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

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JUN 13 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: D-Phenothrin(Sumithrin) - Submission of a 90-Day Inhalation Toxicity Study in Rats (EPA ID 06905)

TOX Chem No.: 652B
PC No.: 069005
DP No.: D202483
Submission No.: S464017

FROM: William B. Greear, M.P.H. William B. Greear 6/6/95
Review Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO: Richard King/Larry Schnaubelt, PM Team #72
Reregistration Branch
Special Review and Reregistration Division (7508W)

THRU: John D. Doherty, Ph.D., Acting Section Head 6/7/95
Review Section IV, Toxicology Branch I
Health Effects Division (7509C)
KB 6/8/95

I. CONCLUSIONS:

The 90-day inhalation toxicity is acceptable and satisfies the guideline requirement fo a series 82-3 subchronic inhalation toxicity study in rats.

II. REQUESTED ACTION:

SRRD has requested tha TOXI evaluate the results of the following study submitted in support of reregistration:

- "Sumithrin T.G. 90-Day Inhalation Toxicity Study in the Rat (ET-91-0122)," Study No. SMO 314/89644, August 21, 1989, MRID 41289201.

III. RESULTS:

In a subchronic inhalation study, groups of 10 male and 10 female Sprague-Dawley rats were exposed by inhalation in whole body exposure chambers to Sumithrin T.G. aerosols at

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concentrations of 0, 0.030, 0.104, 0.291, or 1.066 mg/L, 6 hr/day, 5 days/week for 13 weeks. The mass median aerodynamic diameters (MMAD) of the Sumithrin T.G. particles ranged from 1.38 to 2.00 µm.

There were no effects on survival, body weight, food consumption, and hematologic or clinical chemistry values considered biologically significant in any of the exposure groups. No treatment-related gross lesions were observed and ophthalmoscopic examinations were negative. No adverse effects were noted at 0.030 and 0.104 mg/L. A reduced response to knocks on the chamber door during exposure at 1.066 mg/L was the only clinical sign attributed to treatment with the test material. Evidence suggestive of liver toxicity included increased absolute and relative liver weights in males (23% and 25%, respectively) and females (39% and 38%, respectively) and centrilobular hepatocyte enlargement in females at 1.066 mg/L. In addition, increased absolute thyroid weights (25%) and slight histopathologic changes of the thyroid were seen in females at 1.066 mg/L. Also seen were increased absolute adrenal weights (21%) in females at 1.066 mg/L and minor histopathologic adrenal lesions in males at 0.291 and 1.066 mg/L. The effects on the thyroid and adrenals are of uncertain toxicological significance. Both sexes exhibited an increased incidence and severity of histopathologic lesions in the nasal turbinates (eosinophilic inclusions in olfactory epithelial cells) at 0.291 and 1.066 mg/L. **Based on histopathologic changes in the nasal turbinates in both sexes, the NOEL is 0.104 mg/L and the LOEL is 0.291 mg/L.**

This study is classified as **Core-Minimum** because it was generally conducted according to test guidelines. Effect levels (NOEL and LOEL) were achieved in both male and female rats. Data on homogeneity of test material concentrations in the exposure chambers were provided only for the range-finding study. Magnesium and lactic acid dehydrogenase were not measured.(required according to 82-4 guidelines).

Special Review Criteria (40 CFR 154.7) None

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DATA EVALUATION REPORT

SUMITHRIN T.G. (D-PHENOTHRIN)

Study Type: SUBCHRONIC INHALATION - RAT (82-4)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, TN 37831
Task Order No. 94-32

Primary Reviewer:
Rosmarie A. Faust, Ph.D. — Signature: Rosmarie A. Faust — Date: 1/17/95

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Quality Assurance:
Susan Chang, M.S. — Signature: S S Chang — Date: 1/17/95

Disclaimer

The final Data Evaluation Report may have been altered by the Health Effects Division subsequent to signing by Oak Ridge National Laboratory personnel.

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

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EPA Reviewer: W. Greear, M.P.H., D.A.B.T. William B. Greear Date: 5/15/95
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: M. Copley, D.V.M., D.A.B.T. Marvin Copley Date: 5/15/95
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Inhalation - Rat (82-4)

TOX. CHEM. NO: 652B

P.C.CODE.: 069005

MRID NO.: 412392-01

TEST MATERIAL: Sumithrin T.G. (D-Phenothrin)

SYNONYMS: 2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid (3-phenoxyphenyl)methyl ester; 2,2,-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylic acid *m*-phenoxybenzyl ester; 3-phenoxybenzyl *cis,trans*-chrysanthemate; S-2539

STUDY NUMBER: SMO 314/89644

SPONSOR: Sumitomo Chemical Co., Ltd., Osaka, Japan

TESTING FACILITY: Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridge PE18 6ES, England

TITLE OF REPORT: Sumithrin T.G. 90-Day Inhalation Toxicity Study in the Rat (ET-91-0122) (Amended Version)

AUTHORS: T.J. Kenny, D.W. Coombs, C.J. Hardy, G.C. Clark, D. Crook, and C. Gopinath

REPORT ISSUED: August 21, 1989

EXECUTIVE SUMMARY: In a subchronic inhalation study, groups of 10 male and 10 female Sprague-Dawley rats were exposed by inhalation in whole body exposure chambers to Sumithrin T.G. aerosols at concentrations of 0, 0.030, 0.104, 0.291, or 1.066 mg/L, 6 hr/day, 5 days/week for 13 weeks. The mass median aerodynamic diameters (MMAD) of the Sumithrin T.G. particles ranged from 1.38 to 2.00 μm.

There were no effects on survival, body weight, food consumption, and hematologic or clinical chemistry values considered biologically significant in any of the exposure groups. No treatment-related gross lesions were observed and ophthalmoscopic

examinations were negative. No adverse effects were noted at 0.030 and 0.104 mg/L. A reduced response to knocks on the chamber door during exposure at 1.066 mg/L was the only clinical sign attributed to treatment with the test material. Evidence suggestive of liver toxicity included increased absolute and relative liver weights in males (23% and 25%, respectively) and females (39% and 38%, respectively) and centrilobular hepatocyte enlargement in females at 1.066 mg/L. In addition, increased absolute thyroid weights (25%) and slight histopathologic changes of the thyroid were seen in females at 1.066 mg/L. Also seen were increased absolute adrenal weights (21%) in females at 1.066 mg/L and minor histopathologic adrenal lesions in males at 0.291 and 1.066 mg/L. The effects on the thyroid and adrenals are of uncertain toxicological significance. Both sexes exhibited an increased incidence and severity of histopathologic lesions in the nasal turbinates (eosinophilic inclusions in olfactory epithelial cells) at 0.291 and 1.066 mg/L. **Based on histopathologic changes in the nasal turbinates in both sexes, the NOEL is 0.104 mg/L and the LOEL is 0.291 mg/L.**

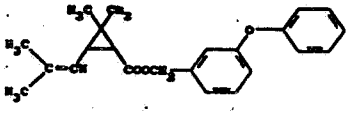
This study is classified as **Core-Minimum** because it was generally conducted according to test guidelines. Effect levels (NOEL and LOEL) were achieved in both male and female rats. Data on homogeneity of test material concentrations in the exposure chambers were provided only for the range-finding study. Magnesium and lactic acid dehydrogenase were not measured.(required according to 82-4 guidelines).

Special Review Criteria (40 CFR 154.7) None

A. MATERIALS

1. Test Material: Sumithrin T.G. (D-Phenothrin)

   Description: pale yellow viscous liquid
   Lot/Batch #: 70505
   Purity: 94.2% a.i.
   Stability of compound: stable for duration of study
   CAS #: 26002-80-2
   Structure:



2. Vehicle and/or positive control

   Air; positive controls were not used.

3. Test animals

Species: rat
Strain: Sprague-Dawley CD
Age and weight at study initiation: 8 1/2 weeks; 258-303 g (males), 164-211 g (females)
Source: Charles River Portage, Portage, MI
Housing: 5 rats/sex/cage in suspended polypropylene cages fitted with stainless steel mesh tops and floors
Environmental conditions:
Temperature: 19.5-22.0°C (extremes were of short duration)
Humidity: 37-54% (extremes were of short duration)
Air changes: approximately 13/hr
Photoperiod: 12 hr light/dark cycle
Acclimation period: 17 days

B. STUDY DESIGN

1. Animal assignment

Animals were assigned randomly to the test groups (10 animals/exposure group/sex) listed in Table 1. The animals were subjected to whole-body exposure for 6 hours/day, 5 days/week for 13 weeks. Controls animals were handled identically, but were exposed to room air only.

TABLE 1. STUDY DESIGN

Test Group	Nominal Concentration (mg/L)	Analytical Concentration (mg/L)	MMAD[a] (µm)	Rats/Sex
1 Control	0	0	NA	10
2 Low (LTD)	0.039	0.030	1.57	10
3 Low Mid (LMTD)	0.122	0.104	1.38	10
4 High Mid (HMTD)	0.357	0.291	1.47	10
5 High (HTD)	1.585	1.066	2.00	10

Data taken from pp. 31 and 32, MRID No. 412892-01.
[a]MMAD = mass median aerodynamic diameter
NA = not applicable

Dose Selection Rationale - The exposure concentrations used in this study were based on the results of a range-finding inhalation study conducted at

Huntingdon Research Centre Ltd. in which rats were exposed to Sumithrin T.G. in whole-body inhalation exposure chambers for 3 weeks. The results of the range-finding study are presented in the Appendix.

2. Generation of the test atmosphere and description of the chamber

Sumithrin T.G. aerosols were generated by metering the test material to stainless steel concentric jet atomizers mounted in the base of glass dispersion columns. Diluent air was also fed into the base of the glass column. Each column was connected to the inlet duct of an exposure chamber. Time to equilibrium was not reported.

Each group of animals (10 males and 10 females) was exposed in stainless steel and glass exposure chambers having square cross sections and fitted with pyramidal tops. The internal volume of the chambers was 0.7 m^3. Individual exposure cages, constructed of stainless steel mesh, were arranged in four levels of each chamber. The chambers were fitted with eight ports for withdrawal of chamber air samples for analysis. The chamber airflow, monitored with a magnehelic pressure gauge at 30-minute intervals, was 150 L/minute (approximately 13 air changes/hour). Temperature was recorded hourly with a thermohygrometer and the relative chamber humidity was calculated from these data. The temperature was in the acceptable range (22 ± 2°C) and the relative humidity was slightly below the recommended range of 40-60% (Table 2). Monitoring of oxygen concentration in the exposure chamber was not mentioned in the study report. However, adequate oxygen was probably provided because of frequent air exchanges.

Test atmosphere concentration - Test atmosphere concentrations are presented in Table 1. The nominal concentrations of Sumithrin T.G. were calculated from the formula: volume used (mL) - run-off (mL) x density (g/mL)/total volume of air used over period of usage (L). To collect a measurable run-off for the low exposure concentration, run-off was only measured every 10 days. The test material concentrations in the exposure chambers were determined three times during each exposure (approximately 1, 3, and 5 hours from the start of exposure). Samples were withdrawn from the eight ports in the chamber at 10 L per minute through a glass fiber filter. The filters were eluted with acetone and analyzed by flame ionization chromatography. The analytical concentrations were in close agreement with the target concentrations of 0.03, 0.1, 0.3, or 1.0 mg/L. The homogeneity of aerosol distribution within the chambers was not reported.

Particle size determination - Particle size data (MMAD) are presented in Table 1 above. The aerosol particle size distribution was determined once during each exposure for all exposed groups. The chamber air was withdrawn using an Andersen cascade impactor (Marple 296) at a rate of 2 L/minute. A breakdown of the particle size distribution showed that 23.7%, 28.8%, 26.8%, or 15.6% of

particles in the low-, low mid-, high mid-, or high-dose groups were smaller than 0.93 μm. In the low- and high-dose groups, 47.9% and 36.3% of particles, respectively, were smaller than 1.55 μm. The Standard Evaluation Procedure (SEP) for Inhalation Toxicity Testing (1988) states that 25% of the particles should be less than 1 μm. This requirement was met in the low mid- and high mid-dose groups, was nearly met in the low-dose group, but not in the high-dose group. However, the major portion (87.7%) of particles in the high-dose group were smaller than 3 μm, an aerodynamic diameter that could deposit throughout the respiratory tract (see Pesticide Rejection Rate Analysis Toxicology, 1993).

TABLE 2. CHAMBER TEMPERATURE AND RELATIVE HUMIDITY [a]

Test Group	Temperature (°C)	Relative Humidity (%)
Control	21.7	50
0.030 mg/L	22.3	38
0.104 mg/L	22.8	38
0.291 mg/L	22.1	39
1.066 mg/L	22.2	38

Data taken from p. 32, MRID No. 412892-01
[a]Mean of daily means

3. Diet

Labsure Diet LAD 1 (Lavendar Mill, Manea, Cambridgeshire, England) and tap water were available ad libitum except during exposure.

4. Statistics

All statistical analyses were carried out separately for males and females. Statistical tests were performed for food consumption, body weight, organ weight, and clinical pathology data. The statistical methods employed are presented in the Appendix.

5. Signed GLP and quality assurance statements (dated 21/08/89) were present.

C. METHODS AND RESULTS

1. Observations

Animals were inspected twice daily for signs of toxicity and mortality.

Results - No deaths occurred during the 13-week exposure period. During exposure, a reduced response to knocks on the chamber door was observed in animals exposed to the highest concentration, 1.066 mg/L. Various clinical signs such as hair loss in a few animals at the lower concentrations and brown or red/brown staining of tail, forelimbs, head areas, and urogenital region at the highest concentration were observed in some animals at other times, but were not considered toxicologically significant. Poorly groomed fur and dirty tails in high-dose males and females and urogenital staining in high-dose females were considered the result of deposition of the relatively high concentration of the test material.

2. Body weight

Animals were weighed at weekly intervals beginning 1 week before treatment and continuing throughout the study. The individual animal weights were also recorded at necropsy.

Results - No treatment-related effects were noted on body weights or body weight gains for either male or female rats exposed for 13 weeks to Sumithrin T.G.

3. Food consumption

Food consumption per cage was measured weekly beginning 1 week prior to the start of exposure until the end of the study.

Results - There were no treatment-related effects on food consumption in either male or female rats.

4. Ophthalmoscopic examination

The eyes of all rats were examined prior to exposure and during week 13.

Results - No ocular lesions attributable to the test material were noted.

5. Blood was collected from the orbital sinus of fasted, lightly ether-anesthetized rats for hematology and clinical chemistry analysis from all animals during Week 12 of the study. The CHECKED (X) parameters were examined.

a. Hematology

X	
X	Hematocrit (HCT)*
X	Hemoglobin (HGB)*
X	Leukocyte count (WBC)*
X	Erythrocyte count (RBC)*
X	Platelet count*
X	Blood clotting measurements
X	(Thrombotest)
	(Clotting time)
	(Prothombin time)

X	
X	Leukocyte differential count*
X	Mean corpuscular HGB (MCH)
X	Mean corpusc HGB conc. (MCHC)
X	Mean corpusc. volume (MCV)
X	Reticulocyte count

*Required for subchronic studies.

Results - Analysis of hematologic parameters did not provide evidence of any treatment-related effects after 12 weeks of exposure. Eosinophils were statistically significantly increased in females exposed to the highest concentration [0.12 x $10^3/mm^3$ vs. 0.02 x $10^3/mm^3$ for controls, $p<0.01$ (Williams' test)]. Statistically significant decreases were also observed in the Thrombotest, affecting males at the highest concentration ($p<0.01$) and females at the low-intermediate, high-intermediate, and highest concentrations (all $p<0.05$). For exposures to 0, 0.030, 0.291, or 1.066 mg/L, respectively, the Thrombotest times were 26, 25, 25, 25, and 23 seconds for males and 21, 20, 19, 20, and 20 seconds for females. Although statistically significant, the effects on eosinophils and Thrombotest time are not biologically significant.

b. Clinical chemistry

X

Electrolytes

X	Calcium*
X	Chloride*
	Magnesium*
X	Phosphorus*
X	Potassium*
X	Sodium*

Enzymes

X	Alkaline phosphatase (ALK)
	Cholinesterase (ChE)
X	Creatinine phosphokinase
	Lactic acid dehydrogenase (LDH)*
X	Serum alanine aminotransferase (also SGPT)*
X	Serum aspartate aminotransferase (also SGOT)*
	Gamma glutamyl transferase (GGT)
	Glutamate dehydrogenase

X

Other

X	Albumin*
X	Blood creatinine*
X	Blood urea nitrogen*
X	Cholesterol*
X	Globulins
X	Glucose*
X	Total bilirubin
X	Total serum protein (TP)*
	Triglycerides
	Serum protein electrophoresis

* Required for subchronic studies.

Results - Analysis of clinical chemistry data showed statistically significant differences in several parameters compared with controls (Table 3). They included decreased glucose in high-dose males ($p<0.01$); increased total protein in high-dose males ($p<0.05$) and in all exposed female groups ($p<0.01$); increased globulin in high-dose males and in all exposed female groups ($p<0.01$); decreased A/G ratios in all exposed male groups ($p<0.05$); increased urea nitrogen in high-dose males ($p<0.05$) and decreased urea nitrogen in high-dose females ($p<0.05$); increased alkaline phosphatase in high-dose females ($p<0.05$); and decreased chloride in high-dose females ($p<0.05$). Although statistically significant, deviations from control values for these parameters were not considered toxicologically significant. The protein values for controls were at the lower quartile of the normal range for this strain and age of rat and the protein values of the treated groups were therefore considered within the normal limits.

TABLE 3. SELECTED CLINICAL CHEMISTRY VALUES IN MALE AND FEMALE RATS EXPOSED TO SUMITHRIN T.G. BY INHALATION FOR 13 WEEKS

Parameter	Exposure Concentration (mg/L)				
	0	0.030	0.104	0.291	1.066
Males					
Glucose (mg/dL)	122	122	138	124	100**
Total protein (g/dL)	7.1	7.1	7.1	7.2	7.4*
Globulin (g/dL)	3.9	4.0	4.0	4.1	4.2**
A/G ratio	0.82	0.77*	0.77*	0.76*	0.7[illegible]
Urea nitrogen (mg/dL)	13	13	13	14	15*
Alkaline phosphatase (mU/mL)	164	169	152	178	188
Chloride (mEq/L)	101	102	102	102	100
Females					
Glucose (mg/dL)	107	112	119	109	100
Total protein (g/dL)	7.7	8.2**	8.3**	7.9**	8.2**
Globulin (g/dL)	3.9	4.1**	4.2**	4.0**	4.2**
A/G ratio	0.98	0.98	0.96	0.97	0.96
Urea nitrogen (mg/dL)	18	18	15	[illegible]	15*
Alkaline phosphatase (mU/mL)	99	75	76	83	128*
Chloride (mEq/L)	103	101	101	103	100*

Data taken from Table 8, pp. 65-68, MRID No. 412892-01.
*Significantly different from control, $p<0.05$ (Williams' test)
**Significantly different from control, $p<0.01$ (Williams' test)

5. Urinalysis

Urinalysis is not required for subchronic inhalation studies and was not performed.

7. Sacrifice and pathology

All animals were sacrificed on schedule by exsanguination (incision of the brachial blood vessels) following anesthesia by intraperitoneal injection of pentobarbitone sodium and subjected to gross pathological examination. The CHECKED (X) tissues were collected for histological examination and the (XX) organs, in addition, were weighed. The liver and thyroids of female rats, the nasal turbinates of male and female rats, and the adrenals of male rats in the low, low-intermediate, and high-intermediate groups were also examined microscopically due to changes seen in high-dose rats.

X	
Digestive system	
X	Tongue
X	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
XX	Liver*+
	Gall Bladder*
X	Pancreas*
Respiratory	
X	Trachea*
XX	Lung*
X	Nose
X	Pharynx
X	Larynx

X	
Cardiovasc./Hemat.	
X	Aorta*
XX	Heart*
X	Bone marrow*
X	Lymph nodes*
XX	Spleen
XX	Thymus*
Urogenital	
XX	Kidneys*+
X	Urinary bladder*
XX	Testes*+
XX	Epididymides
X	Prostate
X	Seminal vesicle
XX	Ovaries*+
X	Uterus*
X	Vagina

X	
Neurologic	
XX	Brain*+
X	Periph. nerve*
X	Spinal cord (3 levels)*
XX	Pituitary*
X	Eye (optic n.)*
Glandular	
XX	Adrenal gland*
	Lacrimal gland
X	Mammary gland*
X	Parathyroids*
XX	Thyroids*
Other	
X	Bone*
X	Skeletal muscle*
X	Skin*
X	All gross lesions and masses*

* Required for subchronic and chronic studies.
\+ Organ weight required in subchronic and chronic studies.

Results –

a. Organ weight - Compared with controls, animals exposed to the highest concentration exhibited a few statistically significant increases in absolute organ weights (Table 4). They included increased absolute liver weights (+23% and +39% for males and females, respectively, $p<0.01$); increased kidney weights (+7% for males, $p<0.05$); increased thyroid weights (+25% for females, $p<0.05$); and increased adrenal weights (+21% for females, $p<0.01$). Relative organ weights were not reported. Employing the T-test (calculated by reviewer),

the relative liver weights were significantly $p<0.001$ increased (+25% for males and +38% for females) at 1.066 mg/L. Only the increased liver weights in both sexes were considered related to treatment with Sumithrin T.G. Dose-related trends were not observed.

TABLE 4. SELECTED ABSOLUTE AND RELATIVE ORGAN WEIGHTS OF MALE AND FEMALE RATS EXPOSED TO SUMITHRIN T.G. BY INHALATION FOR 13 WEEKS

Organ	Exposure Concentration (mg/L)				
	0	0.030	0.104	0.291	1.066
	Males				
Body weight (g)	544	537	546	546	539
Liver (mg)	18300[a] 33.64[b]	18400 34.26	17300 31.68	18500 33.88	22600** 41.93***
Kidney (mg)	32400 59.56	32100 59.78	33200 60.81	32000 58.61	34600* 64.19
Thyroid (mg)	26.5 0.049	24.9 0.046	25.8 0.047	24.5 0.045	27.5 0.051
Adrenal (mg)	45.8 0.084	47.9 0.089	49.7 0.091	47.4 0.087	48.2 0.089
	Females				
Body weight (g)	279	272	277	276	282
Liver (mg)	9200 32.97	8700 31.99	9200 33.21	8800 31.88	12800** 45.39***
Kidney (mg)	18400 65.95	17100 62.87	19100 68.95	18200 65.94	19200 68.09
Thyroid (mg)	18.5 0.066	17.0 0.063	18.1 0.065	18.1 0.066	23.2* 0.082
Adrenal (mg)	53.2 0.19	54.6 0.20	56.0 0.20	52.7 0.19	64.2** 0.23

Data taken from Table 10, pp. 71-72, MRID No. 412892-01.
[a]Absolute organ weight
[b]Relative organ weight (mg/g body weight, calculated by reviewer)
*Significantly different from control, $p<0.05$ (Williams' test)
**Significantly different from control, $p<0.01$ (Williams' test)
***Significantly different from control, $p<0.001$ (T-test, calculated by reviewer)

b. Gross pathology - No treatment-related gross lesions were observed in either male or female rats.

c. Microscopic pathology -

1) Non-neoplastic - Non-neoplastic findings considered treatment-related include lesions in the liver, thyroid, adrenals, and nasal turbinates (Table 5). Most of the female rats exposed to 1.066 mg/L exhibited minimal to moderate hepatocyte enlargement and a minimally increased height of the follicular epithelium of the thyroid. This thyroid effect was also seen in one female exposed to 0.291 mg/L. Liver and thyroid lesions were not seen in female controls or in the lower exposure groups. Cortical vacuolation of the adrenals was seen in all groups of male rats (including controls). The incidence and severity of this lesion, classified as minimal to moderate, increased at 0.291 and 1.066 mg/L. All test groups (including controls) developed eosinophilic inclusions in the olfactory epithelium of the nasal turbinates. The incidence as well as severity of this lesion increased in the higher exposure groups in both males and females. The severity was generally ranked as minimal to moderate.

2) Neoplastic - There was no evidence of neoplastic lesions in any of the treated or control animals.

TABLE 5. INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC LESIONS IN MALE AND FEMALE RATS EXPOSED TO SUMITHRIN T.G. BY INHALATION FOR 13 WEEKS[a]

Organ/Lesion	Exposure Concentration (mg/L)				
	0	0.030	0.104	0.291	1.0 66
	Males				
Liver, centrilobular hepatocyte enlargement	0	not	not	not	0
minimal	0	examine	examine	examine	0
moderate	0	d	d	d	0
Thyroid, increased follicular epithelium height	0	not	not	not	0
minimal	0	examine	examine	examine	0
		d	d	d	
Adrenals, cortical vacuolation	5	4	6	9	7
minimal	5	4	6	8	4
moderate	0	0	0	1	3
Nasal turbinates, eosinophilic inclusions in olfactory epithelial cells	5	7	6	7	9
minimal	4	7	5	3	2
moderate	1	0	1	4	7
	Females				
Liver, centrilobular hepatocyte enlargement	0	0	0	0	8 6
minimal	0	0	0	0	2 2
moderate	0	0	0	0	
Thyroid, increased follicular epithelium height	0	0	0	1	
minimal	0	0	0	1	7**
					7
Adrenals, cortical vacuolation	0				0
minimal	0	not	not	not	0
moderate	0	examine	examine	examine	0
		d	d	d	
Nasal turbinates, eosinophilic inclusions in olfactory epithelial cells	5	5	7	10***	9
minimal	5	5	6	4	3
moderate	0	0	1	6	5
marked	0	0	0	0	1

Data taken from Table 11, pp. 74-81, MRID No. 412892-01.
[a]10 animals/group examined
*p<0.001; **p=0.002; ***p=0.016 (Fisher exact test, calculated by reviewer)

D. DISCUSSION

Male and female Sprague-Dawley rats were exposed by inhalation in whole-body exposure chambers to Sumithrin T.G. aerosol at concentrations up to 1.066 mg/L. The MMAD ranged from to 1.38 to 2.00 μm. All animals survived the 13-week exposure period and treatment with the test material had no observable effect on food consumption or body weight gain. Clinical signs of toxicity were limited to a reduced response to knocks at the chamber door in rats exposed to the highest concentration.

Omission of standard deviation in the organ weight summary tables prohibited easy calculation of homogeneity of variance using the F-test. Because the most pronounced changes were seen in the liver, statistical analysis of relative liver weights was performed by the reviewer from individual organ weight data. Lack of positive clinical chemistry and gross pathologic findings made the statistical analysis of relative thyroid and adrenal weight data less important; therefore, relative thyroid and adrenal data were not analyzed statistically.

Evidence suggestive of liver toxicity includes increased absolute and relative liver weights in males (23% and 25%, respectively) and females (39% and 38%, respectively) and centrilobular hepatocyte enlargement in females at 1.066 mg/L. However, a dose-response was not seen, clinical chemistry values indicative of hepatic effects were not biologically significant, and there were no gross pathological changes.

Slight differences between control and high-dose animals were observed in absolute kidney weights of male rats. In the absence of confirming gross or histopathologic lesions, the kidney weight increase is not considered treatment related.

In females exposed to 1.066 mg/L, absolute thyroid weights were increased (25%) and microscopic examinations of this organ showed an increased height of the follicular epithelium. Also seen in females at 1.066 mg/L were significantly increased adrenal weights (21%) in the absence of histopathologic alterations. Minor increases in cortical vacuolation of the adrenal gland at 0.291 and 1.066 mg/L were observed in males, but not in females. There were no gross pathologic changes in either organ. The effects on the thyroid and adrenals may be related to treatment with the test material, but the toxicological significance of these findings is not known.

Microscopic lesions in the nasal turbinates (eosinophilic inclusions in olfactory epithelial cells) were observed in all exposed and control groups. A clear dose-response was not seen; however, the incidence as well as severity of the microscopic changes increased in both sexes at the mid-high and high exposure concentrations. Therefore, the increase of eosinophilic inclusions in olfactory epithelial cells is considered to be a treatment-related effect.

In conclusion, effects considered treatment-related included increased liver weights in both sexes and histopathologic hepatic changes in females at 1.066 mg/L and effects on the nasal turbinates at 0.291 and 1.066 mg/L in both sexes. Of uncertain toxicological significance are the effects on the thyroid and adrenals. Therefore, the NOEL is 0.104 mg/L and the LOEL is 0.291 mg/L.

The concentrations for the 13-week study were selected from a 3-week range-finding study in which Sprague-Dawley rats were administered the test article in whole body exposure chambers at concentrations of 0, 0.101, 0.310, or 0.992 mg/L, 6 hours/day, 5 days/week for 3 weeks. In this study, the only signs of toxicity observed were mildly irritating effects (licking inside mouth) at 0.310 and 0.992 mg/L and half-closed eyes, lacrimation, and prone posture at 0.992 mg/L. There were no remarkable changes in the lowest dose group.

E. STUDY DEFICIENCIES

Data for homogeneity of the test atmosphere were not included in the report. However, homogeneity of the test atmosphere was determined in the range-finding study (see Appendix).

Magnesium and lactic acid dehydrogenase were not measured. They are omissions according to 82-4 guidelines. Relative organ weights were not calculated.

Standard deviations were not included with group means preventing quick analysis of significance.

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APPENDIX

DOSE SELECTION STUDY IN RATS

Study Type: 3-week inhalation range-finding in rats
Test Material: Sumithrin T.G. (D-Phenothrin), 94.2%
Testing Facility: Huntingdon Research Centre Ltd., England
Study Title: SMO/304. Addendum to SMO/314 HRC Report No. 89644. Sumithrin T.G. 3-Week Preliminary Inhalation Study in Rats
Authors: T.J. Kenny, D.W. Coombs, and C.J. Hardy

Methods:

Test Animals: 6-week-old male and female Sprague-Dawley CD rats
Group Size: 5 males, 5 females
Test Concentrations (mg/L): 0, 0.101, 0.310, or 0.992
Particle Size (MMAD, μm): 1.73 (LTD), 1.74 (MTD), 2.34 (HTD)
Particle size distribution: <0.9 μm: 26.9% (LTD), 26.3% (MTD), 15.1% (HTD)
Chamber variation of test atmosphere (homogeneity): 28.3% (LTD), 12.4% (MTD), 18.7% (HTD)
Exposure Protocol: whole-body exposures, 6 hours/day, 5 days/week for 3 weeks

Results:

Mortality: None

Clinical observations: No clinical signs of toxicity were seen in controls or in rats exposed to 0.101 mg/L. During exposure, licking of the inside of the mouth, a sign typical of a mild irritant, was seen at 0.310 and 0.992 mg/L in most animals during week 3. Clinical signs of toxicity seen only at 0.992 mg/L included lacrimation during week 1 and half-closed eyes, blinking of eyes and prone posture in all animals during the entire exposure period. Clinical observations noted at other times were not related to exposure to the test material.

Body weight gain and food consumption: For male rats exposed to 0.101, 0.310, or 0.992 mg/L, the respective weight gain was 11%, 8%, or 17% lower than controls and the respective food consumption was 8%, 10%, or 7% lower than controls. For female rats exposed to 0.101, 0.310, or 0.992 mg/L, the respective weight gain was 17%, 9%, or 9% greater than controls and the respective food consumption was 7%, 6%, or 5% greater than controls. The effects on body weight gain and food consumption in either male or female rats were not considered a result of exposure to the test material.

Organ weights: No compound-related effects were observed.

Macroscopic pathology: A higher incidence (details not provided) of fluid retention of the uterus seen in female exposed groups was not considered a compound-related effect.

Basis of dose selection: Clinical observations.

Core Classification: Not applicable; range-finding study

STATISTICAL ANALYSIS SMC/314

All statistical analyses were carried out separately for males and females.

Data relating to food were analysed on a cage basis. For all other parameters the analyses were carried out using the individual animal as the basic experimental unit. Food consumption data were analysed using cumulative cage weekly average intake per group. Bodyweight data were analysed using weight gains. The following sequence of statistical tests was used for food consumption. bodyweight, organ weight and clinical pathology data:

(i) If the data consisted predominantly of one particular value (relative frequency of the mode exceeds 75%) the proportion of animals with values different from the mode was analysed by appropriate methods. Otherwise:

(ii) Bartlett's test (1) was applied to test for heterogeneity of variance between treatments; where significant (at the 1% level) heterogeneity was found, a logarithmic transformation was tried to see if a more stable variance structure could be obtained.

(iii) If no significant heterogeneity was detected (or if a satisfactory transformation was found), a one-way analysis of variance was carried out. If significant heterogeneity of variance was present, and could not be removed by a transformation, the Kruskal-Wallis analysis of ranks (2) was used.

(iv) Except for pre-exposure data, analysis of variance were followed by Student's 't' test and Williams' test (3) for a dose-related response, although only Williams' test was reported. The Kruskal-Wallis analyses were followed by Shirley's test (4), the non-parametric equivalent of the 't' and Williams' tests.

Where appropriate, analysis of covariance was used in place of analysis of variance in the above sequence. For organ weight data, the final bodyweight was used as covariate in an attempt to allow for differences in bodyweight which might affect the organ weights.

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D - Phenothrin

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82-4 Subchronic Inhalation Toxicity (90-day) in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only)
2. ✓ Product is a gas, a solid which may produce a sig[illegible]nt vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3. ✓ At least 10 young adult rats/sex/group
4. ✓ Dosing, 6 hours per day, 5 days per week for 13 weeks.
5. ✓ Food and water should be withheld during dosing.
6.* ✓ Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content. not reported
7. ✓ Chamber temperature, 22° C (±2°), relative humidity 40-60%.
8.* ___ Alternatively, oro-nasal or head only exposures may be used.
9. ✓ Monitor rate of air flow.
10. ✓ Monitor actual concentrations of test material in breathing zone.
11. ✓ Monitor aerodynamic particle size for aerosols.
12. ✓ Individual daily observations.
13. ✓ Individual body weights.
14. ✓ Individual or cage food consumption.
15.* ✓ Opthalmoscopic examination (at least pretest and at term) control and high dose.
16. ✓ Clinical pathology data of 17 & 18 in all animals at termination.
17. ✓ Hematology.
    - ✓ Erythrocyte count
    - ✓ Hemoglobin
    - ✓ Hematocrit (PCV)
    - ✓ Leucocyte count
    - * ✓ Differential count
    - ✓ Platelet count (or clotting measure)
18. ___ Clinical chemistry.
    - ✓ Alkaline phosphatase
    - ✓ Aspartate aminotransferase
    - * ✓ Creatinine kinase
    - ___ Lactic dehydrogenase
    - ✓ Glucose
    - ✓ Bilirubin
    - ✓ Cholesterol
    - * ✓ Creatinine
    - ✓ Total Protein
    - ✓ Albumin
    - ✓ Urea
    - ✓ Inorganic phosphate
    - ✓ Calcium
    - * ✓ Potassium
    - ✓ Sodium
    - * ✓ Chloride
19.* ___ Urinalysis, only when indicated by expected or observed activity. As scheduled in 16.
    - ___ Blood
    - ___ Protein
    - ___ Ketone bodies
    - ___ Appearance
    - ___ Glucose
    - ___ Total bilirubin
    - * ___ Urobilirubin
    - ___ Sediment
    - ___ Specific gravity (osmolality)
    - * ___ Volume

Criteria marked with a * are supplemental and may not be required for every study.

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20. ✓ Individual necropsy of all animals.
21. ✓ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

✓ aorta	✓ jejunum	✓ peripheral nerve
✓ eyes	bone marrow	✓✓ kidneys†
✓ caecum	✓✓ liver†	✓ esophagus
✓ colon	✓✓ lung†	✓✓ ovaries†
✓ duodenum	✓ lymph nodes	oviduct
✓✓ brain†	✓ stomach	✓ pancreas
✓ skin	✓ mammary gland	✓ rectum
✓✓ heart†	✓✓ spleen†	✓ spinal cord (3x)
✓✓ testes†	✓ musculature	✓ thyroid / parathyroids
✓ pituitary	✓ epididymis	✓ salivary glands
✓ ileum	✓✓ adrenals†	✓ thymus
✓ trachea	✓ uterus	✓ urinary bladder

† organs to be weighed

Criteria marked with a * are supplemental and may not be required for every study.

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