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FINAL

DATA EVALUATION REPORT

TETRAMETHRIN

Study Title:
Three-Month Inhalation Toxicity Study
of Tetramethrin in Rats

Prepared for:

Office of Pesticide Programs
U.S. Environmental Protection Agency
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Arlington, VA 22202

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DATA EVALUATION REPORT

STUDY TYPE: Guideline Series (82-4): Subchronic inhalation study in rats.

TEST MATERIAL: Tetramethrin

MRID Number: 420121-01

SYNONYMS: Neo-Pynamin

STUDY NUMBER: 2189

SPONSOR: Sumitomo Chemical Co., Ltd., Baltimore, MD.

TESTING FACILITY: Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan.

TITLE OF REPORT: Three-Month Inhalation Toxicity Study of Tetramethrin in Rats.

AUTHOR: Shinobu Kawaguchi

REPORT ISSUED: August 9, 1991

CONCLUSIONS: Tetramethrin (0, 20.3, 134, or 824 mg/m^3) was administered to Crj:CD(SD) rats (SPF) by inhalation for 6 hours/day, 5 days/week for 13 weeks, plus 3 days into week 14. Gross findings in the livers of mid- and high-concentration males and females consisted of soft and/or enlarged livers and dark-red discoloration. Histopathological data suggest that the liver (in both sexes) and the kidney (in males) may be possible target organs. Hepatocellular hypertrophy was noted in both mid- and high-concentration rats of both sexes. Focal necrosis of the liver was seen in the high-concentration males. The pathological changes in the liver correlated with an increase in absolute and relative liver weights. An increased incidence of hyaline droplets in renal tubules was present in the mid- and high-concentration males. The presence of hyaline droplets in the renal tubules corresponded to an increase in relative kidney weights in the mid- and high-concentration males. Absolute and relative kidney weights were increased in all exposed females. A significant increase in relative liver weights was seen in the low-concentration males and females. There were no macroscopic or microscopic

lesions in the low-concentration rats. An increase in total protein levels was noted in the low-concentration males.

Administration of 134 or 824 mg/m^3 tetramethrin was also associated with changes in hematology, clinical chemistry and urinalysis parameters, and decreases in body weight gains. Clinical signs were also seen in the mid- and high-concentration rats. There was no effect of dosing on mortality, ophthalmology or food consumption.

A clear, no-observed-effects level (NOEL) based on increases in liver weights in males and females was not established.

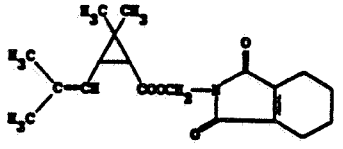
CORE CLASSIFICATION: Core Supplementary. This study does not satisfy the requirements for a subchronic inhalation toxicity study (82-4) since a NOEL for liver weight increases was not established. In addition, exposure characterization was only conducted 2 days/week.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Tetramethrin

Formula: 2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid (1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)methyl ester



Lot Number: 90304

Purity: 95.3%; impurities not identified

Physical Property: White solid

Stability: Not reported

Storage: Dark at 2-4°C

Vehicle: Corn oil

2. Test Article Analyses for Purity and Stability

No data were provided regarding analyses of test material for purity and stability. The test material was dissolved in corn oil and three different concentrations of tetramethrin solutions were prepared just before each exposure. The actual aerial concentration of the test material in the exposure chamber was determined twice during exposure 2 days a week. Test atmospheres were collected on a glass column

containing silica gel. The tetramethrin content was analyzed by gas chromatography with flame ionization detection after extraction with acetone.

Table 1 presents summary data for nominal and analyzed concentrations. The study report did not indicate the intended target concentrations except for the highest concentration (a target of 800 mg/m^3). Exposure levels were based on results of a previous three-week inhalation toxicity study of tetramethrin in rats (Sumitomo Chemical Co., Ltd., Technical Report, Study No. 2123, 1991); this study was not available for review.

A target of 800 mg/m^3 was expected to produce toxic effects in the liver and kidney based on the results of the three-week inhalation toxicity study. The lowest exposure level (92.1 mg/m^3) in the three-week inhalation study was associated with only slight changes such as a decrease in lymphocyte count in females and an increase in hepatocellular hypertrophy in males. Consequently, about one-fourth of the lowest exposure level in the three-week inhalation study was selected as the exposure level in group 3 (20.3 mg/m^3) in order to determine a NOEL.

3. Exposure Conditions

Rats were exposed for 6 hours/day, 5 days/week, in a whole-body exposure chamber (illustrated in Figure 1) for 13 weeks plus 3 days. The animals were individually placed in wire-mesh exposure cages during the exposure period. The animals received no food or water during exposure. Test material solution was automatically injected into an atomizer using a tube pump and sprayed under compressed air. The mist aerosol generated was immediately transported into the exposure chamber (0.56 m^3 in inner volume). The flow rate of the exhausted air was adjusted to 0.12 m^3/min by means of a blower pump to keep the inner pressure of the chamber constant (about -7 mmH_2O). Temperature, relative humidity, air flow, and air pressure in the exposure chamber were continuously monitored and checked at 0, 1, 2, 4, and 6 hours after initiation of exposure.

The nominal aerial concentration of test material was calculated each exposure day from the amount of air blown through the exposure chamber, and the amount of tetramethrin consumed. The distribution of the aerodynamic diameter of mist particles in the exposure chamber was measured 5 times during exposure 2 days a week using a Microscopic Sedimentation Analyzer. The median aerodynamic diameter of mist particles and the log-standard geometric deviation (LSD) were then estimated by the computerized probit analysis. Table 1 summarizes data on particle size, nominal concentrations and actual aerial concentrations. The particle sizes were well within the respiratory range.

A

MRID # 420121-01

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TABLE 1. Characteristics of Exposure Atmospheres[a]

Parameter	Actual Exposure Level (mg/m^3)			
	0[b]	20.3	134	824
Mean nominal tetramethrin concentration (g/m^3)	–	0.117	0.803	3.52
MMAD (μm)				
lower limit	0.68	0.65	0.70	0.69
upper limit	0.92	0.94	0.95	0.90
Logarithmic Standard Geometric Deviation				
Minimum	1.43	1.37	1.39	1.43
Maximum	1.94	2.00	2.05	1.92
Mean chamber temp. (°C)	24.6	24.5	24.7	24.9
Mean relative humidity (%)	54.5	55.0	55.5	55.5

[a]Data extracted from Tables 3-7 of the study report.
[b]Vehicle controls.

4. Animals

Five-week old Crj:CD(SD) rats (SPF) of both sexes were obtained from Charles River Japan Inc. (Hino Breeding Center, Shiga). From the results of clinical observation, body weight changes, and ophthalmological examination, 50 males and 50 females were selected for the study after a quarantine period of 7 days followed by "preliminary breeding for 4 days". The rationale for preliminary breeding for 4 days was not provided by the study author. However, judging by the absence of any evidence to the contrary, it is assumed that the study animals satisfied the Guideline (82-4) requirement that females be nulliparous and non-pregnant. Two rats of the same sex from the same study group were placed in a suspending aluminum cage with wire-mesh floor in a room with temperature and humidity controls set at 24°C ± 2°C and 50% ± 10%, respectively, with a 12-hour light/dark cycle. Water and food were provided ad libitum except during the exposure period. Prior to treatment, males weighed 210-250 g and females weighed 155-189 g.

Rats were randomly assigned by body weights (utilizing a computer-generated procedure) to the following test groups:

Exposure Concentration (mg/m^3)	13 Weeks	
	Males	Females
0 (vehicle control)	10	10
0 (air control)	10	10
20.3 (low)	10	10
134 (mid)	10	10
824 (high)	10	10

5. Statistics

Body weight, food and water consumption, hematology, blood chemistry, and organ weight data were analyzed using the analysis of variance in one-way classifications. If the difference was significant ($p<0.05$), the least significant difference (LSD) method was also applied between the vehicle control group and the other study groups. The Kruskal-Wallis test and Scheffe's rank sum test were utilized to analyze urinalysis data.

6. Quality Assurance

A quality assurance statement was signed and dated August 9, 1991.

7. General Observations

(a) Mortality/moribundity/survival

All animals were observed for mortality prior to exposure, 1, 2, 4, and 6 hours after initiation of exposure, and 1 hour after termination of exposure every exposure day and also once a day on non-exposure days.

No deaths occurred during the study.

(b) Clinical observations

Rats were examined for clinical signs prior to exposure, 1, 2, 4 and 6 hours after initiation of exposure, and 1 hour after termination of exposure every exposure day, and also once a day on non-exposure days.

Increased incidences of irregular respiration and bradypnea were noted in males and females receiving 134 or 824 mg/m^3. Decrease of spontaneous activity, focal loss of hair, nasal discharge, dark red substance surrounding the snout, red tear, salivation and urinary incontinence were also noted in animals of both sexes receiving 824 mg/m^3.

(c) Body weights and food consumption

Body weights. Individual body weights were recorded prior to the initiation of exposure, twice a week thereafter, and on the day of sacrifice.

Tables 2 and 3 summarize data on mean body weights and mean body weight gains, respectively, at selected intervals. Reductions in body weight gains were noted in the high-concentration males (throughout the treatment period), the high-concentration females (from day 36 to the termination of treatment) and in mid-concentration males (from day 12 to the end of the treatment period). Mean body weight gains in the high-concentration males and females were 30% and 19% lower, respectively, than vehicle controls at day 89. Mean body weight gain in the mid-concentration males was 16% lower than vehicle controls at day 89.

Food and water consumption. Food and water consumption was calculated as the average consumption of 2 rats/cage at day 5 and weekly thereafter.

TABLE 2. Mean Body Weights (g ± S.D.) at Selected Intervals for Rats Exposed to Tetramethrin for 3 months[a]

Days	Exposure Concentration (mg/m^3)			
	0[b]	20.3	134	824
		Males		
1	233 ± 9.2	231 ± 6.9	230 ± 10.2	230 ± 10.1
8	287 ± 13.4	285 ± 10.2	281 ± 13.0	270 ± 12.7**
43	453 ± 37.0	447 ± 38.6	414 ± 23.5*	389 ± 33.9**
89	552 ± 52.5	550 ± 62.4	498 ± 31.8*	454 ± 43.4**
		Females		
1	172 ± 8.9	172 ± 6.3	170 ± 8.0	172 ± 5.8
8	196 ± 9.7	196 ± 9.9	194 ± 10.1	198 ± 8.1
43	273 ± 22.0	268 ± 19.9	259 ± 19.1	257 ± 15.8
89	311 ± 30.1	305 ± 28.3	295 ± 24.1	286 ± 23.9*

[a]Data extracted from Table 9 of the study report.
[b]Data represent body weights of vehicle control animals.

*Significantly different from vehicle control values, $p<0.05$.
**Significantly different from vehicle control values, $p<0.01$.

TABLE 3. Mean Body Weight Gains (g ± S.D.) at Selected Intervals for Rats Exposed to Tetramethrin for 3 Months[a]

Days	Exposure Concentration (mg/m^3)			
	0[b]	20.3	134	824
		Males		
8	55 ± 6.2	54 ± 6.8	51 ± 4.6	40 ± 4.9**
26	162 ± 21.2	159 ± 24.0	141 ± 14.1*	109 ± 28.7**
43	220 ± 30.9	216 ± 35.8	184 ± 21.6**	159 ± 28.8**
89	320 ± 47.6	319 ± 59.4	268 ± 28.4**	224 ± 39.3**
		Females		
8	24 ± 2.6	24 ± 5.3	24 ± 5.1	26 ± 5.4
26	73 ± 13.6	62 ± 19.1	70 ± 12.9	65 ± 8.7
43	102 ± 14.9	96 ± 16.4	89 ± 14.7	85 ± 13.5*
89	140 ± 22.6	134 ± 25.1	125 ± 21.1	114 ± 21.6*

[a]Data extracted from Table 9 of the study report.
[b]Data represent body weight gains of vehicle control animals.

*Significantly different from vehicle control values, $p < 0.05$.
**Significantly different from vehicle control values, $p < 0.01$.

An increase in food consumption was noted in females receiving 134 mg/m^3 at week 9 and in females receiving 824 mg/m^3 at weeks 8 and 9. However, the increases in food consumption were incidental and very slight and were not considered by the study author to be of any toxicological significance. There were no significant differences in food consumption between treated males and control males. Incidental and sporadic decreases in water consumption were noted in females of all groups exposed to the test material. The decreases in water consumption were not considered by the study author to be toxicologically significant. There were no treatment-related effects on water consumption in males.

(d) Ophthalmoscopic examination

Ophthalmoscopic examinations were performed on all control and high-concentration animals during week 13.

There were no compound-related ophthalmological effects.

8. Clinical Pathology

Blood was collected from the abdominal aorta of all animals for clinical laboratory evaluations at study termination. Animals were fasted overnight prior to blood collections. Those parameters indicated by an "X" were examined:

(a) Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Reticulocyte count (RETIC)
X Red cell morphology
X Leukocyte differential count*
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
X Coagulation: prothombin time (PT)*
X Fibrinogen

* = Recommended by Subdivision F (November 1984) Guidelines

Table 4 summarizes data on selected hematology parameters. Significant effects on hematology parameters were noted primarily in the high-concentration animals. Effects included decreases in monocyte count (in males), mean corpuscular volume (in females), mean corpuscular hemoglobin (in females), mean corpuscular hemoglobin concentration (both sexes), increases in prothrombin time (both sexes), activated partial thromboplastin time (both sexes), and fibrinogen (both sexes). A decrease in monocyte count and a prolongation in prothrombin time and activated partial thromboplastin time were noted in air control males.

TABLE 4. Representative Results of Mean Hematology Parameters in Rats Exposed to Tetramethrin for 3 Months[a]

Parameter	Exposure Concentration (mg/m^3)							
	Males				Females			
	0[b]	20.3	134	824	0[b]	20.3	134	824
MONO ($10^3U/L$)	0.25	0.22	0.17*	0.17*	0.18	0.18	0.13	0.13
MCV (Fl)	48.2	48.6	48.9	48.1	52.4	51.4	51.7	49.9**
MCH (pg)	16.8	16.9	16.9	16.2	18.4	18.1	18.1	17.3**
MCHC (g/dL)	34.8	34.8	34.5	33.7**	35.0	35.2	35.0	34.7*
PT (sec)	17.7	17.3	18.9	21.3**	14.0	13.9	14.1	14.5**
APPT (sec)	24.0	23.3	24.9	27.3**	20.7	20.2	20.6	22.4**
FIB (mg/dL)	233.9	234.0	235.2	261.2**	173.7	162.1	163.8	190.8*

[a]Data extracted from Table 15 of the study report.
[b]Data represent hematology values of vehicle control animals.

*Significantly different from vehicle control values, $p<0.05$.
**Significantly different from vehicle control values, $p<0.01$.

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(b) Blood (clinical) chemistry

Electrolytes

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

Enzymes

X Alkaline phosphatase (ALP)
X Cholinesterase
X Creatinine phosphokinase
X Lactic acid dehydrogenase
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
X Gamma glutamyltransferase (GGT)
X Leucine aminopeptidase

Other

X Albumin*
X Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol*
X Globulins
X Glucose*
X Total bilirubin*
Direct bilirubin
X Total protein*
X Triglycerides
X Phospholipid

* = Recommended by Subdivision F (November 1984) Guidelines

Table 5 summarizes data on selected clinical chemistry parameters. An increase in total protein levels was noted in low-concentration males. Effects observed in mid-concentration animals included increases in total protein (males), β-globulin (females), total cholesterol (males), phospholipid (males), gamma-glutamyl transpeptidase (males) and inorganic phosphorous (males), and decreases in glucose (females) and leucine aminopeptidase (males). Effects seen at the high-concentration consisted of increases in total protein (both sexes), α_1-globulin (in both sexes), total cholesterol (both sexes), glucose (females), glutamic-oxaloacetic transaminase (males), alkaline phosphatase (males) and leucine aminopeptidase (males). An increase in β-globulin and decreases in glutamic-oxaloacetic transaminase and alkaline phosphatase were noted in air control males, while decreases in gamma-globulin were noted in air control males and females.

(c) Urinalysis

Urinalysis was performed on all animals during week 13. The checked ("X") parameters were examined:

X Appearance*
Volume
Specific gravity*
X pH*

Sediment (microscopic)
X Protein*
X Glucose*
X Ketones*

X Bilirubin
X Blood*
Nitrate
X Urobilinogen

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TABLE 5. Representative Results of Mean Clinical Chemistry Parameters in Rats Exposed to Tetrametrin for 3 Months[a,b]

	Exposure Concentration (mg/m^3)							
	Males				Females			
Parameter	0[b]	20.3	134	824	0[b]	20.3	134	824
TP (g/dL)	6.0	6.2*	6.2*	6.5**	6.5	6.5	6.6	7.1**
Glu (mg/dL)	138	140	136	143	143	132	126**	107**
TCHOL (mg/dL)	70	72	92*	114**	80	83	91	117**
LAP (U/L)	71	72	65**	60**	63	60	58	60
GTP (U/L)	1	1	4**	13**	1	1	2	9**
PL (mg/dL)	105	110	135*	172**	148	158	162	196**
β-Glob (%)	18.0	18.6	18.5	19.8**	15.4	15.5	17.0*	18.0**
P (mg/dL)	7.6	7.9	8.4**	8.4**	6.7	6.9	7.1	7.6

[a]Data extracted from Table 16 of the study report.
[b]Data represent clinical chemistry values of vehicle control animals

Abbreviations are as follows:

TP = total protein
Glu = glucose
TCHOL = total cholesterol
LAP = leucine aminopeptidase
GTP = gamma-glutamyl transpeptidase
PL = phospholipid
β-Glob = beta-globulin
P = inorganic phosphorous

*Significantly different from vehicle control values, $p<0.05$.
**Significantly different from vehicle control values, $p<0.01$.

* = Recommended by Subdivision F (November 1984) Guidelines

Bilirubin levels were increased in the mid-concentration females and in the high-concentration males and females. Urobilinogen levels were increased in both sexes receiving the high concentration.

9. Sacrifice and Pathology

After 3 months of treatment, all animals were necropsied. At necropsy, macroscopic abnormalities were recorded, organ weights were obtained, and tissues placed in fixative. Microscopic examinations were performed on all tissues from control rats and high-concentration rats. In addition, microscopic examinations were performed on the liver and kidneys of all animals. Those tissues indicated by an "X" were collected for histopathological examination; those organs indicated by "XX" were weighed:

Digestive System	Cardiovascular/Hematologic	Neurologic
X Tongue	X Aorta*	XX Brain*
Salivary glands*	XX Heart*	X Peripheral nerve (sciatic nerve)*
X Esophagus*	X Bone marrow*	X Spinal cord (three levels)
X Stomach*	X Lymph nodes*	XX Pituitary*
X Duodenum*	XX Spleen*	X Eyes*
X Jejunum*	XX Thymus*	(Optic nerve)*
X Ileum*		
X Cecum*	Urogenital	Glandular
X Colon*		
X Rectum*	XX Kidneys*	XX Adrenals*
XX Liver*	X Urinary bladder*	Lacrimal gland
Gallbladder*	XX Testes*	X Mammary gland
X Pancreas*	X Epididymides	XX Thyroid*
	XX Prostate	Parathyroid*
Respiratory	X Seminal vesicle	X Harderian glands
	XX Ovaries	X Submandibular gland
X Trachea*	X Uterus*	Other
XX Lung*	X Vagina	
X Larynx		
X Nasal cavity (3 sections)		
X Bone (sternum and femur)		
X Skeletal muscle*		
X Skin		
X All gross lesions and masses.*		

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Macroscopic

Gross lesions in the liver were observed in the mid- and high-concentration rats. Lesions included dark-red discoloration,

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soft liver and enlarged liver. The incidences of these hepatic lesions observed at terminal sacrifice are as follows:

Liver parameter	Vehicle control		20.3 mg/m^3		134 mg/m^3		824 mg/m^3	
	M	F	M	F	M	F	M	F
Number examined	10	10	10	10	10	10	10	10
Dark-red	0	0	0	0	4	1	9	7
Soft	0	0	0	0	3	0	3	1
Enlarged	0	0	0	0	4	2	6	7

(b) Organ weights and body weight ratios

Table 6 summarizes absolute and relative weight data.

Treatment-related increases in liver weights in males and females receiving 20.3, 134 or 824 mg/m^3 were noted. Absolute liver weights were significantly increased in mid- and high-concentration males and females, and nonsignificantly increased in low-concentration males. Relative liver weights were significantly increased in all treated males and females. Absolute and relative kidney weights were significantly increased in all treated females. Absolute kidney weights were slightly but nonsignificantly increased in the mid- and high-concentration males. Relative kidney weights were significantly increased in mid- and high-concentration males.

(c) Microscopic

The primary histological findings noted in this study consisted of hepatic and renal lesions. Table 7 summarizes the incidence of renal and hepatic lesions in rats exposed to tetramethrin for 3 months. Increased incidences of hepatocellular hypertrophy were observed in the mid- and high-concentration males and females. A decrease in the incidence of cytoplasmic vacuoles in hepatocytes was present in the mid- and high-concentration males. An increase in the incidence of focal necrosis of the liver was seen in the high-concentration males. Hyaline droplet in renal tubules were present in the mid- and high-concentration rats. An increase in the incidences of hyaline cast in renal tubules and basophilic renal tubules were noted in the high-concentration males. No treatment-related changes were noted in the nose or lungs.

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TABLE 6. Absolute and Relative Liver and Kidney Organ Weights in Rats Exposed to Tetramethrin for 3 Months[a]

	Exposure Concentration (mg/m^3)							
	Males				Females			
Organ	0[b]	20.3	134	824	0[b]	20.3	134	824
				Absolute Organ Weight (g)				
Liver	14.20±1.945	15.58±2.532	16.09±1.480*	17.68±2.212**	7.48±0.885	7.96±1.341	8.78±0.811**	10.24±0.639**
Kidney	3.44±0.440	3.54±0.561	3.66±0.374	3.76±0.417	1.87±0.144	2.12±0.271**	2.19±0.190**	2.26±0.135**
				Relative Organ Weight (g%)				
Liver	2.71±0.156	2.98±0.217*	3.42±0.194**	4.19±0.369**	2.57±0.135	2.77±0.288*	3.21±0.071**	3.97±0.273**
Kidney	0.66±0.042	0.68±0.053	0.78±0.065**	0.89±0.079**	0.65±0.037	0.74±0.058**	0.80±0.055**	0.88±0.049**

[a]Data were extracted from Tables 18 and 19 of the study report.

[b]Vehicle control

*Significantly different from vehicle control; $p<0.05$

**Significantly different from vehicle control; $p<0.01$

TABLE 7. Representative Histological Lesions in Rats Exposed to Tetramethrin for 3 months[a]

Organ/Finding	Exposure Concentration (mg/m^3)							
	Males				Females			
	0[b]	20.3	134	824	0[b]	20.3	134	824
	(10)[c]	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Liver								
Hepatocellular hypertrophy								
Slight	0	0	5	5	0	0	2	9
Mild	0	0	0	4	0	0	0	0
Focal necrosis	1	0	0	3	0	0	0	0
Cytoplasmic vacuolation								
Mild	4	4	3	0	1	1	0	0
Moderate	5	5	0	0	0	0	0	0
Kidneys								
Hyaline droplets,								
Mild	0	0	4	3	0	0	0	0
Moderate	0	0	1	5	0	0	0	0
Hyaline cast,								
Slight	1	0	1	3	0	1	0	0
Mild	0	0	0	2	0	0	0	0

[a]Data extracted from Table 21 of the study report.
[b]Data represent histological findings of the vehicle controls.
[c]Numbers in parentheses indicate the number of animals examined.

B. REVIEWERS' DISCUSSION

The study protocol was acceptable for a subchronic inhalation study in rats. The conduct and reporting of the study were adequate. However, individual food consumptions were not determined. As a result, it is difficult to evaluate individual body weight changes and health status with respect to food intake.

The results of histological examinations indicated the liver (in both sexes) and the kidney (in male rats) as possible target organs. The primary hepatic lesion noted in the mid- and high-concentration males and female was hepatocellular hypertrophy. In addition, a decrease in the incidence of cytoplasmic vacuoles in hepatocytes was noted in the mid- and high-concentration males and an increase in the incidence of focal necrosis of the liver was noted in the high-concentration males. In mid- and high-concentration males, renal alterations included hyaline droplets in kidney tubules. An increase in the incidences of hyaline cast in renal tubules and basophilic renal tubules was also noted in the high-concentration males. Hyaline droplet nephropathy is regarded as a lesion specific to male rats. The histological changes in the liver and kidney in the mid- and high concentration animals correlated with increases in liver and kidney weights. The microscopic findings in the liver also correlated with gross findings (i.e., dark-red discoloration, soft liver and enlarged liver) in the mid- and high-concentration rats. Clinical chemistry findings, including increases in urinary bilirubin and urobilinogen, increases in serum protein, serum lipids, and serum gamma-glutamyl transpeptidase, and a decrease in serum glucose, support the gross and microscopic findings in the liver. Histological changes in the kidney and liver were not present in the low-concentration animals. However, liver and kidney weight changes were noted in the low-concentration rats. Absolute and relative kidney weights were significantly increased in the low-concentration females. A significant increase in relative liver weight was observed in low-concentration males and females. Effects on absolute or relative kidney weights in the low-concentration males were not statistically significantly different than those of controls. The increase in kidney weights in the low-concentration females is of questionable toxicological importance since there were no corresponding histopathological renal lesions in the low-, mid-, or high-concentration females. Also, the increase in kidney weights did not correlate with any changes in clinical chemistry findings, for example blood urea nitrogen and LAP.

The reviewers agree with the study author's assessment that the no-observed-effect level is slightly lower than 20.3 mg/m^3 for rats of both sexes. Besides liver weight changes in low-concentration males, an increase in total protein levels was also noted in the low-concentration males. Administration of 134 or 824 mg/m^3 tetramethrin to rats was also associated with changes in hematology parameters (decreases in monocyte count, MCV, MCH, MCHC, and increases in prothrombin time, APTT, and fibrinogen) and reductions in body weight

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gains. Irregular respiration and bradypnea were noted in mid- and high-concentration rats; however, no gross histopathological changes were noted in the lungs, and there was no evidence of irritation in the nasal cavity. It is possible that the irregular respiration and bradypnea were CNS-mediated. Other clinical signs seen in the high-concentration animals included a decrease in spontaneous activity, focal loss of hair, nasal discharge, salivation and urinary incontinence.

There was no effect of dosing on mortality, ophthalmology, or group food consumption.

In summary, a clear no-effect level for increase in liver weight was not determined. Although there were no histologic signs of liver damage in the low-concentration animals, hepatic lesions were present in the mid- and high-concentration rats. Renal lesions, primarily hyaline droplets in renal tubules, were observed in the mid- and high-concentration males. Hyaline droplet nephropathy is unique to the male rat and is considered to be nonrelevant to humans.[1]

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[1]EPA 1991. Alpha-2U-Globulin: Associated with Chemically-Induced Renal Toxicity and Neoplasia in the Male Rat. U.S. Environmental Protection Agency, Washington, D.C. EPA/625/3-91/019F.