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Attention: Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

8EHQ-01-14902

Ref.: Letter, March 27, 2001, describing the voluntary review of certain categories of health and environmental studies recently acquired by Rohm and Haas Company.

Dear Coordinator:

Rohm and Haas Company submits this notice in accordance with Section 8(e) of the Toxic Substances Control Act.

This letter transmits results of two 90-day subchronic feeding studies with albino rats exposed to monomethyltin trisisooctylthioglycolate (CAS No = 54849-38-6) at dietary levels of 0, 3, 10 for the first experiment and 0, 0.1, 0.3, 1, and 3 ppm for the second experiment.

General appearance, behavior, and survival were not adversely affected at any of the dietary levels.

In the 10 ppm dose group, the following treatment-related effects were seen: decreased feed intake, and efficiency in males, decreased eisinophils in females, and increased serum phosphatase activity in both sexes. Impaired kidney function was revealed by increased activity of glutamic-oxalacetic transminase and decrease in specific gravity of the urine. The relative kidney weights were distinctly increased, while the relative liver weights were slightly increased. Tin content of the blood was distinctly increased but there were no indications of any tin storage in the kidneys, liver, brain, or bone.

In the 3 ppm group, increased relative kidney weights were seen. Tin content of the blood was distinctly increased but there were no indications of any tin storage in the kidneys, liver, brain, or bone.

Treatment-related histopathologic changes were observed in the kidneys (degeneration of tubular cells) of males and females at 3 and 10 ppm and in the brain (necrotic pyramidal neurons of the hypocampus) in two females at 10 ppm.

It was concluded the no-toxic effect of trimethyltin isooctylthioglycolate was 1 ppm when fed in the diet of rats for a three-month period.

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CENTRAAL INSTITUUT VOOR VOEDINGSONDERZOEK

CENTRAL INSTITUTE FOR NUTRITION AND FOOD RESEARCH

Utrechtseweg 48
Zeist

74RM-1004

CAS # = 5484-38-6

RAPPORT NR. R 4530

Title: Sub-chronic (90-day) toxicity studies with trimethyltin isooctylthioglycolate in rats

Authors: Dr. H.P. Til

Drs. C.A. van der Heijden

At the request of: Cincinnati Milacron Chemicals Inc., Reading, Ohio

Approved by: Dr. A.P. de Groot

Date: November 1974

Gehele of gedeeltelijke publikatie van dit rapport is zonder schriftelijke toestemming verboden.

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S U M M A R Y

1. The toxicity of trimethyltin isooctylthioglycolate was examined in two sub-chronic (90-day) feeding studies with albino rats. In one experiment the test material was fed at dietary levels of 0, 3 and 10 ppm in the other experiment at levels of 0, 0.1, 0.3, 1 and 3 ppm.

2. General appearance, behaviour and survival were not adversely affected at any of the dietary levels.

3. Growth, food intake and food efficiency were slightly decreased at the 10 ppm level in males only.

4. Eosinophil counts were significantly decreased in females fed 10 ppm.

5. Serum alkaline phosphatase activities were increased at 10 ppm in both sexes.

6. An impaired kidney function was revealed by an increase in the activity of glutamic-oxalacetic transaminase and a decrease in specific gravity of the urine in the 10 ppm group.

7. The relative weights of the kidneys were distinctly increased at 3 and 10 ppm, while the relative weights of the liver were slightly increased at 10 ppm in males only.

8. The tin content in the blood was distinctly increased at 3 and 10 ppm. There were no distinct indications of any storage of tin in the kidneys, liver, brain or bone.

9. Gross examination did not reveal any changes that could be related to the ingestion of the test compound. Treatment-related histopathological changes were observed in the kidneys of males and females of the 3 and 10 ppm group and in the brain of two females of the 10 ppm group.

10. It was concluded that the no-toxic effect level of trimethyltin isooctylthioglycolate was 1 ppm in the diet of rats for three

Sub-chronic (90-day) toxicity studies with trimethyltin isooctylthioglycolate in rats

1. INTRODUCTION

At the request of Cincinnati Milacron Chemicals Inc., Reading, Ohio, the toxicity of trimethyltin isooctylthioglycolate was examined by feeding the material at various dietary levels to albino rats.

From a previous range-finding study in rats it appeared that dietary levels of 30 ppm and above caused growth depression, diminished food intake and mortality. The weights of the kidneys were distinctly increased and those of the thymus were decreased at 10 ppm. Degeneration of tubular cells in the kidneys were noticed at 10 ppm (CIVO-Report No. R 4392, June 1974).

The present two studies included clinical, haematological and pathological observations during a three-month experimental period.

2. EXPERIMENTAL

2.1 Material

The test compound was stated to be trimethyltin isooctylthioglycolate. Four 50 ml samples of the same batch (No. 1083-45) were received from the principal on February 2nd, 1974. The product was a clear, colourless liquid.

2.2 Diets

The test material was thoroughly mixed into stock diet at levels of 0, 3 or 10 ppm in the first experiment and at levels of 0, 0.1, 0.3, 1 or 3 ppm in the second experiment. The percentage composition of the stock diet was as follows:

yellow maize	29.05	brewer's yeast	3
whole wheat	36	grass meal	3
soyabean-oil meal	10	soyabean-oil	3
meat scraps	4	vitamin preparations	0.7
fish meal	8	trace mineralized salt	0.5
dried whey	2	steamed bone meal	0.75

The trimethyltin compound was first diluted with soyabean-oil (3 g test substance in 997 g oil). The experimental diets were prepared from a premix containing 10 g diluted tin compound per kg

stock diet and further diluting with stock diet. Homogeneous distribution was obtained by means of a meat cutter (Stephan).

The diets were freshly prepared once a fortnight and stored at room temperature.

2.3 Animals

Newly weaned albino rats from the CIVO-colony (Wistar derived) were used as the experimental animals. Three groups of ten males and ten females each received the tin compound at levels of 0, 3 and 10 ppm in stock diet, while in a second experiment five groups of ten males and ten females each received diets containing 0, 0.1, 0.3, 1 and 3 ppm.

The animals were housed in screen-bottomed cages (five to a cage) at 24 - 26°C in a room of constant temperature. Diets and tap water were given ad libitum.

2.4 Experimental design and conduct

When, during the first study, it became doubtful whether a no-effect level would be found, it was decided to start a second study using lower dietary levels. Both studies ran four weeks apart.

Individual body weights were recorded weekly. The food intake of each group was measured during the first four weeks and in week 10 to 12.

At week 13 blood samples were collected from the tip of the tail of ten rats/sex/group. All blood samples were examined for haemoglobin concentration, packed cell volume and counts of erythrocytes and of total and differential leucocytes.

Fasting blood glucose and urea nitrogen levels were determined at week 12, using the Technicon AutoAnalyzer method N-9a for glucose and the automated phenazone/diacetyl monoxime technique of Ceriotti and Spandrio (1965) for urea.

At autopsy blood was collected from ten males and ten females of each group and examined for serum enzyme activities, viz. glutamic-oxalacetic transaminase (Reitman and Frankel, 1957), glutamic-pyruvic transaminase (Reitman and Frankel, 1957) and alkaline phosphatase (Bessey, Lowry and Brock, 1946). Total serum protein determinations (biuret method) and serum albumin determinations (De Leeuw-Israel, Arp-Neefjes and Hollander, 1967) were also carried out in these blood samples.

Urine examinations (including appearance, pH, glucose, protein, occult blood, ketones and microscopy of the sediment), were made in pooled urine samples from ten rats of each sex from each group in week 13. Readings of pH, glucose, protein, occult blood and ketones were done with Hemocombistix from Ames Laboratories. Kidney function was examined in all rats from the first experiment by determinations of specific gravity and glutamic-oxalacetic transaminase (Reitman and Frankel, 1957) in urine samples collected during the last 16 hours of a 24-hour period of deprivation of food and water in week 13.

In week 14 all animals were killed by decapitation and subjected to autopsy during which a careful search was made for gross changes. The following organs were weighed: heart, kidneys, liver, spleen, gonads, thymus, thyroid and adrenals. Samples of these organs and of a wide range of other organs were fixed in a 4 % neutralized formaldehyde solution.

Complete microscopical examination was carried out on the control and 10 ppm groups. Haematoxylin-eosin stained paraffin sections of the organs weighed and also of the following organs were examined: lung, salivary glands, pituitary, trachea, thoracic aorta, skeletal muscle, axillary and mesenteric lymph nodes, pancreas, urinary bladder, prostate, epididymis, uterus, mammary gland, esophagus, fore- and glandular stomach, duodenum, ileum and colon. Histopathology of the 0.1, 0.3, 1 and 3 ppm groups of the second experiment was restricted to the kidneys and brain.

3. RESULTS

3.1 General appearance, growth and food intake

During the course of the two experiments no abnormalities of condition or behaviour were observed. One male rat of the 10 ppm group was killed by handling in week 12.

Mean body weights are shown in table 1.

Table 1. Mean body weights of rats fed trimethyltin isooctylthioglycolate in the diet for 13 weeks

group no.	ppm tin compound in diet	mean body weights (in g) at end of week									
		0	1	2	3	4	6	8	10	12	13
Experiment I											
		males									
7226	0	57	86	115	148	180	223	265	291	313	317
7227	3	57	86	119	153	187	230	272	297	317	322
7228	10	57	86	114	138	165**	205	245	271	285	289
		females									
7226	0	53	76	98	117	133	153	174	183	191	191
7227	3	53	74	100	117	130	149	172	181	185	187
7228	10	53	74	101	118	128	149	177	197	210	205
Experiment II											
		males									
7265	0.0	63	91	120	148	181	204	247	265	278	282
7266	0.1	63	94	123	152	186	208	255	278	294	297
7267	0.3	63	95	122	148	181	202	247	266	277	279
7268	1.0	63	96	123	154	190	214	263	285	302	305
7269	3.0	62	96	126	157	189	213	260	285	298	302
		females									
7265	0.0	63	84	101	116	132	145	170	177	182	186
7266	0.1	64	84	101	116	131	143	165	174	181	185
7267	0.3	64	84	101	115	134	144	166	176	181	184
7268	1.0	63	83	101	117	132	143	168	178	184	187
7269	3.0	64	82	100	114	131	143	162	174	179	183

**P < 0.01.

Indication of slight growth depression occurred in males of the 10 ppm group, but the differences with the controls were statistically significant only at week 4. In females the mean body weights of all groups were very similar.

at the 10 ppm dosage level in males (table 2). At lower dietary levels in males and at all dietary levels in females food intake and food efficiency were comparable to the controls.

Table 2. Average food intake and food efficiency

ppm tin compound in diet	food intake (g/rat/day) in week						food efficiency during week 1-4		
	1	2	3	4	11	12	gain	food	gain/food
Experiment I									
				males					
0	10.1	12.3	14.2	15.1	16.5	16.9	123	362	0.34
3	9.9	13.1	14.7	15.2	16.9	16.8	130	370	0.35
10	9.9	13.0	13.0	13.6	15.7	16.1	108	346	0.31
				females					
0	8.4	10.5	11.6	11.9	11.6	11.3	80	297	0.27
3	8.1	10.7	11.3	10.9	11.5	10.6	77	287	0.27
10	8.0	10.9	11.4	9.9	13.3	13.7	75	281	0.27
Experiment II									
				males					
0.0	9.1	11.7	13.1	12.4	14.0	14.6	118	325	0.36
0.1	9.4	11.8	13.5	12.6	15.7	15.4	123	332	0.37
0.3	9.6	12.1	12.7	12.3	14.8	14.1	118	328	0.35
1.0	9.7	12.7	13.6	13.2	16.0	15.8	127	345	0.36
3.0	9.3	13.5	14.0	12.9	16.1	15.9	128	349	0.36
				females					
0.0	8.2	9.6	9.7	9.3	11.5	11.3	69	259	0.26
0.1	8.3	9.7	9.9	9.0	10.8	10.6	67	259	0.25
0.3	7.9	9.4	9.4	8.0	10.3	10.7	70	244	0.28
1.0	8.3	9.9	10.1	10.1	10.8	10.8	69	270	0.25
3.0	7.6	9.3	9.6	9.2	10.7	10.8	67	251	0.26

3.2 Haematology

Eosinophil counts were significantly decreased in females receiving diets containing 10 ppm of the test substance (table 3). Otherwise, no distinct or consistent differences were observed between the test groups and the controls.

Table 3. Mean haematological data recorded at week 12

ppm tin compound in diet	haemoglobin g/100 ml	packed cell volume %	erythrocytes $x10^6/mm^3$	leucocytes total $x10^3/mm^3$	differential count % lymph	neutr	eos	mono
Experiment I								
			males					
0	16.1	48.6	7.9	12.3	85.1	12.8	1.8	0.3
3	16.7	49.9	7.7	13.7	83.2	15.0	1.6	0.2
10	16.6	49.0	7.9	15.0	82.8	15.8	1.0	0.4
			females					
0	17.1	50.9	7.4	10.4	89.4	8.7	1.9	0.0
3	17.2	49.6	7.4	9.1	85.2	13.0*	1.8	0.0
10	17.0	49.2	7.3	11.5	88.8	10.8	0.4**	0.0
Experiment II								
			males					
0.0	17.0	48.9	8.1	12.2	-')	-	-	-
0.1	17.3	50.9	8.3	12.8	-	-	-	-
0.3	17.4	48.4	8.5	14.1	-	-	-	-
1.0	16.9	48.5	8.3	13.2	-	-	-	-
3.0	17.2	48.1	8.3	13.7	-	-	-	-
			females					
0.0	16.3	46.4	8.0	11.0	-	-	-	-
0.1	16.7	47.9	7.9	9.1	-	-	-	-
0.3	16.3	47.6	7.9	9.7	-	-	-	-
1.0	16.7	48.1	8.1	9.2	-	-	-	-
3.0	16.4	47.5	7.8	10.1	-	-	-	-

*P < 0.05; **P < 0.01.

')- = not determined.

3.3 Biochemical blood parameters

Mean biochemical blood values recorded at the end of the experimental period are summarized in table 4.

Serum alkaline phosphatase activities were slightly, though significantly increased in the highest dosage group in both sexes. The fact that a few transaminase activities differed in a mathematically significant way from the controls is not regarded as being of toxicological significance, since there was no evidence of a dose-related response.

Table 4. Mean blood biochemical values recorded terminally

ppm tin compound in diet	sugar mg%	BUN mg%	bilirubin mg%	SGOT R-F units	SGPT R-F units	SAP B-L units	TSP g%	albumin g%
Experiment I								
			males					
0	87	18	0.45	168	36	8.4	7.2	3.8
3	90	19	0.50	157	33	8.3	7.5	3.8
10	101	18	0.50	164	35	12.6**	8.1	3.9
			females					
0	102	20	0.52	213	33	8.4	7.2	4.0
3	107	23	0.50	207	36	8.3	7.2	4.1
10	96	20	0.62	194	31	10.6*	7.5	4.1
Experiment II								
			males					
0.0	75	16	0.26	200	38	7.9	-')	-
0.1	77	18	0.23	188	40	8.0	-	-
0.3	78	16	0.34	186	37	9.0	-	-
1.0	79	16	0.26	157*	37	10.1	-	-
3.0	77	15	0.36	180	41	8.4	-	-
			females					
0.0	80	18	0.26	204	36	7.0	-	-
0.1	82	19	0.22	187	32	5.6	-	-
0.3	74	17	0.26	211	34	7.4	-	-
1.0	77	18	0.21	228	32	5.4	-	-
3.0	73	20	0.27	182	30*	5.9	-	-

BUN = blood urea nitrogen; SGOT = serum glutamic-oxalacetic trahsaminase; SGPT = serum glutamic-pyruvic transaminase; SAP = serm alkaline phosphatase; R-F = Reitman-Frankel; B-L = Bessey-Lowry; TSP = total serum protein.

*P < 0.05; **P 0.01.

')- = not determined.

3.4 Urine analyses

There were no changes in the composition of the urine which could be ascribed to the ingestion of the test material (table 5).

Table 5. Results of urine analyses recorded at week 13

ppm tin compound in diet	appearance	pH	sugar	protein	occult blood	ketones	microscopic findings							
							RBC	WBC	epith	amorph	cryst	casts	bact	WE	sperm
Experiment I															
					males										
0	yellow	7	-	++	-	-	-	-	+	++	+++	-	++	+	+
3	yellow	7	-	++	-	-	-	-	+	++	+++	-	++	-	+
10	yellow	7	-	+	-	-	-	-	+	++	+++	-	++	-	+
					females										
0	yellow	6	-	++	-	-	-	-	+	+	++	-	++	+	
3	yellow	6	-	++	-	-	-	-	+	+	++	-	++	-	
10	yellow	8	-	++	-	-	-	-	+	+	+++	-	++	-	
Experiment II															
					males										
0.0	yellow	6	-	±	-	-	-	-	±	±	++	-	+	+	+
0.1	yellow	6	-	+	-	-	-	-	±	+	+	-	+	-	+
0.3	yellow	6	-	+	-	-	-	-	±	±	++	-	+	-	+
1.0	yellow	6	-	+	-	-	-	-	±	+	+	-	++	-	+
3.0	yellow	6	-	+	±	-	-	-	±	+	++	-	++	-	+

e 5. Continued

tin com- nd in diet	appearance	pH	sugar	protein	occult blood	ketones	microscopic findings						
							RBC	WBC	epith	amorph	cryst	casts	bact	WE	sperm
					females										
0.0	yellow	6	-	±	-	-	-	-	±	±	±	-	++	-	
0.1	yellow	6	-	±	-	-	-	-	+	+	±	-	+	-	
0.3	yellow	6	-	±	-	-	-	-	±	±	+	-	+	-	
1.0	yellow	6	-	±	-	-	-	±	+	±	+	-	+	-	
3.0	yellow	6	-	±	-	-	-	-	+	+	++	-	+	-	

+ red blood cells; WBC = white blood cells; WE = worm eggs.

ding system: - = negative; ± = minimal; + = slight; ++ = moderate; +++ = high.

The results of the kidney function tests are given in table 6.

Table 6. Urinary findings at week 13

ppm tin compound in diet	males		females	
	UGOT R-F units	specific gravity	UGOT R-F units	specific gravity
0	24.0	1.0680	21.1	1.0592
3	25.3	1.0674	19.6	1.0653
10	33.6	1.0479***	49.1***	1.0543

UGOT = urine glutamic-oxalacetic transaminase; R-F = Reitman-Frankel.
*P < 0.05; ***P < 0.001.

The values of glutamic-oxalacetic transaminase in the urine were distinctly increased at 10 ppm in both sexes, while the specific gravity values were decreased at 10 ppm in males only. At the lower level these effects were not observed.

3.5 Organ weights

Mean relative organ weights are presented in tables 7 and 8.

At the highest dietary level of 10 ppm in experiment I the relative weight of the kidneys was distinctly increased in both sexes, while the relative liver weight was slightly increased in males only. No weight changes in these organs were observed at the 3 ppm dietary level. In males of the second experiment, however, the relative weight of the kidneys was also increased at 3 and 1 ppm, although at 1 ppm the effect was not statistically significant. Slight increases in liver weights were also observed at 0.3, 1 and 3 ppm in males only, but at 3.0 ppm the weight was not higher than at 0.3 ppm.

The slight decrease in relative brain weight in females fed 10 ppm is ascribed to the higher body weights of the rats at this level and the well-known inverse correlation between body weight and brain weight.

le 7 . Body weights (in g), relative organ weights (in g/100 g body weight) and their standard deviations of groups of ten male and ten female rats after an experimental period of 13 weeks

up	ppm trimethyltin isooctylthioglycolate in the diet	body weight	heart	kidney	liver	spleen	brain	testicle/ ovary	thymus	thyroid	adrenal
					MALES						
226	0	320.	.339	.71	3.42	.175	.56	.89	.097	.0057	.0147
		(13.)	(.007)	(.02)	(.09)	(.005)	(.02)	(.04)	(.014)	(.0005)	(.0012)
227	3	324.	.340	.70	3.47	.190	.54	.85	.093	.0054	.0141
		(13.)	(.009)	(.02)	(.11)	(.010)	(.03)	(.05)	(.009)	(.0004)	(.0010)
228	10	290.	.350	.84***	3.80*	.202	.58	.86	.091	.0058	.0156
		(13.)	(.009)	(.02)	(.10)	(.012)	(.03)	(.03)	(.011)	(.0005)	(.0005)
					FEMALES						
226	0	192.	.400	.74	3.45	.224	.88	.0337	.151	.0070	.0292
		(5.)	(.014)	(.02)	(.10)	(.009)	(.02)	(.0017)	(.011)	(.0003)	(.0017)
227	3	188.	.399	.71	3.35	.226	.91	.0320	.132	.0089	.0246
		(7.)	(.009)	(.02)	(.06)	(.004)	(.03)	(.0016)	(.011)	(.0011)	(.0015)
228	10	205.	.391	.88***	3.57	.238	.77**	.0313	.119	.0079	.0270
		(8.)	(.013)	(.02)	(.09)	(.013)	(.03)	(.0024)	(.013)	(.0008)	(.0016)

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

NDER EACH MEAN ITS STANDARD-DEVIATION (IN BRACKETS) IS GIVEN.

Table 8 . Body weights (in g), relative organ weights (in g/100 g body weight) and their standard deviations of groups of ten male and ten female rats after an experimental period of 13 weeks

group no.	ppm trimethyltin isooctylthioglycolate in the diet	body weight	heart	kidney	liver	spleen	brain	testicle/ ovary	thymus	thyroid	adrenal
MALES											
7265	0	282.	.356	.70	3.15	.177	.62	.96	.101	.0082	.0154
		(10.)	(.014)	(.01)	(.09)	(.010)	(.02)	(.03)	(.006)	(.0011)	(.0009)
7266	0.1	297.	.348	.71	3.30	.180	.61	.91	.139*	.0089	.0143
		(9.)	(.016)	(.03)	(.11)	(.008)	(.02)	(.04)	(.015)	(.0010)	(.0009)
7267	0.3	279.	.362	.72	3.49**	.178	.61	.97	.108	.0114	.0182
		(10.)	(.006)	(.02)	(.07)	(.007)	(.03)	(.03)	(.007)	(.0030)	(.0028)
7268	1.0	304.	.363	.76	3.74***	.216	.59	.85	.112	.0101	.0138
		(10.)	(.010)	(.03)	(.10)	(.028)	(.02)	(.09)	(.010)	(.0010)	(.0011)
7269	3.0	302.	.369	.76**	3.43*	.186	.59	.94	.113	.0082	.0156
		(9.)	(.015)	(.01)	(.06)	(.007)	(.01)	(.02)	(.012)	(.0012)	(.0011)
FEMALES											
7265	0	188.	.389	.74	3.18	.211	.87	.0348	.162	.0102	.0262
		(5.)	(.011)	(.02)	(.07)	(.010)	(.03)	(.0024)	(.010)	(.0011)	(.0014)
7266	0.1	188.	.377	.69	3.05	.216	.87	.0312	.161	.0090	.0223*
		(4.)	(.009)	(.01)	(.10)	(.006)	(.02)	(.0011)	(.010)	(.0004)	(.0012)
7267	0.3	185.	.386	.71	3.19	.209	.89	.0345	.181	.0116	.0276
		(5.)	(.015)	(.03)	(.17)	(.012)	(.02)	(.0021)	(.016)	(.0015)	(.0018)
7268	1.0	189.	.397	.71	3.05	.196	.87	.0306	.169	.0114	.0260
		(5.)	(.013)	(.02)	(.10)	(.006)	(.03)	(.0020)	(.008)	(.0013)	(.0011)
7269	3.0	184.	.409	.76	3.15	.223	.90	.0322	.163	.0111	.0251
		(4.)	(.012)	(.02)	(.08)	(.010)	(.02)	(.0026)	(.011)	(.0008)	(.0012)

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

Under each mean its standard-deviation (in brackets) is given

3.6 Tin content in the kidneys, liver, brain, bone and blood

The tin content in the various tissues and in blood are shown in table 9.

Table 9. Tin content in the kidneys, liver, brain, bone or blood

ppm tin compound in diet	mg tin/kg fresh tissue or blood				
	kidneys	liver	brain	bone	blood
		males			
0	4	6	4	4	5
3	4	4	5	6	31
10	6	5	3	1	34
		females			
0	11	1	3	3	4
3	1	2	5	5	9
10	8	11	5	10	27

The tin content in the blood at 3 and 10 ppm was distinctly higher than in controls. This effect was slightly more pronounced in males than in females.

The tin content in the liver and bone at 10 ppm was slightly higher than in controls in females only.

There were no noticeable increases in the tin content of the kidneys and brain.

3.7 Pathology

3.7.1 Gross pathology

At autopsy gross examination revealed no relevant pathological findings that could be ascribed to the ingestion of the test compound.

3.7.2 Microscopical examination

The histological abnormalities observed are detailed in tables 10 and 11.

Table 10. Histopathology and the number of animals showing the observed lesions in the different groups*)

abnormalities	males			females		
	ppm tin compound in diet					
	0	3	10	0	3	10
Number of animals examined	10	10	10	10	10')	10')
KIDNEYS						
1. PROTEINACEOUS DROPLETS WITHIN THE CYTOPLASM OF TUBULAR EPITHELIAL CELLS:						
a. Slight	2	2	0	0	0	0
b. Moderate	5	7	0	0	0	0
2. SWOLLEN TUBULAR CELLS WITH ENLARGED NUCLEI IN THE INNER CORTEX:						
a. Minimal	0	3	6	0	0	4
b. Mild to moderate	0	0	2	0	0	1
3. NECROSIS AND LYSIS OF TUBULAR EPITHELIAL CELLS IN THE INNER CORTEX:						
a. Minimal	0	3	5	0	2	1
b. Mild to moderate	0	0	4	0	0	3
4. TUBULAR REGENERATION SEEN AS ACCUMULATIONS OF NUCLEI IN THE DISTAL TUBULES OF THE INNER CORTEX AND OUTER MEDULLA:						
a. Minimal	0	10	2	0	4	2
b. Moderate to marked	0	0	8	0	0	3
5. Tubular nephrosis:						
a. Slight	4	3	4	2	2	2
b. Moderate	6	4	4	3	1	2
6. Nephrocalcinosis in the cortico-medullary area:						
a. Slight	0	0	0	4	1	2
b. Moderate	0	0	0	2	0	0
7. Slight focal pyelitis	2	2	2	0	0	1
8. Slight perivascular infiltration of mononuclear inflammatory cells	2	3	2	2	1	0
BRAIN						
1. A SMALL NUMBER OF NECROTIC PYRAMIDAL NEURONS IN THE HYPOCAMPUS	0	0	0	0	0	2
LIVER						
1. A few small foci of RES cell proliferations, at times accompanied with acidophilic bodies	4	-")	5	5	-	4
2. Slight periportal infiltrates of mainly plasma cells	5	-	2	8	-	6
3. Slight scattered liver cell necrosis	2	-	2	0	-	1
4. Slight bile duct proliferation	1	-	1	3	-	2
LUNG						
1. Peribronchial, peribronchiolar and/or perivascular cuffing with lymphocytes:						
a. Slight	2	-	3	2	-	2
b. Moderate	4	-	1	5	-	2
c. Marked	1	-	3	0	-	3
2. Focal interstitial pneumonia	3	-	3	2	-	1
3. Focal accumulations of foam cells	3	-	1	3	-	4
4. Focal histiocytic proliferation:						
a. Slight	4	-	5	4	-	4

Table 10. Continued

abnormalities	males			females		
	ppm tin compound in diet					
	0	3	10	0	3	10
THYROID						
1. Activated appearance seen as small follicles lined by cuboidal epithelium	4	-	4	3	-	2
2. Slight desquamation of follucular epithelium	3	-	1	3	-	2
3. Psammoma bodies	0	-	2	3	-	1
PANCREAS						
1. Slight lymphocytic infiltrates	2	-	0	0	-	0
ADRENAL						
1. Slight lymphocytic infiltrates in zona fasciculata	0	-	1	1	-	0
2. Fatty metamorphosis of zona fasciculata cells	1	-	0	0	-	0
HEART						
1. Focal myocarditis:						
a. Slight	4	-	2	0	-	0
b. Moderate	1	-	2	0	-	0
SPLEEN						
1. Increased haemosiderin in the red pulp	2	-	2	6	-	2
2. Increased haematopoietic activity	0	-	0	1	-	0
PAROTID SALIVARY GLAND						
1. Slight lymphocytic infiltrates	0	-	1	0	-	0
URINARY BLADDER						
1. Parasite (Trichosmoides crassicauda)	1	-	3	2	-	0
2. Sub-epithelial infiltrates of lymphocytes	1	-	0	3	-	1
3. Proteinaceous plug	3	-	1	1	-	0
STOMACH						
1. Small simple cysts in glandular epithelium	0	-	1	1	-	0
PITUITARY						
1. Colloid cyst in pars distalis	0	-	1	0	-	0
PROSTATE						
1. Lymphocytic prostatitis	1	-	0			
TESTICLES						
1. Slight number of atrophic tubules	0	-	1			
UTERUS						
1. Hydrometria				1	-	0

*) Treatment-related changes are written in capitals.

') The kidneys of five animals were not available for microscopic examination.

")- = not examined.

REMARK: The organs examined microscopically, which are not mentioned in this table, did not show pathological changes at all.

Table 11. Histopathology of kidneys and brain and the number of animals showing the observed lesions in the different groups*)

abnormalities	males				females			
	ppm tin compound in diet							
	0.1	0.3	1.0	3.0	0.1	0.3	1.0	3.0
Number of animals examined	10	10	10	10	10	10	10	10
KIDNEYS								
1. NECROSIS AND LYSIS OF TUBULAR EPITHELIAL CELLS IN THE INNER CORTEX:								
a. Minimal	0	0	0	4	0	0	0	1
2. TUBULAR REGENERATION SEEN AS ACCUMULATIONS OF NUCLEI IN THE DISTAL TUBULES OF THE INNER CORTEX AND OUTER MEDULLA:								
a. Minimal	0	0	0	8	0	0	0	5
3. Tubular nephrosis:								
a. Slight	4	3	5	6	4	3	2	3
b. Moderate	4	2	2	3	1	0	1	0
4. Nephrocalcinosis in the cortico-medullary area:								
a. Slight	0	0	0	0	6	5	4	5
b. Moderate	0	0	0	0	1	2	2	1
5. Slight focal pyelitis	1	0	0	1	3	3	1	2
6. Slight perivascular infiltrations of mononuclear inflammatory cells	2	2	3	3	0	0	0	0
7. Proteinaceous droplets within the cytoplasm of tubular cells:								
a. Slight	4	2	2	3	0	0	0	0
b. Moderate	5	5	7	5	0	0	0	0

*) Treatment-related changes written in capitals.

REMARK: No abnormalities were found in the brain of the animals fed 0.1, 0.3, 1.0 or 3.0 ppm of the tin compound in the diet.

Treatment-related histopathological changes were observed in the kidneys of males and females of the 10 and 3 ppm groups, and in the brain in females of the 10 ppm group.

The kidney findings were characterized by a) swollen tubular cells having pale, enlarged nuclei; b) focal necrosis and lysis of tubular epithelial cells in the inner cortex and c) distinct regeneration of tubular cells seen as accumulations of nuclei in the distal tubules of the inner cortex and outer medulla. In addition there was a marked decrease of the normally occurring proteinaceous droplets within the tubular epithelial cells of the males of the 10 ppm group. The kidney changes were pronounced in the 10 ppm group, very minimal in the 3 ppm group and completely absent in

the other treatment groups.

The brain lesions seen in only two females of the 10 ppm group consisted of a small number of necrotic pyramidal neurons in the hypocampus. Though the incidence was low, this finding was considered to be treatment-related, because this brain lesion was also observed in the 28-day toxicity study with the same compound (CIVO-report No. R 4392) and moreover, this abnormality has never been observed in our control series.

The histopathological changes observed in other organs were generally equally distributed amongst control and test animals or occurred only in a single animal. Moreover, these lesions are common findings in the strain of rats used.

4. DISCUSSION

The continuous feeding of trimethyltin isooctylthioglycolate to young rats at various dietary levels up to 10 ppm for three months resulted in distinct ill effects at the highest level. These effects included slightly decreased growth and food intake in males, increased serum alkaline phosphatase activities, increased glutamic-oxalacetic transaminase values in the urine, decreased specific gravity of the urine and increased weights of the kidneys. The renal changes also included histological lesions. Other changes, observed at the 10 ppm level, consisted of histological changes in the brain of two females and decreases in the eosinophil counts in females.

At the next lower level of 3 ppm the only treatment-related changes were increases in kidney weights accompanied with microscopical lesions.

The relative weights of the liver were significantly increased in males at 0.3, 1.0, 3.0 and 10 ppm in one of the two experiments. They were, however, not accompanied with treatment-related changes at the cellular level. Since moreover, there was no evidence of a dose-related response, the increased weights are considered incidental findings.

On the basis of the present results, the no-effect level of trimethyltin isooctylthioglycolate is 1 ppm in the diet of rats for three months, which is equivalent to 0.05 mg/kg body weight/day.

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