 were 0, 95, 96, 97 and 95 percent, respectively.

C. METHODS:

1. Observations: Animals were observed twice each day for mortality and signs of toxicity and were palpated weekly for swellings. Severely debilitated and moribund animals were sacrificed.

2. Body Weights: All animals were weighed weekly.

3. Food Consumption, Water Consumption, Food Conversion Ratio and Compound Intake: Food consumption, food conversion and compound intake were determined for individual animals on a weekly basis. Water consumption was checked daily by visual inspection of water bottles.

4. Blood Collection: No pre-test blood sampling was performed. However, after five weeks of treatment, blood from all mice was collected from the retro-orbital sinus and examined. The mice were not deprived of food or water prior to collection of the samples.

The following hematological parameters were examined:

Packed Cell Volume (PCV)
Hemoglobin (HCB)
Leukocyte Count (WBC)
Erythrocyte Count (RBC)
Mean Cell Hemoglobin (MCHC)
Mean Cell Volume (MCV)
Mean Cell Hemoglobin (MCH)

The following blood chemistries were examined:

Alanine amino-transferase (ALT)
Aspartate amino-transferase (AST)
Alkaline phosphatase (AP)
Urea
Glucose
Total Protein
Electrophoretic protein fractions
Sodium
Potassium

5. Gross Necropsy: All animals were subjected to a standardized gross necropsy procedure which included:

- a. preparation of femoral bone marrow smear,
- b. examination of the external surfaces, the contents of the cranial, thoracic and abdominal cavities and the residual carcass,
- c. weighing of selected organs (described below) and,
- d. removal and fixation of the following organs and/or tissues: adrenals, aortic arch, bone (joint), brain including brain stem, bronchi, caecum, carcass, colon.

duodenum, epididymides (left and right), eyes and optic nerve, gall bladder, harderian glands (right and left), heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (cervical and mesenteric), mammary glands, marrow smear, esophagus, ovaries, pancreas, pituitary, prostate, salivary glands sciatic nerve, skeletal nerve, skin, spinal cord (thoracic-lumbar), spleen, stomach, testes, thymus, thyroids (right and left), tongue, trachea, urinary bladder, uterine cervix, uterus.

6. Organ Weights: Weighing of the following selected organs for all groups at termination of the study: brain, heart, kidneys, liver spleen and testes.

7. Histology: Histological examination of the following tissues for male and female treatment groups 1 (control) and 5 (10000 ppm sumithrin): abnormalities, adrenals, brain, heart, kidneys, ovaries, pituitary, spleen testes, thyroids. Sections of the liver were taken for examination from each animal in all groups.

D. RESULTS

1. Observations: Signs of toxicity, appearance and behavior observed in this study were typical of mice of the strain and age employed.

One male animal in the 3000 ppm group (Animal No. 41) was sacrificed following "entrapment of its tail between the cage lid and cage body." All other animals on study survived to terminal sacrifice after five weeks on study.

No palpable swellings were reported in any treatment group.

2. Body Weights: Group absolute body weights and group mean body weight changes were similar for both males and females throughout the study (Table 1, registrant submitted report). Mean weight gain for all male groups was reported to be between 4 and 5 grams over the five week study and between 3 and 4 grams for females.

3. Food Consumption, Water Consumption, Food Conversion Ratio and Compound Intake:

3.1 Food Consumption: Food consumption was similar for all groups on throughout the five week study.

3.2 Water Consumption: Increased water consumption was reported in the 10000 ppm males and females following the first week on test when compared to respective control groups. The percentage increase for high dose males and females was calculated to be 32 and 26 percent, respectively. At termination of the study at five weeks, only high dose males were reported to

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TABLE 1

Bodyweight - group mean values (g)

Group	:	1	2	3	4	5
Compound	:	Control	----- Sumithrin -----			
Level (ppm)	:	0	300	1000	3000	10000

Week number	1M		2M		3M		4M		5M	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	19	1	19	1	18	1	18	2	19	1
1	20	1	21	1	20	1	20	1	20	2
2	21	1	21	1	21	1	21	2	20	1
3	22	1	22	1	22	1	22	1	21	1
4	22	1	22	1	22	1	22	1	22	1
5	23	1	23	1	23	1	22	1	23	2

Bodyweight

gain

Weeks 0-5	4	4	5	4	4
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SD Standard deviation

TABLE 1 - continued

Bodyweight - group mean values (g)

Group	:	1	2	3	4	5
Compound	:	Control	----- Sumithrin -----			
Level (ppm)	:	0	300	1000	3000	10000

Week number	1F		2F		3F		4F		5F	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	17	1	17	1	17	1	17	1	17	1
1	17	1	18	1	18	1	18	1	18	1
2	18	1	18	1	18	1	18	1	18	1
3	19	1	19	1	19	1	19	1	19	1
4	20	1	20	1	20	1	20	1	19	1
5	21	1	20	1	20	1	20	0	20	1

Bodyweight

gain

Weeks 0-5	1	1	3	1	3
-----------	---	---	---	---	---

SD Standard deviation

have increased (13 percent) water consumption. The significance of this finding is questionable although mean group kidney weights were decreased for these groups and may represent very limited evidence of treatment related toxicity.

3.3 Food Conversion: Food conversion ratios (amount of food consumed per unit gain in body weight) were calculated weekly. Both high dose male and female mice (10000 ppm) were reported to have higher food conversion ratios (increases of 24 and 20 percent, respectively) when compared to concurrent control animals over the five week time frame.

3.4 Compound Intake: Compound intake, calculated as group mean values in units of mg/kg/day, is reported as follows:

Group	Dietary Dose (ppm)	Compound Intake (mg/kg/day)	
		Males	Females
1	0	---	---
2	300	57	71
3	1000	190	230
4	3000	565	710
5	10000	1958	2339

4. Blood Collection:

4.1 Hematological Examination: Statistically significant (Student's t-test) decreases of group mean Packed Cell Volume in both the 10000 ppm male and female mice were observed when compared to respective control mice. However, in the absence of other meaningful hematological parameters and since the inter-group differences are extremely small as well as no dose-response relationship, the toxicological significance of this finding is questionable.

<u>Packed Cell Volume^a</u>		
Dietary Dose (ppm)	Male	Female
0	46	46
300	46	46
1000	46	46
3000	46	45
10000	45**	45*

*P<0.05

**P<0.01

^aTable 5, Registrant submitted text.

Additionally, a statistically significant decrease in mean cell hemoglobin was reported in the 10000 ppm female mice when compared to controls. However, as shown in the Table below, the relevance of this finding is of little importance since there is

no inter-group variation and other treated groups were not considered to show statistical significance when compared to controls. 007502

Mean Cell Hemoglobin^a

<u>Dose (ppm)</u>	<u>Females</u>
0	18
300	17
1000	17
3000	17
10000	17*

*P<0.05

^aTable 6, Registrant submitted test.

Other examined blood parameters were similar for treated and control animals.

4.2 Clinical Chemistries: Several examined parameters showed statistically significant changes (Student's t-test) between treated groups and respective controls. These noted differences are discussed below.

Group mean values for liver enzyme alkaline phosphatase were reported to be significantly higher in both high dose males and females (10000 ppm) when compared to controls. Based on other histopathological findings reported in this study (increased liver weights and increased incidence of periacinar hepatotoxic hypertrophy), the increase in liver enzymes is considered a possible treatment related effect.

Alkaline Phosphatase^a

<u>Dose (ppm)</u>	<u>Males</u>	<u>Female</u>
C	103	133
300	107	129
1000	100	135
3000	100	121
10000	145***	172***

***P<0.001

^aTable 7, Registrant submitted test.

Other parameters which showed significant variation from control values are presented below. The toxicological significance of these findings is considered to be of minor biological relevance since the variation between groups was very small and no other corroborative evidence was seen in other examined parameters.

Clinical Chemistries^a

Dose (ppm)	Urea (mg%)	Glucose (mg%)	Albumin	Globins
	Females	Female	Female	Male
0	42	165	3.1	0.9
300	45	162	3.1	0.9
1000	43	173	3.2	0.9
3000	43	178*	3.2	1.0
10000	50**	152*	3.3*	1.2***

*P<0.05

**P<0.01

***P<0.001

^aTable 7, Registrant submitted test.

5. Gross Necropsy: Gross pathological findings were consistent with what would be expected in this strain and age of mice used in this study with the possible exception of the noted "pale subcapsular area" in the liver in the 10000 ppm females (2/12 animals examined).

Results of the femoral bone marrow smears were not reported.

6. Organ Weights: Group mean values for liver weights are presented below. For male mice, absolute and relative (to body weight) were significantly increased for the 3000 and 10000 ppm treatment animals when compared to controls (Student's t-test). Similar increases were reported for the 1000, 3000 and 10000 ppm females. These findings are suggestive of establishing the liver as a possible target organ and are considered to be suggestive of a treatment related response.

Organ Weights: Group Mean Values^a For Liver (G)

Dose (ppm)	0	300	1000	3000	10000
<u>Male</u>					
<u>-Absolute</u>					
5-wks	1.32	1.38	1.36	1.52**	2.16***
<u>-Relative to Bodyweight</u>					
5-wks	5.5	5.7	5.7	6.5***	9.2***
<u>Female</u>					
<u>-Absolute</u>					
5-wks	1.16	1.21	1.25	1.38*	2.01***
<u>-Relative to Bodyweight</u>					
5-wks	5.5	5.8	5.9*	6.6***	9.7***

* P<0.05

** P<0.01

*** P<0.001

^aTable 9, Registrant submitted text

Group mean values for kidney weights (males only) are presented below. Reported significant decreases in both absolute and relative to body weight ratios of kidneys in the 3000 and 10000 ppm males were observed. Although decreased kidney weights are considered to be suggestive of possible treatment related toxicity, the biological significance is difficult to interpret since there is no corroborative evidence of toxicological concern in other examined parameters.

Organ Weights: Group Mean Values^a For Male Kidney (G)

<u>Dose (ppm)</u>	<u>0</u>	<u>300</u>	<u>1000</u>	<u>3000</u>	<u>10000</u>
<u>-Absolute</u> 5-wks	0.39	0.39	0.39	0.36**	0.34***
<u>-Relative to Body weight</u> 5-wks	1.63	1.63	1.63	1.53*	1.44***

* P<0.05

** P<0.01

*** P<0.001

^aTable 9, Registrant submitted text.

7. Histopathology Examination: The submitted individual histopathology data (Appendix 12a and Appendix 12b) is incomplete as presented. As indicated in the protocol section of the text, selected organs (heart, brain, spleen, etc.) were identified as the tissues which were to be examined from Groups 1 (control) and 5 (10000 ppm); livers were to be examined in all animals from each group. However, the individual animal data that has been provided does not indicate whether all designated tissues were actually examined since appropriate notation was frequently absent in the column used to identify the tissue examined. The registrant should provide the following information for each animal: Group Number, Animal Number, identify each tissue examined, identify the corresponding microscopic observation for each tissue examined. In addition, the submission does not include any individual animal data for male Groups 3 and 4 microscopic examination of livers. The registrant should provide these data as soon as possible.

7.1 Non-Neoplastic: In the liver, an increased incidence of peri-acinar hepatocytic hypertrophy in the 3000 and 10000 ppm males and females was reported. (NOTE: Incidence data for the 1000 and 3000 ppm male animals were taken from the registrant's submitted summary table, Table 11; individual animal data for these groups were not provided.) In addition, necrosis of the liver was noted in the 3000 and 10000 ppm females and only in the 1000 ppm male group. Although these data are suggestive of mild

liver toxicity, they are not considered to be severe or life-threatening.

Liver Non-Neoplastic Observations^a

<u>Dose (ppm)</u>	<u>Hypertrophy¹</u>		<u>Necrosis²</u>	
	<u>Males</u>	<u>Females</u>	<u>Males</u>	<u>Females</u>
0	0/12	0/12	0/12	0/12
300	0/11	0/12	0/11	0/12
1000	0/12	0/12	1/12	0/12
3000	4/11	1/11	0/11	1/11
10000	9/12	4/12	0/12	1/12

^aTable 11, Registrant submitted text.

¹Periacinar hepatocytic hypertrophy

²Unifocal and multiple foci

Other noted microscopic observations were: testicular atrophy (1/12 animals) in the 10000 ppm male group and cortical hyperplasia of the adrenals (1/12 animals) in the 10000 ppm male group.

7.2 Neoplastic: No neoplastic lesion was reported for any animal in any dose group.

Sumithrin: Toxic and Pathologic Effects (WHO 45, 1970, 1971)

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TABLE 11

Micropathological entities recorded
in mice sacrificed after 5 weeks of treatment

Group	1	2	3	4	5					
Compound	Control	-----	Sumithrin	-----						
Level (ppm)	0	300	1000	3000	10000					
Micropathology	Group and sex									
	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Number of animals examined	12	11	12	11	12	12	12	12	11	12
Adrenal glands										
- focal cortical hyperplasia	0	-	-	-	1	0	-	-	-	0
Liver										
- very slight periacinar hepatocytic hypertrophy	0	0	0	4	0	0	0	0	1	0
- slight periacinar hepatocytic hypertrophy	0	0	0	0	9	0	0	0	0	4
- unifocal necrosis	0	0	1	0	0	0	0	0	1	0
- multiple foci of necrosis	0	0	0	0	0	0	0	0	0	1
Testes										
- focal tubular atrophy	0	-	-	-	1	-	-	-	-	-
Trachea										
- mucus in lumen	1	-	-	-	0	0	-	-	-	0
Uterine fat pad										
- necrosis	-	-	-	-	-	0	-	-	-	1

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