UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 16 1989

007088

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sumithrin (d-phenothrin) - Review of Toxicity Studies Submitted by Sumitomo Chemical Company in Support of PAP#1H5283 and EPA Registration No. 10308-6

HED Project No.: 7-0927
Record No.: 200982
TOX Chem No.: 552B

FROM: Edwin R. Budd, Section Head
Review Section I
Toxicology Branch I, Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Joseph M. Tavano, PM Team 17
Insecticide-Rodenticide Branch
Registration Division (H7505C)

THRU: Judith W. Hauswirth, Chief Judith W. Hauswirth 3/15/89
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C

The Sumitomo Chemical Company has submitted five toxicity studies in support of PAP#1H5283 and EPA Registration No. 10308-6. Detailed reviews of four of these studies are attached. The fifth study (Multigeneration Reproduction Study in Rats, Life Science Research, Ltd. Report No. 85/SUM009/331, November 1988, Sumitomo Reference No. ET-61-0101) is still under review in Toxicology Branch. Preliminary review indicates that this study is likely to be fully acceptable in fulfillment of the requirement for a multigeneration reproduction study. Furthermore, the results in this study are not likely to significantly affect the toxicological assessment of this chemical in terms of it being the most sensitive study or the [illegible] related endpoints such as the [illegible] the detailed review of this study will be forwarded to Registration Division as soon as it is available.

Summaries of pertinent information from the remaining four studies are presented below.

1. Combined Chronic Feeding/Oncogenicity Study in Mice, Life Science Research (England), LSR Report No. 86/SIM007/166, April 198[illegible], Sumitomo Reference No. ET-71-0109.

   Test Material - Sumithrin, technical grade.

   Conclusions - This study is classified as Core Supplementary pending submission and review of the additional information and explanations briefly itemized below. Full discussions and more detailed requirements are presented in the detailed review and should be consulted. See especially, pages 5-6 and 25-27.

   a. Appropriate statistical analyses of group mean absolute body weight data for male and female mice in both the Lifespan Study and the Toxicity Study.

   b. More detailed and sophisticated statistical analyses of group mean body weight changes for male and female mice in both the Lifespan Study and the Toxicity Study.

   c. Justification for the strain of mouse used in this study, particularly with respect to its sensitivity to liver tumors.

   d. Historical control data for liver tumors in the strain of mouse used in this study, particularly from the same animal supplier and testing laboratory.

   e. Justification for the dosage levels used in this study, particularly with regard to a "maximum tolerated dose."

   f. The full and complete report on the preliminary range-finding study (LSR Report No. 83/SIM004[illegible]).

   g. Preparation and histopathological examination of microscopic slides of liver tissues from all mice in the Toxicity Study that were not previously examined.

In the interim, the tentative conclusions in this study are as follows:

a. For Male Mice

NOEL = 300 ppm (or 45 mg/kg/day)
LOEL = 1000 ppm (or 150 mg/kg/day). At this dosage level, increased liver weights and decreased kidney weights were observed.
At 3000 ppm (or 450 mg/kg/day, HDT) possibly decreased body weight gains, increased liver weights and decreased kidney weights were observed.
Oncogenic potential - Undetermined at this time.

b. For Female Mice

NOEL = 1000 ppm (or 150 mg/kg/day)
LOEL = 3000 ppm (or 450 mg/kg/day, HDT). At this dosage level, possibly decreased body weight gains, increased liver weights, and possibly increased kidney weights were observed.
Oncogenic potential - Undetermined at this time.

Classification (Core-Grade) - Core-Supplementary, pending submission of additional information and explanations (see above under "Conclusions").

2. Combined Chronic Feeding/Oncogenicity Study in Rats, Life Science Research (England), LSR Report No. 85/SMM03 586, January 1987, Sumitomo Reference No. [illegible].

Test Material - Sumithrin, technical grade.

Conclusions - This study is classified as Core Supplementary pending submission and review of the additional information and explanations itemized below.

a. Justification for the dosage levels used in this study, and particularly with regard to whether a "maximum tolerated dose" was used in this study.

b. The full and complete report on the 13-week preliminary study (LSR Report No. 82/SMM02/022).

In the interim, the tentative conclusions for this study are as follows:

NOEL = 1000 ppm (or 50 mg/kg/day)
LOEL = 3000 ppm (or 150 mg/kg/day). At this dosage level, possibly decreased body weight gain in females, increased relative liver/body weight ratios in males, increased cystic dilatation of sinuses in mesenteric lymph nodes in males, and increased periacinar hepatocytic hypertrophy in liver in males.
Oncogenic potential - Not fully determined at this time.

Classification (Core-Grade) - Core-Supplementary, pending submission of additional information and explanations (see above under "Conclusions").

3. Chronic Feeding Study in Dogs, Hazleton Laboratories America (Vienna, Virginia), HLA Report No. 343-173, April 2, 1987, Sumitomo Reference No. ET-71-0108.

Test Material - Sumithrin, technical grade.

Conclusions - The conclusions for this study are as follows:

NOEL = 300 ppm (8.2 mg/kg/day in males and 7.1 mg/kg/day in females).

LOEL = 1000 ppm (27.7 mg/kg/day in males and 26.8 mg/kg/day in females). At this dosage level, hepatocellular enlargement in liver, focal degeneration in adrenal cortex.

At 3000 ppm (HDT), also signs of anemia (decreased RBC, hemoglobin and hematocrit), decreased serum albumin and total protein, and increased absolute and relative liver weights, all in both males and females.

Classification (Core-Grade) - Core-Guideline

4. Metabolism Study in Rats, Sumitomo Chemical Company, Report Nos. 340, 341, 342, 343, 502, and 503, April 6, 1987, Sumitomo Reference No. EM-70-0017.

Test Material - (1R,trans) and (1R,cis) [benzyl-C^{14}] phenothrin.

Conclusions - Nearly 96 to 100 percent of C^{14} phenothrin was eliminated in the urine and feces within seven (7) days. Of the low amounts in tissues, the cis isomer was present at 2 to 10 higher levels in fat than the trans isomer. In addition to fat, the skin with hair and the carcass also had low amounts of radioactivity.

There were few differences between sexes in the amount of C^{14} in excreta, in tissues, or in amounts and identity of metabolites in excreta for the low-dose and high-dose groups. The repeated dose groups had higher levels of urinary metabolites indicating improved absorption.

The major urinary metabolite was 3-(4-hydroxyphenoxy) benzoic acid sulfate (4'-OH-PB acid surfate) which was present at levels ranging from 6.8 to 17.9 percent for the cis isomer and from 14.8 to 55.4 percent for the trans isomer.

The major metabolic pathway proposed based on the data involves hydrolysis of the ester linkage, followed by conjugation with glucuronic acid, glycine, or sulfuric acid.

Classification - Core-Guideline

Attachments

Reviewed By: Edwin R. Budd
Section I, Toxicology Branch I - IRS (TS-769C) Budd 3/6/89
Secondary Reviewer: Judith Hauswirth
Toxicology Branch I - IRS (TS-769C) Judith W. Hauswirth 3/6/89

DATA EVALUATION REPORT

Study Type: 83-5, Combined Chronic Toxicity/Oncogenicity Study - Mice

TOX Chem No.: 652B

Accession No.: None

Test Material: Sumithrin, technical grade (Purity 92.9%)

MRID No.: 402764-02 (5 Volumes

Synonyms: d-phenothrin

Sponsor: Sumitomo Chemical Company, Ltd. (Sumitomo Reference No. ET-71-0109)

Testing Facility: Life Science Research (Suffolk, England)

Study Number: LSR #86/SUM007/166

Title of Report: Sumithrin: Oncogenicity and Toxicity Study in Mice.

Author: S.J. Ames

Report Issued: April 1987

Conclusions:

This study is classified as Core Supplementary pending submission and review of the additional information and explanations briefly itemized below. Full discussions and more detailed requirements are presented in the body of this review and should be consulted. See especially, pages 5-6, and 25-27.

1. Appropriate statistical analyses of group mean absolute body weight data for male and female mice in both the Lifespan Study and the Toxicity Study.

2. More detailed and sophisticated statistical analyses of group mean body weight changes for male and female mice in both the Lifespan Study and the Toxicity Study.

3. Justification for the strain of mouse used in this study, particularly with respect to its sensitivity to liver tumors.

6

4. Historical control data for liver tumors in the strain of mouse used in this study, particularly from the same animal supplier and testing laboratory.

5. Justification for the dosage levels used in this study, particularly with regard to a "maximum tolerated dose."

6. The full and complete report on the preliminary range-finding study (LSR Report No. 83/SUM006/024).

7. Preparation and histopathological examination of microscopic slides of liver tissues from all mice in the Toxicity Study that were not previously examined.

In the interim, the tentative conclusions in this study are as follows:

1. For Male Mice

NOEL = 300 ppm (or 45 mg/kg/day.
LOEL = 1000 ppm (or 150 mg/kg/day). At this dosage level, increased liver weights and decreased kidney weights were observed.
At 3000 ppm (or 450 mg/kg/day, HDT) possibly decreased body weight gains, increased liver weights and decreased kidney weights were observed.
Oncogenic potential - Undetermined at this time.

2. For Female Mice

NOEL = 1000 ppm (or 150 mg/kg/day)
LOEL = 3000 ppm (or 450 mg/kg/day, HDT). At this dosage level, possibly decreased body weight gains, increased liver weights, and possibly increased kidney weights were observed.
Oncogenic potential - Undetermined at this time.

Classification (Core-Grade):

Core-Supplementary, pending submission of additional information and explanations see above under "Conclusions".

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

Quality Assurance Statement:

A quality assurance statement, dated April 22, 1987 and signed by D.D. Ford Head of Quality Assurance Unit, LSR was provided.

A. Materials:

1. Test Compound - Sumithrin, technical grade, Lot No.: 21005, Purity: 92.9%, clear amber liquid, stored at 4 °C.

2. Test Animals - B6C3F1 hybrid strain mice, specified pathogen-free, Supplier: Charles River (Kent, England), 21 to 31 days old on arrival; Body weights (2 days after arrival): Males, 8 to 23 g; Females, 8 to 19 g; Acclimatization period: 7 days; Housing: Individually in polypropylene cages.

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:

Test Group	Dosage Level in Diet (ppm)	Lifespan Study[1] 104 Weeks		Toxicity Study[2] 26, 53, and 78 Weeks	
		Males	Females	Males	Females
Control	0	50	50	40	40
Low (LDT)	300	50	50	40	40
Mid (MDT)	1000	50	50	40	40
High (HDT)	3000	50	50	40	40

[1]All mice in the Lifespan Study were permitted, if possible, to live the full duration of the study. Surviving males were actually sacrificed at 105 weeks and surviving females at 106 weeks.
[2]Ten mice/sex/group in the Toxicity Study were sacrificed at 26 and 53 weeks and all remaining survivors at 78 weeks.

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

2. Dosage Levels - The dosage levels used in this study were stated to be "selected in consultation with the sponsor (Sumitomo) after consideration of the results obtained in a preliminary range-finding study (IRI Report No. 83/SUI 008 004)."

3. Diet Preparation - The diet was prepared weekly and stored at room temperature in the animal room within light-proof plastic storage bins. The stability of the test material

in the diets was determined after 1 and 2 weeks storage at 21 °C and found to be acceptable. Homogeneity of test material in the diet was determined prior to treatment and was found to be acceptable. Concentration of test material in the diet was analytically determined at weeks 1, 13, 26, 39, 52, 65, 78, 91, and 104. The mean percentages of intended values for the low, mid, and high dosage level groups were 99 ± 6.1, 94 ± 2.0, and 97 ± 4.1 percent, respectively.

C. Methods and Results:

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.

Survival of animals in the Lifespan Study was relatively high with 80 to 84 percent of the males and 72 to 78 percent of the females surviving the entire duration of the study. The test material had no effect on the distribution or time of deaths.

Cumulative Mortality in Lifespan Study

	Males				Females			
Week No.	Cont.	300	1000	3000	Cont.	300	1000	3000
52	0	0	0	0	1	2	1	0
78	2	1	1	3	2	3	1	1
91	3	4	2	5	5	5	5	6
105 106	10	8	8	9	11	14	13	14

The numbers of survivors in the Lifespan Study at 105 weeks for males were 40 (80%), 42 (84%), 42 (84%), and 41 (82%) for the control, low, mid, and high dosage levels, respectively. The corresponding numbers of survivors at 106 weeks for females were 39 (78%), 36 (72%), 37 (74%), and 36 (72%).

Signs of toxicity, appearance, and behavior observed in the animals were typical of mice of the strain and age employed in this study. There was no apparent relationship to treatment with the test material.

The numbers of mice with palpable swellings observed at various times during the study were unrelated to treatment. For males, the incidences were 23, 16, 16, and 14 for the control, low, mid, and high dosage level groups, respectively. For females, the respective incidences were 14, 27, 19, and 16.

2. Body Weights - All animals were weighed weekly for the first 14 weeks and at 2-week intervals thereafter.

Overall, the body weight data for absolute weight and for body weight changes were quite difficult to interpret because 1) the differences, if any, between groups were quite small; and 2) statistical analyses of the data provided in the report were incomplete and/or inadequate. The registrant is requested to provide appropriate statistical analyses of the group mean absolute body weight data (see below) and to also provide a more detailed and sophisticated statistical analysis of group mean body weight changes that will permit a more confident interpretation of the body weight data (see below). These analyses should be provided for both male and female mice in both the Lifespan and the Toxicity studies. In the interim, body weight changes and differences observed in the study, and particularly at the high dosage level, for both male and female mice will be regarded as equivocal and only possibly induced by the test material.

Lifespan Study:

Group Mean Absolute Body Weights - Graphical representations of group mean body weights are presented in Figure 2A and 2C (from the study report, attached). For the high dosage level male mice, group mean body weights were consistently lower than for control male mice from about week 6 to the end of the study. The difference, however, appeared to be rather small (generally less than 2 g). For the high dosage level female mice, group mean body weights were consistently lower than for control female mice from about week 82 to the end of the study. As with males, the difference again appeared to be rather small (generally less than 3 g). A table listing group mean body weights (with standard deviations) for each weekly or biweekly weighing was also presented. These data, however, were not statistically analyzed so it was not possible to conclude whether differences in group mean absolute body weights were or were not statistically significant.

The registrant is requested to provide statistical analyses of these data to EPA.

Group Mean Body Weight Changes - A summary table of group mean body weight changes for male and female mice in the Lifespan Study is presented in Table 3B (from the study report, attached). For mid and high dosage level male mice, a statistically significant (p [illegible] Student's t-test, decrease in body weight gain was observed during weeks 1 to 14. The percentage decrease compared to the

control male group, was calculated by this reviewer to be -6.4 and -7.5 percent for the mid and high dosage level groups, respectively. A nonsignificant decrease of -7.5 percent was also calculated for high dosage level male mice, compared to control male mice for the entire study (weeks 0 to 104). For female mice, no statistically significant differences in group mean body weight changes were noted. A nonsignificant decrease of -9.9 percent was calculated, however, for high dosage level female mice compared to control female mice for the entire study (weeks 0 to 104).

The statistical analysis of body weight changes provided in the report is generally inadequate in that it does not permit a confident interpretation of the study data. The time intervals chosen for analysis (for males, 0 to 60 weeks, 60 to 104 weeks, and 0 to 104 weeks; and for females, 0 to 52 weeks, 52 to 72 weeks, 72 to 104 weeks, and 0 to 104 weeks) are too long and provide too few time points for meaningful comparison of intergroup differences.

Toxicity Study:

Graphical representation of group mean absolute body weights for male and female mice in the Toxicity Study are presented in Figures 2B and 2D from the study report, attached. A summary table of group mean body weight changes is also presented in Table 3D (from the study report, attached).

In general, comments made on the body weight data for the Lifespan Study are equally applicable to the Toxicity Study. The registrant is again requested to provide missing and/or more detailed statistical analyses of the body weight data in the Toxicity Study (as was previously requested for the Lifespan Study).

2. Food Consumption, Water Consumption, Food Conversion Ratio, and Compound Intake - Food consumption determined for individual animals on a weekly basis for the duration of the study, was not affected by the test material.

Water consumption was checked by daily visual inspection of water bottles. In addition, accurate measurements of water consumption over a 4-day period were made on 10 mice per group during weeks 26, 51, 78, and 105. Water consumption was not affected by treatment with the test material.

Food [illegible] ratios, amount of food consumed per unit gain in body weight, were calculated weekly for the first 26 weeks of the study. Although male mice [illegible]

11

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Pages 12 through 17 are not included.

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____ Identity of product inert ingredients.

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highest dosage level (3000 ppm) were reported to have had slightly higher food conversion ratios than male control mice over the first 14 weeks in the Lifespan Study, this difference was probably not biologically meaningful because a similar increase was not also observed in the Toxicity Study and body weight and food consumption differences during this time, when considered separately, were not appreciable.

Compound intake, calculated as group mean values in units of mg/kg/day, was determined weekly for the first 14 weeks and at 2-week intervals thereafter. No attempt was made in the report, however, to determine mean compound intake for the various groups over the entire duration of the study or any major portions thereof. A cursory inspection of the data by this reviewer indicates that the mean compound intake over the duration of the study for the treated groups, in units of mg/kg/day, is likely to be quite similar to what one would obtain by utilizing the standard Lehman conversion factor of 0.15, namely:

Dosage Level in Diet (ppm)	Compound Intake (mg/kg/day)
0	0
300	45
1000	150
3000	450

e. Ophthalmological Examinations were performed on all mice in the Lifespan Study prior to initiation of treatment and on 10 mice/sex/group from the control and high dosage level groups at 26, 52, 77, and 104 weeks. No effects attributable to the test material were observed.

f. Blood Collection - Prior to treatment, blood samples were collected from the retro-orbital sinus of 24 male and 24 female mice for clinical patnology examinations. Hematological examinations were performed on 8 of these mice/sex and clinical chemistries on 16 of these mice/sex (8 mice/sex for each clinical chemistry test due to the small size of the animals). Blood samples were also similarly collected from 10 mice/sex/group from animals in the Toxicity Study during weeks 25, 54, 79 (males), 80 (females), and from 10 mice sex/group from animals in the Lifespan Study during week 103. Both hematological examinations and clinical chemistries were performed on blood samples from the same animals during the treatment period. The mice were not deprived of food or water prior to collection of blood samples.

a. Hematological Examinations - The following "checked" parameters were examined.

X		X	
X	Hematocrit (HCT)		Total plasma protein (TP)
X	Hemoglobin (HCB)	X	Leukocyte differential count
X	Leukocyte count (WBC)	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)	X	Mean corpuscular HGB concentration (MCHC)
X	Platelet count	X	Mean corpuscular volume (MCV)

No hematological effects attributable to the test material were observed.

b. Clinical Chemistries - The following "checked" parameters were examined.

X		X	
	Electrolytes:		Other:
X	Calcium		Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
	Phosphorus	X	Cholesterol
	Potassium		Globulins
X	Sodium	X	Glucose
	Enzymes	X	Total Bilirubin
X	Alkaline phosphatase (AP)	X	Total Protein
X	Cholinesterase		Triglycerides
	Creatinine phospho-kinase	X	Direct Bilirubin
X	Lactic acid dehydrogenase (LDH)	X	Electrophoretic protein fractions
X	Serum alanine aminotransferase (ALT)		
X	Serum aspartate aminotransferase (AST)		

No treatment-related changes in clinical chemistries were observed. Of particular note was that increased enzyme levels indicative of liver toxicity (AP, LDH, ALT, and AST) were not observed in this study.

c. Urinalysis - Urine was collected from 10 mice/sex/group from animals in the Lifespan Study during weeks 25, 51, 78, and 104. The following "checked" parameters were examined.

X	Appearance	X	Glucose
	Volume	X	Ketones
	Specific gravity	X	Bilirubin

X	pH	X	Blood
X	Sediment (microscopic)	X	Nitrite
X	Protein	X	Urobilinogen
		X	Total reducing substances

No effects attributable to the test material were observed.

7. Gross Necropsy - All animals in both the Lifespan Study and the Toxicity Study, regardless of the time or manner of death, were subjected to a gross pathological examination. In addition, all animals sacrificed during the study (on humane grounds or in extremis) and all animals sacrificed at scheduled sacrifice times were subjected to a standardized gross necropsy procedure which included 1) preparation of blood smears and/or femoral bone marrow smears; 2) examination of the external surfaces, the contents of the cranial, thoracic and abdominal cavities, and the residual carcass; 3) weighing of selected organs (scheduled sacrifice animals only) as described below under C.8; and 4) removal and fixation of organs and/or tissues for subsequent histopathological examinations as described below under C.9.

Blood smears revealed no effects attributable to the test material (also see C.5.a. above). Femoral bone marrow smears taken from mice killed during the treatment period and from mice sacrificed at 53 weeks and at 104 weeks were examined. Neither cellularity nor composition of the bone marrow was altered by treatment with the test material.

With the exception of liver masses, which are discussed below, gross pathological examinations did not reveal any lesions or effects related to the test material. Findings were of a nature and incidence that would be expected in this strain of mouse in animals of comparable age. An increased incidence of pulmonary congestion in high dosage level male and female mice at 26 weeks (only) was discounted as being of no meaningful biological significance.

The incidences of liver masses noted at gross pathological examinations are presented below.

Liver Masses

Dose (ppm)	Males 0	300	1000	3000	Females 0	300	1000	3000
Lifespan Study								
During study[1]	6/13	5/8	7/8	8/9	1/11	2/14	5/13	6/14
Term. Sac.[2]	17/42	24/42	29/42	26/41	5/39	12/36	8/37	10/36
Total	23/50	29/50	36/50	34/50	6/50	14/50	13/50	16/50
Toxicity Study								
During study[1]	1/2	0/4	0/3	0/2	0/0	0/0	0/0	1/1
At 26 weeks[3]	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
At 53 weeks[3]	0/10	1/10	3/10	5/10	0/10	0/10	0/10	0/10
At 78 weeks[3]	4/18	2/16	7/17	7/18	0/20	3/20	0/20	4/19
Total	5/40	3/40	10/40	12/40	0/40	3/40	0/40	5/40

[1]Animals sacrificed or died during study.
[2]Terminal sacrifice (104 weeks).
[3]Scheduled interim sacrifice.

Slightly increased incidences of liver masses in treated male and female mice were observed in the study, and particularly during the last 6 months of the study. The increases, however, were generally small and only suggested a possible relationship to the test material. An obvious and clear-cut dose response was not evident.

Since lung tumors have been associated with the administration of certain other synthetic pyrethroid chemicals, special attention is given here to pulmonary effects/lesions observed in this study. The incidences of lung masses noted at gross pathological examinations in this study are presented below.

Lung Masses

Dose (ppm)	Males				Females			
Lifespan Study								
During study[1]	6/13	0/8	4/8	3/9	0/11	2/14	1/13	2/14
Term. Sac.[2]	7/42	4/42	5/42	2/41	2/39	1/36	2/37	0/36
Total	13/55	4/50	9/50	5/50	2/50	3/50	3/50	2/50

[1]Animals sacrificed or died during study.
[2]Terminal sacrifice (104 weeks).

Lung Masses (cont'd)

Dose (ppm)	Males 0	300	1000	3000	Females 0	300	1000	3000
Toxicity Study								
During study[1]	0/2	0/4	0/3	0/2	0/0	0/0	0/0	0/1
At 26 weeks[3]	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
At 53 weeks[3]	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
At 78 weeks[3]	0/18	0/16	0/17	0/18	0/20	0/20	0/20	0/19
Total	0/40	0/40	0/40	0/40	0/40	0/40	0/40	0/40

[1]Animals sacrificed or died during study.
[3]Scheduled interim sacrifice.

The above incidences of lung masses clearly show no relationship to the test material.

8. Organ Weights - Absolute organ weights and relative organ/body weight ratios (expressed as percentages) were determined for all mice killed at the scheduled sacrifice times (i.e., at 26, 53, and 78 weeks for the Toxicity Study and at 104 weeks at the Lifespan Study). Organ weights and ratios were determined for the following 12 organs: adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pituitary gland (not at 26 weeks), spleen, testes, thymus, and uterus with cervix.

Group mean values for liver weights are presented below. For male mice, absolute and/or relative liver weights were significantly increased at 1000 and 3000 ppm at most scheduled sacrifice times during the study. For female mice, similar significant increases were observed, for the most part, only at 3000 ppm. The increases in absolute and relative liver weights for male mice at 1000 and 3000 ppm and for female mice at 3000 ppm are considered to be related to the test material.

Liver Weights
(Group Mean Values)

Dose (ppm)	Males				Females			
	0	300	1000	3000	0	300	1000	3000
Absolute Weights (g)								
26 weeks[1]	2.1	1.9	2.0	2.4	1.6	1.6	1.6	2.0**
53 weeks[1]	2.3	2.3	2.8*	2.5	1.9	1.8	2.1	2.2
78 weeks[1]	2.6	2.7	3.2	3.4**	1.9	2.1	2.2*	2.4**
Term. Sac.[2]	2.7	2.6	3.3*	3.6**	2.3	2.5	2.6	2.7*
Relative Weights (%)								
26 weeks[1]	5.51	5.06	5.52	6.68**	5.27	5.26	5.32	5.26**
53 weeks[1]	5.32	5.30	6.37*	6.56**	4.77	4.36*	4.68	5.47**
78 weeks[1]	5.76	6.55	7.75*	8.11**	4.48	4.74	4.75	6.10**
Term. Sac.[2]	6.24	6.28	8.18*	8.97**	5.18	5.41	5.82	6.45**

[1]Scheduled interim sacrifice.
[2]Terminal sacrifice (104 weeks).
*$p < 0.05$ (Dunnett's test).
**$p < 0.01$ (Dunnett's test).

Group mean values for kidney weights are presented below. For male mice, absolute and/or relative kidney weights were significantly decreased at 1000 and 3000 ppm at scheduled sacrifice times during the study. At 300 ppm, statistically significant decreases in absolute kidney weights were also observed at 78 and 104 weeks, but the relative kidney/body weight ratios for these same groups were not statistically different from the control groups. This equivocal finding at 300 ppm could not be clearly related to administration of the test material. For female mice, significant increases (rather than decreases) were observed during the last 6 months of the study at 3000 ppm. The decreases in absolute and relative kidney weights for male mice at 1000 and 3000 ppm may be related to the test material. The increased kidney weights at 3000 ppm in female mice may also possibly be related to the test material, but the evidence is less convincing and particularly since an increase, rather than a decrease, in weights was observed.

Kidney Weights
(Group Mean Values)

Dose (ppm)	Males 0	300	1000	3000	Females 0	300	1000	3000
Absolute Weights (g)								
26 weeks[1]	0.66	0.62	0.59**	0.55**	0.43	0.46	0.46	0.45
53 weeks[1]	0.71	0.69	0.67	0.62*	0.47	0.45	0.50	0.48
78 weeks[1]	0.78	0.72*	0.71*	0.68**	0.50	0.54	0.54	0.57**
Term. Sac.[2]	0.84	0.77**	0.77**	0.75**	0.60	0.73	0.60	0.65**
Relative Weights (%)								
26 weeks[1]	1.776	1.676	1.678	1.557*	1.454	1.474	1.472	1.451
53 weeks[1]	1.681	1.623	1.529*	1.602	1.183	1.116	1.140	1.221
78 weeks[1]	1.788	1.680	1.704	1.600**	1.158	1.208	1.205	1.469**
Term. Sac.[2]	1.951	1.845	1.853	1.810*	1.329	1.635	1.339	1.556**

[1]Scheduled interim sacrifice.
[2]Terminal sacrifice (104 weeks).
* $p < 0.05$ (Dunnett's test).
** $p < 0.01$ (Dunnett's test).

Organ weight changes in other organs were not remarkable.

f. Histopathological Examinations - Full sets of tissues, as described below, were excised and fixed from all animals in the Lifespan and Toxicity Studies. However, only tissues from the following groups of animals were processed (H&E stained) and examined microscopically: all animals from the Lifespan Study (regardless of time or manner of death) and all animals from the Toxicity Study sacrificed at 53 weeks. Tissues from Toxicity Study animals sacrificed at 26 or 78 weeks and those which died or were sacrificed during the study were not examined microscopically.

Abnormalities	Mammary gland - caudal
Adrenal glands	- cranial[1]
Aortic arch[1]	Marrow smear
Blood smears (Lifespan Study only)	Oesophagus
Bone (sternum with marrow)	Ovaries[1]
Brain (cerebrum, cerebellum and brain stem)	Pancreas
	Pituitary gland
	Preputial gland (both taken, left examined)
	Prostate gland

[1]Fixed and retained but not examined microscopically.

Carcass†	Salivary glands
Caecum	Sciatic nerves (both taken, left examined
Colon	Seminal vesicles
Duodenum	Skeletal muscle
Epididymides	Skin
Eyes and optic nerve (Lifespan Study - both examined; Toxicity Study - left examined)	Spinal cord - lumbar - thoracic
Gallbladder	Spleen
Harderian glands	Stomach - keratinised - glandular
Heart (auricular and ventricular sections)	Testes
Ileum	Thymus (if present)
Jejunum	Thyroid and parathyroid glands
Kidneys	Tongue (†Toxicity Study only)
Liver (two lobes)	Trachea
Lungs with mainstem bronchi (two sections)	Urinary bladder
Lymph nodes - cervical - mesenteric	Uterus (with cervix)

†Fixed and retained but not examined microscopically.

Non-neoplastic Findings - Non-neoplastic lesions observed in this study were of a type and incidence that would normally be expected to be seen in mice of this strain and age. Findings attributable to the test material were not observed. The study report indicated statistically significant decreases in renal basophilic tubules and nephrocalcinosis in 3000 ppm male mice (at terminal sacrifice), statistically significant decreases in dilatation of the seminal vesicles in 3000 ppm male mice (at terminal sacrifice) and statistically significant decreases in congestion of mesenteric lymph nodes in all treated male mice (at terminal sacrifice), but did not consider any of these findings to be adverse in nature. This reviewer concurs with that interpretation and does not consider these observations to be biologically meaningful.

Since the liver appears to be a potential target organ in this study, a more detailed consideration of liver findings is warranted. A summary of incidences of all non-neoplastic liver lesions observed in all animals in the Lifespan Study is presented in the attached 2 pages copied from the study report.

Overall, with respect to non-neoplastic microscopic [illegible] there did not appear to be a clear effect of the test material on the liver of either male or fema[illegible]

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mice in this study. Increased incidences (not dose-related) in treated male and female mice of nodular hyperplasia and in treated male mice of clear cell foci/area are, nevertheless, noted.

Neoplastic Findings - With the possible exception of liver tumors (see below), there was no increased incidence of any tumor type in any organ/tissue in male or female mice in this study that was suggestive of a possible relationship to the test material. Frequently observed tumors were malignant lymphomas in hematopoietic tissues (up to 20 percent in male mice groups and up to 62 percent in female mice groups), but these tumors were more or less evenly distributed among the treated groups and the control group for each sex, respectively, and were clearly not dose related. Other frequently observed tumors were pulmonary adenomas/carcinomas in the lungs and hepatocellular adenomas/carcinomas in the liver which are discussed below. All other tumor types observed in this study occurred relatively infrequently, were not dose related, and suggested no relationship to the test material.

Since pulmonary tumors have been associated with the administration of certain other synthetic pyrethroids, the incidences of these tumors in this study are presented below largely for the sake of completeness. No relationship to the test material is indicated by these data.

Lung Neoplasms[1]

	Males				Females			
Dose (ppm)	0	300	1000	3000	0	300	1000	3000
Pulmonary Adenomas								
At 53 weeks[2]	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
During study[3]	3/10	0/8	1/8	1/9	0/11	0/14	0/13	0/14
Term. Sac.[4]	8/40	5/42	7/42	1/41	0/39	2/36	1/37	0/36
Total Lifespan[5]	11/50	5/50	8/50	2/50	0/50	2/50	1/50	0/50

[1] Incidences presented are number of animals with the lesion/number of animals examined. Animals with both an adenoma and a carcinoma are counted only once under carcinoma.
[2] Scheduled interim sacrifice at 53 weeks (Toxicity Study).
[3] Animals sacrificed or died during study (Lifespan Study only).
[4] Terminal sacrifice at 104 weeks (Lifespan Study).
[5] Lifespan Study only - 50 mice sex group.

Lung Neoplasms[1] (cont'd)

Dose (ppm)	Males 0	300	1000	3000	Females 0	300	1000	3000
Pulmonary Carcinomas								
At 53 weeks[2]	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
During study[3]	2/10	1/8	1/8	0/9	0/11	1/14	0/13	2/14
Term. Sac.[4]	2/40	2/42	0/42	1/41	1/39	0/36	0/37	0/36
Total Lifespan[5]	4/50	3/50	1/50	1/50	1/50	1/50	0/50	2/50
Pulmonary Combined Ad/Ca								
At 53 weeks[2]	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
During study[3]	5/10	1/8	2/8	1/9	0/11	1/14	0/13	2/14
Term. Sac.[4]	10/40	7/42	7/42	2/41	1/39	2/36	1/37	0/36
Total Lifespan[5]	15/50	8/50	9/50	3/50	1/50	3/50	1/50	2/50

[1]Incidences presented are number of animals with the lesion/number of animals examined. Animals with both an adenoma and a carcinoma are counted only once under carcinoma.
[2]Scheduled interim sacrifice at 53 weeks (Toxicity Study).
[3]Animals sacrificed or died during study (Lifespan Study only).
[4]Terminal sacrifice at 104 weeks (Lifespan Study).
[5]Lifespan Study only 50 mice sex/group.

Incidences of hepatocellular adenomas and carcinomas in the liver are presented below.

Liver Neoplasms[1]

Dose (ppm)	Males 0	300	1000	3000	Females 0	300	1000	3000
Hepatocellular Adenomas								
At 53 weeks[2]	2/10	2/10	4/10	4/10	0/10	0/10	0/10	0/10
During study[3]	1/10	2/8	2/8	1/9	0/11	0/14	0/13	0/14

[1]Incidences presented are number of animals with the lesion number of animals examined. Animals with both an adenoma and a carcinoma are counted only once under carcinoma.
[2]Scheduled interim sacrifice at 53 weeks (Toxicity Study).
[3]Animals sacrificed or died during study (Lifespan Study only).
[4]Terminal sacrifice at 104 weeks (Lifespan Study).
[5]Lifespan Study only 50 mice sex group.

Liver Neoplasms[1] (cont'd)

Dose (ppm)	Males 0	300	1000	3000	Females 0	300	1000	3000
Hepatocellular Adenomas (cont'd)								
Term. Sac.[4]	10/40	12/42	16/42	14/41	3/39	5/36	7/37	6/36
Total Lifespan[5]	11/50	14/50	18/50	15/50	3/50	5/50	7/50	6/50
Hepatocellular Carcinomas								
At 53 weeks[2]	0/10	0/10	0/10	1/10	0/10	0/10	0/10	0/10
During study[3]	6/10	3/8	5/8	6/9	1/11	2/14	2/13	7/14
Term. Sac.[4]	8/40	12/42	10/42	9/41	3/39	5/36	4/37	2/36
Total Lifespan[5]	14/50	15/50	15/50	15/50	4/50	7/50	6/50	9/50
Hepatocellular Combined Ad/Ca								
At 53 weeks[2]	2/10	2/10	4/10	5/10	0/10	0/10	0/10	0/10
During study[3]	7/10	5/8	7/8	7/9	2/11	2/14	2/13	7/14
Term. Sac.[4]	18/40	24/42	26/42	23/41	6/39	10/36	11/37	8/36
Total Lifespan[5]	25/50	29/50	33/50	30/50	7/50	12/50	13/50	15/50

[1]Incidences presented here are number of animals with the lesion/number of animals examined. Animals with both an adenoma and a carcinoma are counted only once under carcinoma.
[2]Scheduled interim sacrifice at 53 weeks (Toxicity Study).
[3]Animals sacrificed or died during study (Lifespan Study only).
[4]Terminal sacrifice at 104 weeks (Lifespan Study).
[5]Lifespan Study only (50 mice/sex/group).

At this time, a full and complete assessment of the oncogenic potential of the test material in the liver is confounded by several presently unresolved problems and issues.

First, the selection of the mouse strain used in this study (B6C3F1 hybrid, Charles River, Kent, England) must be questioned. In this study, the spontaneously occurring incidences of hepatocellular adenomas carcinomas combined in the male control groups were 20 percent at the 53-week interim sacrifice (Toxicity Study) and 50 percent among male mice permitted, if possible, to live the full duration of the study (Lifespan Study). From both a biological and a statistical point of view, the spontaneously occurring early tumors (i.e. at 53 weeks) and the high incidence of tumors at termination of the

study (50% at 104 weeks) would make it most difficult to detect a liver oncogen with respect to either decreased latency (time to tumor) or incidence. Meaningful and statistically significant differences between control and test groups would only be evident for strongly positive or potent liver oncogens. Also, inasmuch as it is well known that liver tumors have been associated with the administration of other synthetic pyrethroids to mice, the selection of this particular strain of mouse for this study is questionable. Accordingly, the registrant is requested to 1) justify, in writing, the selection of the $B6C3F_1$ strain of mouse used in this study, and particularly in regard to its demonstrated sensitivity to spontaneous liver tumors; and 2) provide suitable historical control data for liver tumors in this strain of mouse, and particularly data on mice from the same animal supplier and testing laboratory as were used in this study. Historical control data on both male and female mice, separately, should be submitted for individual studies. Furthermore, for each individual study, obviously pertinent information including strain and supplier of test animals, testing laboratory, duration of study, numbers of animals actually histologically examined, date of study, etc., should be submitted. Summary data should also be submitted, but not in lieu of the required information on individual studies.

Second, the lack of serious adverse effects at the highest dosage level tested (3000 ppm) indicates that the test material may not have been administered at a sufficiently high dosage level in this study. In fact, the only effects attributable to the test material in this study (excluding potential oncogenicity) were possibly decreased body weight gains in high dosage level male and female mice, increased liver weights in male mice at 1000 and 3000 ppm and in female mice at 3000 ppm, decreased kidney weights in male mice at 1000 ppm and 3000 ppm, and possibly increased kidney weights in female mice at 3000 ppm. In order to address this issue more fully, the registrant is requested to 1) justify, in writing, the selection of the dosage levels used in this study, and particularly address the question of whether or not the test material was administered at a "maximum tolerated dose" (MTD); and 2) submit the full and complete report on the preliminary range-finding study (HLR Report No. 33/SUMC86 024, referred to on page 3 (vol. 1, introduction) of the final study report. Resolution of this "MTD issue" is of special concern since higher incidences of hepatocellular neoplasms were generally observed in the treated mice in this study as compared to incidences in control groups, particularly in female mice, and the matter of potentially greater differences at a higher dosage level may need to be considered.

Third, the presently unresolved issues and problems discussed above, when considered together with the higher incidence of hepatocellular tumors in the treated animals in this study, raise sufficient concern at this time regarding the oncogenic potential of the test material to warrant further histopathological examination of all readily available liver tissues that have not yet been examined. Therefore, the registrant is requested to 1) prepare and examine microscopic slides of liver tissues from all male and female mice in the Toxicity Study that were not previously examined; and 2) submit the results of these examinations to the Agency in an appropriate format, which includes data on individual animals and also appropriate summaries of data. It is essential that this additional processing and examination of liver tissues be performed in a manner fully comparable to that previously used for the liver tissues in this study (e.g., two sections of liver from the same two lobes, identical processing, etc.).

Until the information requested above is submitted and reviewed, the oncogenic potential of the test material in mice, particularly in the liver, remains undetermined.

D. Recommendation:

This study is classified as Core Supplementary pending submission and review of the additional information and explanations discussed and required in the body of this review and briefly reiterated in the "Conclusions" section at the beginning of this review.

In the interim, the tentative conclusions in this study are as follows:

1. For Male Mice

NOEL = 300 ppm (or 45 mg/kg/day)
LOEL = 1000 ppm (or 150 mg/kg/day). At this dosage level, increased liver weights and decreased kidney weights were observed.
At 3000 ppm (or 450 mg/kg/day, HDT, possibly decreased body weight gains, increased liver weights and decreased kidney weights were observed.
Oncogenic potential - Undetermined at this time.

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2. For Female Mice

NOEL = 1000 ppm (or 150 mg/kg/day)
LOEL = 3000 ppm (or 450 mg/kg/day, HDT). At this dosage level, possibly decreased body weight gains, increased liver weights, and possibly increased kidney weights were observed.

Oncogenic potential - Undetermined at this time.

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R:53898:Budd:C.Disk:KENCO:12/14/88:de:vo:rw

Reviewed By: Edwin R. Budd
Section I, Toxicology Branch I - IRS (TS-769C)
Secondary Reviewer: Judy W. Hauswirth
Chief, Toxicology Branch I - IRS (TS-769C)

RD 2/24/89 1/31/89 007088

2/24/89

DATA EVALUATION REPORT

Study Type: 83-5 - Combined Chronic Toxicity/Oncogenicity Study - Rats

TOX Chem No.: 652B
MRID No.: 402764-05 (7 Volumes)

Accession No.: None

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

Synonyms: d-phenothrin

Sponsor: Sumitomo Chemical Company, Ltd. (Sumitomo Ref. No. ET-71-0102)

Testing Facility: Life Science Research Suffolk, England)

Study No.: LSR #85/SUM003/586

Title of Report: Sumithrin: Combined Toxicity and Oncogenicity Study in Rats.

Author: P.A. Martin

Report Issued: January 1987

Conclusions:

This study is classified as Core Supplementary pending submission and review of the additional information and explanations itemized below.

1. Justification for the dosage levels used in this study, and particularly with regard to whether a "maximum tolerated dose" was used in this study.

2. The full and complete report on the 13-week preliminary study (LSR Report No. 82/SUM001 222 .

In the interim, the tentative conclusions for this study are as follows:

NOEL = 1000 ppm (or 50 mg/kg/day .

LOEL = 3000 ppm (or 150 mg/kg/day). At this dosage level, possibly decreased body weight gain in females, increased relative liver/body weight ratios in males, increased cystic dilatation of sinuses in mesenteric lymph nodes in males, and increased periacinar hepatocytic hypertrophy in liver in males.

Oncogenic potential - Not fully determined at this time.

Classification (Core-Grade):

Core-Supplementary, pending submission of additional information and explanations (see above under "Conclusions").

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

Quality Assurance Statement:

A quality assurance statement, dated December 17, 1986 and signed by D.J. Ford (Head of Quality Assurance Unit, LSR), was present.

A. Materials:

1. Test Compound - Sumithrin, technical grade, Batch No. 10102, purity 92.6%, pale yellow-liquid, stored at 4 °C.

2. Test Animals - F-344 strain rats, specified pathogen-free, Supplier: Charles River (Kent, England), 3 to 5 weeks old on arrival; Body weights (2 days after arrival): males, 58 to 97 g; females, 58 to 90 g; Acclimatization period: 8 days; Housing: individually in polypropylene cages.

3. Diet - Laboratory Animal Diet No. 2, Powdered; Initial Supplier: Spratt's Patent Limited (Essex, England); Subsequent Supplier: Labsure, K and K Greeff Chemicals Limited (Surrey, England).

B. Study Design:

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

Test Group	Dosage Level in Diet (ppm)	Lifespan Study[1]		Toxicity Study[2]	
		Males	Females	Males	Females
Control	0	50	50	30	30
Low (LDT)	300	50	50	30	30
Mid (MDT)	1000	50	50	30	30
High (HDT)	3000	50	50	30	30

[1] All rats in the Lifespan Study were permitted, if possible, to live the full duration of the study. Terminal sacrifices were scheduled for each sex separately when survival in any group fell to 30 percent. Terminal sacrifice for male rats occurred after week 105 (actually during weeks 106 to 108) and for female rats occurred after week 118 (actually weeks 119 to 121).

[2] Ten rats/sex/group in the Toxicity Study were sacrificed at 52 weeks and all remaining survivors after week 105 (male rats) or after week 118 (female rats).

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

2. Dosage Levels - The dosage levels used in this study were stated to be "selected in consultation with the sponsor [Sumitomo] after consideration of the results obtained in a 13-week preliminary study (LSR Report No. 82 SUM 002/002)."

3. Diet Preparation - The diet was prepared weekly and stored at room temperature in the animal room within light-proof plastic storage bins. The stability of the test material in the diets was determined prior to commencement of treatment and was found to be stable over a 2-week period at room temperature. Homogeneity of test material in the low and high dosage level diets was checked prior to commencement of treatment and was found to be acceptable. Concentration of test material in the diet was analytically determined before commencement of treatment, at week 13, at 13-week intervals thereafter, and at termination of the study. The range of percentages of intended values for the low, mid, and high dosage level groups were 90 to 109, 91 to 104, and 92 to 106 percent, respectively, over the duration of the study.

C. Methods and Results:

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.

Overall survival of animals in the Lifespan Study was acceptable with 24 to 54 percent of the males surviving to termination at 108 weeks and 30 to 52 percent of the females surviving to termination at 121 weeks. The test material had no effect on the distribution or times of deaths.

Cumulative Mortality in Lifespan Study

Week No.	Males				Females			
	Cont.	300	1000	3000	Cont.	300	1000	3000
52	1	1	2	0	2	0	0	0
65	3	1	4	0	2	0	0	0
78	5	5	7	3	4	1	2	0
91	12	8	12	7	9	4	6	3
105	30	26	32	23	19	8	8	11
108[1]	32	30	38	23	20	9	11	13
118	--	--	--	--	30	20	21	26
121[2]	--	--	--	--	35	25	24	29

[1] Includes male rats which died during time of terminal sacrifice (weeks 106 to 108).
[2] Includes female rats which died during time of terminal sacrifice (weeks 119 to 121).

The numbers of survivors in the Lifespan Study at study termination for males (108 weeks) were 18 (36%), 20

(40%), 12 (24%), and 27 (54%) for the control, low, mid, and high dosage levels, respectively. The corresponding numbers of survivors at study termination for females (121 weeks) were 15 (30%), 25 (50%), 26 (52%), and 21 (42%).

The numbers of survivors in the Toxicity Study at study termination for males (108 weeks) were 8 (40%), 8 (40%), 6 (30%), and 8 (40%) for the control, low, mid, and high dosage levels, respectively. The corresponding numbers of survivors at study termination for females (121 weeks) were 3 (15%), 6 (30%), 7 (35%), and 7 (35%).

Signs of toxicity, appearance, and behavior observed in the animals were typical of rats of the strain and age employed in this study. There was no apparent relationship to treatment with the test material. During weeks 20 to 21 and 56 to 58, signs of a mild transitory infection were observed in a small number of animals. The affected animals quickly recovered. These infections were not dose-related or treatment-related and are not considered to be biologically meaningful.

Palpable swellings observed at various times during the study could not be related to treatment with the test material. For males in the Lifespan Study, the numbers of animals with one or more swellings were 27, 21, 21, and 27 for the control, low, mid, and high dosage level groups, respectively. For females, the corresponding numbers of animals were 28, 28, 26, and 29.

C. Body Weights - All animals were weighed weekly for the first 14 weeks and at 2-week intervals thereafter.

Group Mean Absolute Body Weights - For both the Lifespan Study and the Toxicity Study, a table listing group mean body weights (with standard deviations) for each weekly or biweekly weighing was presented. These data, however, were not subjected to statistical analysis. Visual inspection of the tables, and of graphical representations of the same data, did not indicate any obvious effect of the test material on the treated male or female rats in either study.

Group Mean Body Weight Changes - Summary tables of group mean body weight changes for male and female rats in both the Lifespan Study and the Toxicity Study are presented in Tables 3B and 3D, respectively (copied from the study report, attached). For male rats, no differences in body weight changes between control and treated rats were observed in either study and it is therefore concluded that the test material, at dosage levels up to and including 3000 ppm (HDT, had no effect on the body

weights of male rats in this study. For female rats, statistically significant ($p < 0.05$) decreases in body weight gains compared to the control groups were noted as shown below.

At 3000 ppm (HDT): 4.9% decrease between weeks 0 to 56 (Lifespan Study)

6.5% decrease between weeks 0 to 76 (Toxicity Study)

At 1000 ppm (MDT): 6.0% decrease between weeks 0 to 76 (Toxicity Study)

The small magnitude of these changes (up to 6.5%) suggest only a marginal effect at best. These decreases in body weight gain for the 3000 ppm females, then, are regarded at this time to be equivocal and only possibly induced by the test material. To assist in the resolution of this matter (and to further address the issue of whether or not a "maximum tolerated dose" was used in this study; see Section D. Discussion later in this same review), the registrant is requested to submit the full and complete report of the 13-week preliminary study (LSR Report No. 82/SUM 022/2221 which was previously considered when the dosage levels for this Lifetime Study were selected.

3. Food Consumption, Water Consumption, Food Conversion Ratio, and Compound Intake - Food consumption, determined for individual animals on a weekly basis for the duration of the study, was not affected by the test material.

Water consumption was checked by daily visual inspection of water bottles. In addition, accurate measurements of water consumption over a 1-day period were made on 10 rats/sex/group for the first 13 weeks of the study and monthly thereafter. Water consumption was not affected by treatment with the test material.

Food conversion ratios (amount of food consumed per unit gain in body weight) were calculated weekly for the first 14 weeks of the study. These ratios were not affected by the test material.

Compound intake (calculated as group mean values in units of mg/kg/day) was determined weekly for the first 14 weeks and at 13-week intervals thereafter. No attempt was made in the report however to determine mean compound intake for the individual sexes over the entire duration of the study or any major portions thereof. A cursory inspection of the data in this review indicates that the mean compound intake over the duration of the study

for the treated groups, in units of mg/kg/day, is likely to be quite similar to what one would obtain by utilizing the standard Lehman conversion factor of 0.05, namely:

Dosage Level in Diet (ppm)	Compound Intake mg/kg/day
0	0
300	15
1000	50
3000	150

4. Ophthalmological Examinations were performed on all rats in both the Lifespan and the Toxicity Studies prior to initiation of treatment. Similar examinations were again performed on 10 rats/sex from the control and high dosage level groups of the Lifespan Study at weeks 26, 52, 78, 104, 106 (males only) and 119 (females only). No effects attributable to the test material were observed.

5. Blood Collection - Prior to treatment, blood samples were collected from the retro-orbital sinus of an additional 10 male and 10 female rats for clinical pathology examinations. Blood samples were similarly collected from up to 10 rats/sex/group from animals in the Toxicity Study during weeks 26, 50, 78, 104, 106 (males only), and 119 (females only). When sufficient numbers of animals from the Toxicity Study were not available, additional animals from the Lifespan Study were used. Both hematological examinations and clinical chemistries were performed on blood samples from the same animals during the treatment period. The rats were not deprived of food or water prior to collection of blood samples.

a. Hematological Examinations - The following "checked" parameters were examined.

X	Packed cell volume (PCV)	X	Reticulocyte count
X	Hemoglobin (Hb)	X	Leukocyte differential count
X	Leukocyte count (WBC)	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)	X	Mean corpuscular HGB concentration (MCHC)
X	Platelet count	X	Mean corpuscular volume (MCV)

No hematological effects attributable to the test material were observed.

TABLE 3B

Bodyweight change - group mean values (g) -
animals assigned to the Lifespan Study

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

	Group and sex			
Weeks	1M	2M	3M	4M
0-74	367	361	365	359
74-104	-98	-87	-104	-75
0-104	278	275	261	285

	Group and sex			
Weeks	1F	2F	3F	4F
0-56	182	180	180	173[a]
56-90	61	64	64	65
0-90	243	244	245	239
90-118	-38	-23	-17	-15
0-118	211	216	231	227

Group mean values without a superscript not significantly different from controls, $P > 0.05$

a Significantly different from controls, $P < 0.05$

TABLE 3D

Bodyweight change - group mean values (g) - animals assigned to the Toxicity Study

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

Weeks	Group and sex 1M	2M	3M	4M
0-74	368	369	353	348
74-104	-89	-88	-89	-58
0-104	287	265	252	298

Weeks	Group and sex 1F	2F	3F	4F
0-76	232	236	218[a]	217[a]
76-90	14	20	20	24[a]
0-90	246	255	240	241
90-118	-16	-35	-37	-12
0-118	227	231	202	224

Group mean values without a superscript not significantly different from controls, $P > 0.05$

a Significantly different from controls, $P < 0.05$

b. Clinical Chemistries - The following "checked" parameters were examined.

X		X	
	Electrolytes:		Other:
X	Calcium		Albumin
X	Chloride	X	Creatinine concentration
	Magnesium	X	Urea concentration
	Phosphorus	X	Total cholesterol concentration
X	Potassium		Globulins
X	Sodium	X	Glucose
	Enzymes:	X	Total bilirubin concentration
X	Alkaline phosphatase (AP)	X	Total protein
			Triglycerides
	Cholinesterase	X	Direct bilirubin concentration
	Creatinine phospho-kinase	X	Electrophoretic protein fractions
X	Lactic acid dehydrogenase (LDH)		
X	Plasma alanine aminotransferase (ALT)		
X	Plasma aspartate aminotransferase (AST)		

Group mean values for female rats for alanine aminotransferase (ALT) and for aspartate aminotransferase (AST) are presented below. Although statistically significant decreases were observed in the 3000 ppm female rats at 25, 49, and 77 weeks, no toxicological significance is attached to this finding, since the findings were not also observed at 103 or 118 weeks and the observed difference was a decrease (rather than an increase). The increased ALT and AST observed in 300 ppm female rats at the terminal sacrifice are also not considered to be related to the test material because the increases were not dose-related and were observed on only one occasion. In addition, it appears that the control values for both ALT and AST at the terminal sacrifice were quite low when compared to earlier control values.

Female Rats

Dose (ppm)	ALT (iu/L) Cont.	300	1000	3000	AST (iu/L) Cont.	300	1000	3000
Prior[1]	46	--	--	--	88	--	--	--
25 Weeks	57	48	46	36**	69	64	59	54**
49 Weeks	61	64	53	47**	69	76	62	52*
77 Weeks	45	50	39	35*	57	66	54	46*
103 Weeks[2]	41	51	53	50	47	54	80	52
118 Weeks	34	58**	45	43	35	110*	54	42

[1]Prior to treatment
[2]Terminal sacrifice
*p < 0.05
**p < 0.01

No other clinical chemistries suggested a relationship to the test material in either the male or female rats.

6. Urinalysis - Urine was collected from 10 rats/sex/group from, as far as possible, the same animals used to provide blood samples. Urine was collected during weeks 25 (females), 27 (males), 51, 78, 104, 106 (males) and 119 (females). The following "checked" parameters were examined.

X	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic	X	Nitrite
X	Protein	X	Urobilinogen
		X	Total reducing substances

No effects attributable to the test material were observed.

7. Gross Necropsy - All animals in both the Lifespan Study and the Toxicity Study, regardless of the time or manner of death, were subjected to a gross pathological examination. In addition, all animals sacrificed during the study (on humane grounds or in extremis) and all animals sacrificed at scheduled sacrifice times were subjected to a standardized gross necropsy procedure which included 1) preparation of blood smears and/or femoral bone marrow smears; 2) examination of the external surfaces, the contents of the cranial, thoracic and abdominal cavities, and the residual carcass; 3) weighing of selected organs (scheduled sacrifice animals only) as described below under C.8; and 4) removal and fixation of organs and or

tissues for subsequent histopathological examinations as described below under C.9.

Blood smears revealed no effects attributable to the test material (also see C.5.a. above). Femoral bone marrow smears taken from rats killed during the treatment period and from rats sacrificed at 52 weeks and at 106 weeks (males) and at 119 weeks (females) were also examined. Neither cellularity nor composition of the bone marrow was altered by treatment with the test material.

Gross pathological examinations did not reveal any lesions or effects related to the test material. Findings were of a nature and incidence that would be expected in this strain of rat in animals of comparable age.

8. Organ Weights - Absolute organ weights and relative organ/body weight ratios (expressed as percentages) were determined for all rats killed at the scheduled sacrifice times (i.e., at 52 weeks for the Toxicity Study and at 106 weeks (males) and 119 weeks (females) for all surviving animals). Organ weights and ratios were determined for the following 15 organs: adrenal glands, brain, epididymides, heart, kidneys, liver, lung, ovaries, pituitary gland, prostate, spleen, testes, thymus (Toxicity Study only), thyroid glands (with parathyroids, weighed after fixation), and uterus (with cervix).

Group mean values for liver weights are presented below. For male rats, a statistically significant increase in mean liver/body weight ratio was observed in the 3000 ppm animals at the terminal sacrifice. Since no other statistically significant changes in absolute or relative liver weights were observed for the male rats in this study at any time, this increase in interpreted as being only possibly related to the test material. For female rats, a statistically significant increase in mean liver/body weight ratio was observed in the 3000 ppm animals at the 52-week interim sacrifice. Since no suggestion of a similar increase was also observed in female rats at the terminal sacrifice, the observation at 52 weeks is considered to be probably not related to the test material.

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Liver Weights
(Group Mean Values)

Dose (ppm)	Males				Females			
	0	300	1000	3000	0	300	1000	3000
Absolute Weights (g)								
52 Weeks[1]	17.9	18.8	17.9	19.2	9.7	10.3	10.4	10.3
Term. Sac.[2]	17.4	16.6	19.2	18.8	14.6	15.2	14.7	15.1
Relative Weights (%)								
52 Weeks[1]	3.92	3.95	3.95	4.14	3.85	3.97	4.09	4.28*
Term. Sac.[2]	4.74	4.42	5.11	5.55*	4.90	5.12	4.85	4.93

[1]Scheduled interim sacrifice (9 to 10 rats/sex/group; Toxicity Study).
[2]Terminal sacrifice (106 weeks for males, 119 weeks for females; Lifespan Study).
*$p < 0.05$ (Dunnett's test).

No other absolute organ weights or relative organ/body weight ratios suggested an effect induced by the test material.

9. Histopathological Examinations - Full sets of tissues, as described below, were excised and fixed from all animals in the Lifespan and Toxicity Studies. However, only tissues from the following groups of animals were processed (H&E stained) and examined microscopically: all animals from the Lifespan Study (regardless of time or manner of death) and all animals from the Toxicity Study sacrificed at 52 weeks. Tissues from Toxicity Study animals sacrificed at termination of the study and those which died or were sacrificed during the study were not examined microscopically.

Abnormalities
Adrenal glands
Aortic arch*
Blood smear* (Lifespan study only)
Bone (sternum with marrow)
Brain (forebrain, midbrain, hindbrain, and brain stem)
Carcass*
Caecum
Colon
Duodenum
Epididymides
Marrow smear
Oesophagus
Ovaries
Pancreas
Pituitary gland
Preputial gland (both taken, left examined)
Prostate gland
Salivary glands
Sciatic nerves (both taken, left examined)
Seminal vesicles
Skeletal muscle

Eyes and optic nerve (both taken and examined)
Harderian glands
Head**
Heart (auricular and ventricular sections)
Ileum
Jejunum
Kidneys
Liver (2 lobes)
Lungs and mainstem bronchi (two sections)
Lymph nodes - cervical
- mesenteric
Mammary gland - caudal
- cranial*
Skin
Spinal cord - lumbar
- thoracic
Spleen
Stomach - keratinised
- glandular
Testes
Thymus (if present)
Thyroid and parathyroid glands
Tongue* (Toxicity Study only)
Trachea
Urinary bladder
Uterus (with cervix)

*Fixed and retained but not examined microscopically.
**Three coronal sections, to include oral and nasal cavities, sinuses, nasopharynx, middle ears and tongue were processed and examined for the first five males and five females of each group of each replicate of the Lifespan Study killed at termination of the study. In addition, coronal sections were processed and examined for any animal with clinical or gross evidence of disease at these sites.

Non-neoplastic Findings - Most non-neoplastic lesions observed in this study were of a type and incidence that would normally be expected to be seen in rats of this strain and age. At 52 weeks in the Toxicity Study, the most common non-neoplastic findings were testicular interstitial cell hyperplasia, splenic hemosiderosis, chronic myocarditis, and geriatric nephropathy. These findings occurred in control and treatment groups at similar incidences, were not dose-related and were not considered to be related to the test material. In the Lifespan Study, however, the testing laboratory considered two non-neoplastic lesions to be related to treatment with the test material. These lesions were 1) cystic dilatation of the sinuses in the mesenteric lymph nodes of male rats, and 2) periacinar hepatocytic hypertrophy in the livers of male rats. The incidences of these lesions for animals in the Lifespan Study are presented in the tables below.

Cystic Dilatation of the Sinuses in the Mesenteric Lymph Nodes

Dose (ppm)	Males				Females			
	0	300	1000	3000	0	300	1000	3000
During study[1]	0/29	2/28	4/37	5/20**	0/34	1/25	0/24	1/28
Term. Sac.[2]	2/18	5/20	1/12	10/25*	0/15	0/25	1/26	0/21
Total	2/47	7/48	5/49	15/45**	0/49	1/50	1/50	1/49

[1]Animals sacrificed or died during study (Lifespan Study).
[2]Terminal sacrifice (106 weeks for males, 119 weeks for females; Lifespan Study).
*$p < 0.05$.
**$p < 0.01$.

Periacinar Hepatocytic Hypertrophy in Liver

Dose (ppm)	Males				Females			
	0	300	1000	3000	0	300	1000	3000
During study[1]	0/32	0/30	2/37	4/23*	0/35	0/25	1/24	2/29
Term. Sac.[2]	0/18	1/20	0/12	3/27	0/15	0/25	1/26	0/21
Total	0/50	1/50	2/49	7/50**	0/50	0/50	2/50	2/50

[1]Animals sacrificed or died during study (Lifespan Study).
[2]Terminal sacrifice (106 weeks for males, 119 weeks for females; Lifespan Study).
*$p < 0.05$.
**$p < 0.01$.

The statistically significant increased incidences of cystic dilatation in the high dosage level male rats do suggest the possibility of this being an effect attributable to the test material. The toxicological significance of such an effect, however, would be of minimal concern, even if real.

The statistically significant increase in periacinar hepatocytic hypertrophy in the high dosage level male rats may also be possibly related to the test material. Additional supporting evidence for this interpretation is provided by the significantly increased relative liver/body weight ratio previously noted for the high dosage level male rats at the terminal sacrifice. Hepatocytic hypertrophy in several other locations in the liver architecture was, however, not statistically increased in treated male rats.

Other commonly observed non-neoplastic lesions observed in the animals in the Lifespan Study are listed below. These lesions occurred at similar incidences in control and treatment groups, were not dose-related, and suggested no relationship to the test material.

Adrenals	- Cortical fatty vacuolation (especially in females)
Epididymides	- Lacking spermatozoa (males)
Eyes	- Scleral mineralization (males and females)
Heart	- Chronic myocarditis (males and females)
Kidneys	- Geriatric nephropathy, nephrocalcinosis (males and females)
Liver	- Basophilic foci of alteration, bile duct proliferation, hyaline degeneration of bile ducts, panacinar (glycogen) pallor (males and females)
Lungs	- Congestion (males and females)
Mammary gland	- Acinar hyperplasia, galactocoeles, secretory activity (especially in females)
Parathyroids	- Hyperplasia (especially in males)
Seminal vesicles	- Lacking secretion (males)
Spleen	- Extramedullary hemopoiesis, hemosiderosis (males and females)
Testes	- Degeneration of tubular germinal epithelium, tubular mineralization (males)

Neoplastic Findings - There was no increased incidence of any tumor type in any organ/tissue in male or female rats in this study that suggested a possible relationship to the test material. At the 52-week interim sacrifice (Toxicity Study), only two tumors were noted--a testicular interstitial cell adenoma in a male rat at 300 ppm and a thyroid gland follicular cell adenoma in a male control rat. Among the Lifetime Study animals, the most commonly occurring types of tumors are listed below.

Adrenals	- Benign pheochromocytomas (males and females)
Mammary gland	- Benign fibro-epithelial tumors (especially in females)
Pituitary	- Benign adenomas (males and females
Testes	- Benign interstitial cell tumors (males

These tumors occurred at similar incidence in control and treatment groups, were not dose-related, and suggested no relationship to the test material. In addition, there was no evidence for increased malignancy, decreased latency (time-to-tumor), or rare tumors in this study.

D. Discussion:

The lack of clear toxicity in the treated rats at the highest dosage level used in this study suggests that a "maximum tolerated dose" may not have been used in this study. The only effects observed that were possibly related to the test material were:

1. Statistically significant ($p < 0.05$) decreased body weight gain in female rats during the first 56 or 76 weeks of the study (decreases up to 6.5%);

2. Statistically significant ($p < 0.05$) increased relative liver/body weight ratios in male rats at the terminal sacrifice (increase of 17.1%); and

3. Statistically significant ($p < 0.01$) increased incidence of cystic dilatation of the sinuses in the mesenteric lymph nodes in male rats and of periacinar hepatocytic hypertrophy in the liver in male rats.

None of these possible effects were of sufficient toxicological seriousness or magnitude to indicate that a "maximum tolerated dose" had been used in this study. Therefore the registrant is requested to 1) justify, in writing, the selection of the dosage levels used in this study, and particularly address the question of whether or not the test material was administered at a "maximum tolerated dose" (MTD); and 2) submit the full and complete report on the 13-week preliminary study (LSR Report No. 82/SUMO02/222) referred to on page 2 (Vol. 1, Introduction) of the final study report.

Until the information requested above is submitted and reviewed, the full oncogenic potential of the test material in rats remains undetermined.

E. Recommendation:

This study is classified as Core-Supplementary pending submission and review of the additional information and explanations required above in the "Discussion" section.

In the interim, the tentative conclusions for this study are as follows:

NOEL = 1000 ppm (or 50 mg/kg/day)

LOEL = 3000 ppm (or 150 mg/kg/day). At this dosage level, possibly decreased body weight gain in females, increased relative liver/body weight ratios in males, increased cystic dilatation of sinuses in mesenteric lymph nodes in males, and increased periacinar hepatocytic hypertrophy in liver in males.

Oncogenic potential - Not fully determined at this time.

53897:I:Budd:LHED-3:KENCO:12/14/88:SG:VO:aw
R:53900:Budd:C.Disk:KENCO:01/26/89:DD

Reviewed By: Edwin R. Budd
Section I, Toxicology Branch I - IRS (TS-769C)
Secondary Reviewer: Judy W. Hauswirth, Chief
Toxicology Branch I - IRS (TS-769C)

Budd 1/31/89

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DATA EVALUATION REPORT

Study Type: 83-1 - Chronic Toxicity Study - Dogs

Tox Chem No.: 652B
MRID No.: 402764-01
(1 Volume)

Accession No.: None

Test Material: Sumithrin, technical grade (purity 92.7%)

Synonyms: d-phenothrin

Sponsor: Sumitomo Chemical Company, Ltd.
(Sumitomo Reference No. ET-71-0108)

Testing Facility: Hazleton Laboratories America, Inc.
(Vienna, Virginia)

Study No.: HLA 343-173

Title of Report: Chronic Toxicity Study in Dogs with Sumithrin, T.G.

Author: Raymond H. Cox, Ph.D.

Report Issued: April 2, 1987

Conclusions:

The conclusions for this study are as follows:

NOEL = 300 ppm (8.0 mg/kg/day in males and 7.1 mg/kg/day in females).

LEL = 1000 ppm (27.7 mg/kg/day in males and 26.8 mg/kg/day in females). At this dosage level, hepatocellular enlargement in liver, focal degeneration in adrenal cortex.

At 3000 ppm (HDT), also signs of anemia (decreased RBC, hemoglobin and hematocrit), decreased serum albumin and total protein, and increased absolute and relative liver weights, all in both males and females.

Classification: Core-Grade; Core-Guideline.

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

Quality Assurance Statement:

A quality assurance statement, dated April 3, 1987 and signed by K. Reilly (Final Report Reviewer), was present.

A. Materials:

1. Test Compound - Sumithrin, technical grade, Lot No. 41101, purity 92.7%, brown liquid, stored at room temperature.

2. Test Animals - Purebred beagle dogs, Supplier: Hazleton Research Products, Inc. (Denver, Pennsylvania), quarantined for 3 weeks after arrival, standard vaccinations, 25 to 30 weeks old at initiation of treatment, body weights (at initiation of treatment): males, 7.7 to 10.0 kg; females, 7.2 to 9.7 kg; Housing: individually in stainless steel cages.

3. Diet - Purina Certified Canine Diet No. 5007 was the basal diet in this study. Test material was incorporated into this diet at specified concentrations as described below.

B. Study Design:

1. Animal Assignment - Animals were assigned, using a computerized weight-randomization program, to the following test groups:

Dosage Level in Diet (ppm)	Number of Animals	
	Males	Females
0	4	4
100	4	4
300	4	4
1000	4	4
3000	4	4

All animals were given food and water ad libitum for at least 52 weeks. Following 52 weeks of treatment, all dogs were sacrificed and examined for toxicological effects as described later in this review.

2. Dosage Levels - No rationale was presented for the selection of dosage levels used in this study. It is noted, however, that the selection was adequate as judged by the results of this study.

3. Diet Preparation - The test material, a brown liquid, was incorporated directly into the basal canine diet without the aid of a solvent. Diets were prepared weekly and stored at room temperature. The stability of the test material in the diets was determined following 7 days storage at room temperature and found to be 93.0 to 100.7 percent of expected target levels for all samples. Homogeneity of the test material was determined by

analyzing samples of each mix from the top, middle, and bottom of the mixer prior to commencement of treatment and at 24 weeks. All samples were within ± 6 percent of expected target levels. Concentration of test material in the diet was analytically determined at weeks 1, 2, 3, 4, and every 4 weeks thereafter. All samples were within ± 10 percent of expected target levels over the entire duration of the study.

C. Methods and Results:

1. Observations - Animals were observed twice each day for mortality and moribundity and once each day for toxic and pharmacologic signs. In addition, physical examinations were conducted weekly on each dog.

   No dogs died during the study. No alterations in appearance or behavior were considered attributable to the test material. The most frequently noted clinical signs, none of which suggested any relationship to treatment, were emesis, soft feces, few or no feces, estrus in females, alopecia, sores, lacrimation, and injected sclera of the eye.

2. Body Weight - All dogs were weighed weekly throughout the entire duration of the study.

   No changes in absolute body weight or in body weight gains were observed during the study which could be related to the test material. Representative mean group body weights (at 0, 26, and 52 weeks) are presented below along with mean body weight gains for each group from 0 to 52 weeks.

Mean Body Weights and Body Weight Gains (kg)

Weeks	Dosage Level (ppm) 0	100	300	1000	3000
			Males		
0	9.1	8.8	9.3	8.3	9.7
26	11.4	10.4	10.8	10.3	11.8
52	12.1	11.2	11.3	11.0	12.8
0-52	3.0	2.4	2.0	2.7	3.1
			Females		
0	8.0	8.0	8.8	9.0	8.1
26	10.2	9.6	10.5	10.6	9.6
52	10.8	10.7	11.1	11.8	10.8
0-52	2.8	2.7	2.3	2.8	2.2

3. Food Consumption, Efficiency of Food Utilization, and Compound Consumption - Food consumption, determined for each dog on a weekly basis for the duration of the study, was not affected by the test material.

Individual and mean efficiency of food utilization values (amount of food consumed per unit gain in body weight) were calculated weekly throughout the study. These values were not affected by the test material.

Compound consumption, calculated as group mean values in units of mg/kg/day, was determined weekly. Mean compound intake over the entire duration of the study (0-52 weeks) for the treated groups, in units of mg/kg/day, is presented below:

Dosage Level in Diet (ppm)	Compound Consumption (mg/kg/day) Males	Females
0	0	0
100	2.69	2.63
300	8.24	7.07
1000	27.66	26.77
3000	80.19	79.83

4. Ophthalmological Examinations were performed on all dogs prior to initiation of treatment and at termination of the study at 52 weeks. An indirect ophthalmologic examination, using 1% Mydriacyl® as a mydriatic, was performed each time. No effects attributable to the test material were observed.

5. Blood Collection - Prior to treatment and at weeks 13, 26, 39, and 52, blood samples were collected from the jugular vein of all dogs for clinical pathology examinations. The dogs were deprived of food and water overnight prior to collection of the blood samples. Both hematological examinations and clinical chemistries were performed on blood samples from all dogs.

a. Hematological Examinations - The following parameters were examined.

Erythrocyte count (RBC)	Leukocyte count (WBC)
Hemoglobin (HGB)	Differential leukocyte count
Hematocrit (HCT)	Cell morphology
Platelet count	

At 3000 ppm (HDT), decreased RBC, HGB, and HCT were consistently observed in both male and female dogs at virtually all collection times. Statistical significance ($p \leq 0.05$) was achieved, however, only at 26 weeks. At 1000 and 300 ppm, similar tendencies

toward decreased RBC, HGB, and HCT were also observed in both male and female dogs, but these findings were considerably less consistent than at 3000 ppm. Copies of summary pages for these parameters (from the study report) are presented below.

RIN 2468-93 SUMITHRIN 69005

Page_____ is not included in this copy.

Pages 60 through 61 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

It is concluded that the decreased RBC, HGB, and HCT at 3000 ppm are treatment-related. Although differences from control values were only slight and only occasionally statistically significant, the consistency across time and sexes, nevertheless, strongly suggests a relationship to the test material. At 1000 and 300 ppm, since the consistency of these findings was considerably less and much more equivocal, these findings were not determined to be conclusively related to the test material.

No other hematological effects considered attributable to the test material were observed. It should be noted, however, that the study report indicated an increased number of echinocytes (also known as burr cells; a form of spiculated mature RBC) in the treated dogs on at least one occasion. The toxicological relevance of this, if any, is not known at this time.

b. Clinical Chemistries - The following parameters were examined.

Sodium	Urea nitrogen
Potassium	Glucose
Chloride	Total cholesterol
Total Protein	Aspartate aminotransferase
Albumin	Alanine aminotransferase
Globulin	Alkaline phosphatase
Albumin/Globulin ratio	Lactate dehydrogenase
Calcium	Direct bilirubin
Total bilirubin	

At 3000 ppm (HDT), decreased total protein and decreased albumin were consistently observed in both male and female dogs at all collection times. Statistical significance ($p < 0.05$), however, was only occasionally achieved. Similar decreases were generally not observed at lower dosage levels. Copies of summary pages for these parameters are presented below.

RIN 2468-93 SUMITHRIN 69005

Page_____ is not included in this copy.

Pages 63 through 64 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

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____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

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The decreased total protein and albumin at 3000 ppm are considered to be treatment-related based primarily on the consistency of the findings across time and sexes.

No other clinical chemistry findings were considered attributable to the test material.

6. Urinalysis - Prior to treatment and at weeks 13, 26, 40, and 52, urine samples were collected (cage pan runoff) from all dogs for urinalysis examinations. The dogs were deprived of food and water overnight prior to collection of the samples. The following parameters were examined:

Appearance	Ketones
pH	Bilirubin
Volume	Occult blood
Specific gravity	Urobilinogen
Protein	Microscopic exam. of sediment
Glucose	Reducing substances

No effects attributable to the test material were observed.

7. Gross Necropsy - After 52 weeks of treatment, all dogs were sacrificed by exsanguination while under sodium thiamylal anesthesia. All dogs were subjected to a full gross pathological examination which included examination of the external surface, all orifices, cranial cavity, carcass, external surfaces of the brain (cut surface was examined at the time of tissue processing), nasal cavity and paranasal sinuses, thoracic, abdominal and pelvic cavities and their viscera, and cervical tissues and organs.

The gross pathological examinations did not reveal any lesions or effects related to the test material. Findings were of a nature and incidence that would normally be expected. It is noted that gross examinations of liver and adrenal glands did not reveal any lesions suggesting a relationship to treatment. It is also noted that gross examinations of pituitary glands did not reveal increased incidences of cysts in treated dogs as compared to control dogs (see later under histopathological examinations).

8. Organ Weights - At the time of gross necropsies, organ weights and organ/body weight ratios were determined for the following 12 organs for each dog: liver (with drained gallbladder), kidneys, thyroid (with parathyroid), lungs, ovaries (females), brain (including brain stem), testes with epididymides (males), heart, adrenals, spleen, and pancreas.

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Group mean values for liver weights are presented below. At 3000 ppm, increased absolute liver weights and relative liver/body weight ratios were observed in both male and female dogs. The increases in females were statistically significant and in males, although not statistically significant, were quite substantial. These increases at 3000 ppm are considered to be treatment-related in both the males and females. Lesser equivocal increases at lower dosage levels could not be conclusively related to treatment.

Liver Weights

Dosage Level (ppm)	Absolute Liver Weights (g ± S.D.)		Relative Liver/Body Weight Ratios (% ± S.D.)	
	Males	Females	Males	Females
0	270 ± 60	220 ± 25	2.3 ± 0.1	2.1 ± 0.1
100	240 ± 33	207 ± 34	2.2 ± 0.1	2.0 ± 0.2
300	266 ± 7	239 ± 29	2.4 ± 0.2	2.2 ± 0.3
1000	271 ± 36	249 ± 24	2.6 ± 0.4	2.4 ± 0.3
3000	357 ± 73	288 ± 30*	2.9 ± 0.6	2.9 ± 0.4*

*$p < 0.05$.

No other absolute organ weights or relative organ/body weight ratios suggested an effect induced by the test material. It is noted that pituitary and adrenal weights in treated animals were comparable to weights in control animals (see later under histopathological examinations .

9. Histopathological Examinations - Full sets of tissues from all dogs in the study, as described below, were excised and fixed in 10% neutral buffered formalin, stained with H&E, and examined microscopically.

Skin
Lesions
Brain (entire)
Pituitary
Thyroid (parathyroids)
Thymus
Lungs (two lobes with mainstem bronchi)
Trachea
Heart
Bone marrow (femur)
Salivary glands (mandibular)
Liver (two lobes)
Spleen
Kidneys
Ovaries
Uterus
Mammary gland (females only)
Skeletal muscle (thigh)
Esophagus
Stomach
Duodenum, jejunum, ileum
Colon, cecum, rectum
Urinary bladder
Lymph node (mesenteric)
Lymph node (mandibular)
Sciatic nerve
Cervical spinal cord
Mid-thoracic spinal cord
Lumbar spinal cord

Adrenals	Gallbladder
Pancreas	Aorta (thoracic)
Testes (with epididymides)	Eyes (both)
Prostate	

Nearly all histopathological findings observed in this study were of a nature and incidence that would normally be expected in this type of study. Some few findings considered related to the test material did occur, however, in the liver, adrenal glands, and possibly the pituitary gland.

In the liver, diffuse hepatocellular enlargement (minimum to slight) was observed at 3000 ppm in 4/4 males and in 3/4 females and at 1000 ppm in 1/4 males. These enlargements at 3000 ppm and at 1000 ppm are attributed to treatment with the test material. The increased liver weights at 3000 ppm also support this conclusion.

Liver

Dosage Level (ppm)	Diffuse Hepatocellular Enlargement	
	Males	Females
0	0/4	0/4
100	0/4	0/4
300	0/4	0/4
1000	1/4	0/4
3000	4/4	3/4

In the adrenal cortex, an increased incidence of focal degeneration with acicular crystalline material in the degenerating cells, accompanied by focal mononuclear infiltration, was noted at 3000 ppm in 3/4 males and in 1/4 females and at 1000 ppm in 1/4 males. These lesions are considered to be most likely related to the test material.

Adrenal Cortex

Dosage Level (ppm)	Focal Degeneration		Focal Mononuclear Infiltration	
	Males	Females	Males	Females
0	0/4	0/4	0/4	0/4
100	0/4	0/4	0/4	1/4
300	0/4	0/4	1/4	1/4
1000	1/4	0/4	1/4	1/4
3000	3/4	1/4	3/4	1/4

In the pituitary gland, an increased incidence of microcysts was noted in the treated dogs of both sexes as compared to the control dogs, which had none. It is possible that these microcysts may have been induced by the test material, but in the absence of supporting data in other parameters (e.g., lack of increased pituitary weights), the finding is noted, but remains equivocal and inconclusive at this time. The incidences of microcysts observed microscopically (and also of grossly observed cysts from the gross necropsy examinations) are presented below.

Pituitary Gland

Dosage Level (ppm)	Microcysts (Histopath. Exam.)		Cysts (Gross Exam)	
	Males	Females	Males	Females
0	0/4	0/4	2/4	0/4
100	1/4	1/4	1/4	0/4
300	2/4	1/4	0/4	1/4
1000	2/4	1/4	1/4	0/4
3000	2/4	4/4	0/4	2/4

D. Discussion:

It would have been desirable to have seen more significant and meaningful toxicity at the highest dosage level tested in this study in order to more clearly determine the target organs and major manifestations of toxicity. However, this is not a requirement of a chronic feeding study in nonrodents and the study will not be "down-graded" for that reason. In all other respects, the study was well designed, executed and reported.

E. Conclusions:

This study is classified as Core-Guideline.

The conclusions for this study are as follows:

NOEL = 300 ppm (8.2 mg/kg/day in males and 7.1 mg/kg/day in females)

LEL = 1000 ppm (27.7 mg/kg/day in males and 26.3 mg/kg/day in females). At this dosage level, hepatocellular enlargement in liver, focal degeneration in adrenal cortex.

At 3000 ppm (HDT), also signs of anemia (decreased RBC, hemoglobin and hematocrit), decreased serum albumin and total protein, and increased absolute and relative liver weights, all in both males and females.

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53899:I:Budd:C.Disk:KENCO:1/23/89:SG:DD:SG:vo:rw
R:53900:Budd:C.Disk:KENCO:01/26/89:DD

Reviewed By: William Dykstra 2/25/87
Section I, Toxicology Branch - IRS (TS-769C)
Secondary Reviewer: Edwin Budd
Section I, Toxicology Branch - IRS (TS-769C)

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DATA EVALUATION REPORT

Study Type: 85-1 - Metabolism - Rat TOX Chem No.: 652B

Accession No.: N/A MRID No.: 402704-03

Test Material: (1R,trans) or (1R,cis)[benzyl-C^{14}]phenothrin

Synonyms: Phenothrin

Study Nos.: 340, 341, 342, 343, 502, 503 (EM-70-0017)

Sponsor: Sumitomo Chemical Company, Ltd.

Testing Facility: Sumitomo Chemical Company, Ltd.

Title of Report: Metabolism of (1R,Trans) and (1R,Cis) Isomers of Phenothrin in Rats.

Author(s): M. Isobe

Report Issued: April 6, 1987

Conclusions:

Nearly 96 to 100 percent of C^{14} phenothrin was eliminated in the urine and feces within seven (7) days. Of the low amounts in tissues, the cis isomer was present at 2 to 10 higher levels in fat than the trans isomer. In addition to fat, the skin with hair and the carcass also had low amounts of radioactivity.

There were few differences between sexes in the amount of C^{14} in excreta, in tissues, or in amounts and identity of metabolites in excreta for the low dose and high dose groups. The repeated dose groups had higher levels of urinary metabolites indicating improved absorption.

The major urinary metabolite was 3-(4-hydroxyphenoxy)-benzoic acid sulfate (4'-OH-PB acid sulfate) which was present at levels ranging from 6.8 to 17.9% for the cis isomer and from 14.3 to 55.4% for the trans isomer.

There were no apparent significant sex differences between C^{14}-excreta, C^{14}-tissue residues and amounts and identity of metabolites.

71

The major metabolic pathway proposed based on the data involves hydrolysis of the ester linkage, followed by conjugation with glucuronic acid, glycine or sulfuric acid.

Classification: Core-Guideline

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

Review:

- Metabolism of (1R,trans) and (1R,cis) Isomers of Phenothrin in Rats (Sumitomo Lab Project ID Nos. 340, 341, 342, 343, 502, 503; April 16, 1987)

  Test Material - 1) C^{14}-benzyl labeled (1R,Trans) and (1R, Cis)-phenothrin, and 2) nonlabeled (1R,Trans)-phenothrin (94.7% purity; lot no. Hm-1), and nonlabeled (1R,Cis) phenothrin (lot no. Hm-2; 95.2% purity). Corn oil was used as a vehicle for dosing.

  Animals - Charles River (CD)-derived Sprague-Dawley male and female rats 4 weeks old (repeated dose group) or 6 weeks old (low and high dose groups) were purchased from Charles River Japan, Inc.

  The animals were quarantined and acclimatized for 7 days.

  Randomized groups of 5 males and 5 females were used in the metabolism studies for the low-dose, high-dose, and repeated dose groups.

Methods:

1. Low-Dose Group - Randomized groups of 5 male and 5 female rats each received a single oral dose of cis or trans radiolabeled phenothrin preparations at a rate of 4 mg/kg body weight (bwt) in 5 mL of corn oil.

   The animals were placed in metabolism cages. Urine and feces were collected separately 1, 2, 3, 5, and 7 days after dosing. The rats were sacrificed after 7 days and tissues were collected for combustion analysis by LSC.

2. High-Dose Group - Randomized groups of 5 male and 5 female rats were each dosed with a single oral dose of 200 mg/kg bwt of the cis or trans radiolabeled phenothrin preparation in a volume of 5 mL of corn oil.

   Urine and feces were collected separately in metabolism cages at 1, 2, 3, 5, and 7 days after dosing. The rats were sacrificed after 7 days and tissues were collected for combustion analysis by LSC.

3. Repeated Dose Group - Randomized groups of 5 male and 5 female rats received oral doses of nonradioactive cis or trans technical phenothrin at a rate of 4 mg/kg bwt in 5 mL of corn for 14 successive days. At 24 hours after the last (14th) dose, the rats were then dosed with a single oral dose of radiolabeled cis or trans phenothrin at a rate of 4 mg/kg bwt in 5 mL of corn oil.

007088

Urine and feces was collected separately for 1, 2, 3, 5, and 7 days after the dose of radiolabeled phenothrin. The treated rats were sacrificed after 7 days and tissues were collected for combustion analysis by LSC.

4. Analysis of Excreta and Tissues - Urine and feces were combusted to determine total amount of excreted radioactivity. Urine and feces samples were then extracted with solvents. Metabolites were identified using TLC analysis by comparison to appropriate authentic standards. Tissues were combusted directly and radioactivity was measured by LSC.

Results:

More than 90 percent of the excreted radioactivity for both sexes and for both the cis and trans isomer was collected within the first two (2) days for each dose group (low, high, repeated). The following table shows these results.

Table 1
Percent of Total Radioactivity Recovered

		Days After Administration 0 - 1	0 - 2
Low-Dose (4 mg/kg)			
Males			
Trans	Feces	57.0	60.9
	Urine	36.3	37.6
	Total	93.3	98.5
Cis	Feces	75.1	80.9
	Urine	16.3	17.4
	Total	91.4	98.3
Females			
Trans	Feces	53.4	59.5
	Urine	37.2	39.4
	Total	90.6	98.9
Cis	Feces	66.4	79.3
	Urine	12.1	15.0
	Total	78.5	94.3
High-Dose (200 mg/kg)			
Males			
Trans	Feces	53.4	55.1
	Urine	36.3	37.3
	Total	89.7	92.3

Table 1
Percent of Total Radioactivity Recovered (cont'd)

		Days After Administration 0 - 1	0 - 2
High-Dose (200 mg/kg)			
Cis	Feces	78.0	85.1
	Urine	10.3	11.3
	Total	88.3	96.4
Females			
Trans	Feces	62.1	68.5
	Urine	22.9	24.8
	Total	85.0	93.2
Cis	Feces	69.4	83.8
	Urine	8.6	10.0
	Total	78.0	93.8
Repeated Dose (4 mg/kg, 14 days)			
Males			
Trans	Feces	22.3	23.9
	Urine	72.2	74.0
	Total	94.5	97.9
Cis	Feces	57.1	69.0
	Urine	21.8	23.4
	Total	79.9	92.4
Females			
Trans	Feces	26.0	28.6
	Urine	64.7	69.1
	Total	90.7	97.7
Cis	Feces	56.9	70.6
	Urine	21.2	23.4
	Total	78.0	94.0

It can be seen from the above data that there were no significant differences in C^{14}-excretion between sexes. At the end of the seven (7) day collection period, the total amount of radioactivity collected was close to 100 percent for the various groups.

Excretion into the urine for the trans isomer was higher (at least double) than that with the cis isomer in the low- and high-dose groups.

In the repeated dose group, the excretion was threefold higher for the trans than for the cis isomer.

Although a pharmacokinetic analysis of radioactivity was not reported, the T 1/2 of the cis and trans isomers is considered to be a few hours. This result suggests that there is no significant bioaccumulation of phenothrin in rats.

At the end of 7 days, the maximum percentage of radioactivity which was not in feces or urine was very low. Approximately 1 percent of the dose for low-dose males (cis isomer only) and 4 percent for low-dose females (cis isomer only) was not present in excreta.

In contrast, 100 percent of the trans isomer at the low dose was present in the excreta of both sexes.

At the high dose, 6 percent of the trans and 2 percent of the cis isomer was not present in excreta in males, whereas 6 percent of the trans and 3 percent of the cis isomer was not present in excreta in females.

For the repeated dose group, 1 percent of the trans and 4 percent of the cis was not excreted in males, whereas 1 percent of the trans and 3 percent of the cis was not excreted in females.

Tissue residue analysis by combustion showed that the fat of both sexes contained the highest levels of radioactivity for all groups.

Additionally, the cis isomer was present at 2 to 10 higher levels in fat tissue in comparison to the trans isomer for both sexes and all groups. The only other significant amounts of radioactivity were found in the skin with hair and the carcass.

The following table shows C^{14} tissue residues 7 days after administration of (1R,trans) or (1R,cis) phenothrin.

Table II

Low-Dose (4 mg/kg)	ng Phenothrin Equivalent per Gram of Tissue
Males	
Trans - Fat	41
Skin	4
Carcass	5
Cis - Fat	400
Skin	18
Carcass	25

Table II (cont'd)

	ng Phenothrin Equivalent per Gram of Tissue
Low-Dose (4 mg/kg)	
Females	
Trans - Fat	25
Skin	3
Carcass	5
Cis - Fat	250
Skin	19
Carcass	16
High-Dose (200 mg/kg)	
Males	
Trans - Fat	9.8
Skin	.4
Carcass	.8
Cis - Fat	21.1
Skin	.9
Carcass	1.8
Females	
Trans - Fat	2.6
Skin	.2
Carcass	.3
Cis - Fat	22.4
Skin	1.1
Carcass	1.3
Repeated Dose (4 mg/kg)	
Males	
Trans - Fat	87
Skin	5.2
Carcass	8
Cis - Fat	590
Skin	18
Carcass	45

Table II (cont'd)

Repeated Dose (4 mg/kg)	ng Phenothrin Equivalent per Gram of Tissue
Females	
Trans - Fat	120
Skin	9
Carcass	8
Cis - Fat	670
Skin	43
Carcass	39

There were no substantial differences in the identity or amount of metabolite excreted into the urine and feces for either cis or trans isomers among the three dose groups.

The major urinary metabolite was 4'-OH-PB acid sulfate. This metabolite was present at levels ranging from 10.2 to 28.3 percent for both cis and trans isomers in the low dose, at 6.8 to 27.6 percent for both cis and trans isomers in the high dose, and at 16.7 to 55.4 percent for both the cis and trans isomers in the repeated dose group.

The higher levels of this metabolite in the cis and trans isomers in the repeated dose group indicates higher levels of gastrointestinal (GI) tract absorption at the repeated dose level.

The amount of t-phen and c-phen excreted in the feces is considered to represent the part of the dose that was not absorbed into the GI tract. For the low-dose and high-dose groups, the amount of t-phen and c-phen in the feces ranged from 40.6 to 60.4 percent. In the repeated dose group, t-phen and c-phen levels ranged from 13.8 to 24.8 percent. This finding also demonstrates the increased amount of phenothrin absorbed into the GI tract in the repeated dose group.

The following table illustrates the major excretory metabolites.

Major Excretory Metabolites - Amount (% of Dosed C^{14}) of Metabolite

Metabolites	Low Dose								High Dose								Repeated Dose							
	Male				Female				Male				Female				Male				Female			
	trans		cis		trans		cis		trans		cis		trans		cis		trans		cis		trans		cis	
	F*	U*	F	U	F	U	F	U	F	U	F	U	F	U	F	U	F	U	F	U	F	U	F	U
PB Acid-Free	1.1	2.7		.7	1.5	1.9		.8	1.2	3.4		.7	.7	2.2		.5	.4	5.3		.8	1.0	2.9		.8
4'-OH PB Acid-Free	1.5	.5		.4	1.6	1.9		1.0	1.7	0.9		.4	1.1	2.8		.8	1.6	1.6		0.3	2.9	2.9		1.1
4'-OH PB Acid Sulfate		28.3		13.5		25.2		10.2		27.6		8.5		14.8		6.8		55.4		17.9		51.0		16.7
t-Phen	44.8				44.0				43.8				60.4				13.8				15.5			
c-Phen			40.6				43.6				50.2				58.5				24.8				17.0	

*F = Feces
*U = Urine
PB Acid-Free = 3-phenoxybenzoic acid
4'-OH PB Acid Free = 3-(4-hydroxyphenoxy)benzoic acid
4'-OH PB Acid Sulfate = 3-(4-hydroxyphenoxy)benzoic acid sulfate
t-Phen = 3-phenoxybenzyl (1R,trans)-chrysanthemate
c-Phen = 3-phenoxybenzyl (1R,cis) chrysanthemate

The amount of parent compound excreted into the feces of the repeated dose group was 14 to 16 percent for trans isomer and 17 to 25 percent for cis isomer.

In contrast, the amount of parent compound excreted into the feces of the low-dose group was 44 to 45 percent for the trans isomer and 41 to 44 percent for the cis isomer.

The higher amounts of cis and trans isomer excreted in the feces in the low dose and high-dose groups suggests a lower rate of absorption of the parent into the GI tract in these groups.

This interpretation is supported by the fact that at the repeated dose the urinary major metabolite, 4'-OH-PB acid sulfate, appeared at levels of 51 to 55 percent for the trans isomer and 16 to 18 percent for the cis isomer. In contrast, this metabolite level in the urine of the low-dose group was only 25 to 29 percent for the trans isomer and 10 to 14 percent for the cis isomer.

The metabolic pathway proposed for phenothrin based on these data (as presented in the report) follows.

Ester Metabolites

	R_1	R_2	R_3	R_4
wt-Acid-c-phen	CH_3	COOH	CH_3	H
wc-Alc-c-phen	CH_2OH	CH_3	CH_3	H
wt-Alc-c-phen	CH_3	CH_2OH	CH_3	H
wt-Acid,2-OH(t)-c-phen	CH_3	COOH	CH_2OH	H
4'-OH,wt-Acid,2-OH(t)-c-phen	CH_3	COOH	CH_2OH	OH

*: Labeling position

Discussion:

The results of this metabolism study show that nearly 96 to 100 percent of the orally dosed C^{14}-phenothrin was eliminated in the feces and urine within 7 days. C^{14}-residues in tissues were very low with the exception of the fat tissue in both sexes. Additionally, the cis isomer was present at 2 to 10 higher levels in fat tissue in comparison to the trans isomer for both sexes and all three dose groups. The only other significant amounts of radioactivity were found in the skin with hair and the carcass.

The major urinary metabolite was 4'-OH-PB acid sulfate which accounted for 6.8 to 17.9 percent of the cis isomer and 14.8 to 55.4 percent of the trans isomer.

There were no apparent significant sex differences between C^{14}-excreta, C^{14}-tissue residues, and amounts and identity of metabolites.

The T 1/2 is estimated to be only a few hours. The absorption of phenothrin by the GI tract (reflected in the percent of radioactivity in the urine) was significantly greater for the repeated dose group than the low- or high-dose group.

Excretion into the urine was higher (at least double) for the trans isomer than for the cis isomer in the low- and high-dose groups. Urinary excretion of the trans isomer was threefold higher than the cis isomer in the repeated dose group.

The proposed metabolic pathway of phenothrin shows that hydrolysis of the ester linkage and conjugation with sulfuric acid, glucuronic acid and/or glycine is the predominant pathway.

William Dykstra
William Dykstra, Reviewer

Edwin Budd 11-24-89
Edwin Budd, Section Head