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August 27, 1992

CONFIDENTIAL BUSINESS INFORMATION

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Document Processing Center
Office of Pollution Prevention &
Toxics (TS-790)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460



INIT 09/01/92



88920069389

Attention: Section 8(e) Coordinator (CAP Agreement)

**RE: SECTION 8(e) SUPPLEMENTAL REPORT AND NOTIFICATION ON
AGREEMENT NO. 8E CAP-0071**

Dear Sir/Madam:

Morton International, Inc. presents the following supplemental report and notification on its examination of internal company records. This examination is provided for in Phase I of the TSCA Section 8E Compliance Audit Program Agreement No. 8E CAP-0071.

Observations and comments on the materials being submitted are as follows:

- i. The following reports were submitted to the Environmental Protection Agency as a supplement to Section 8(e) Information submission on May 31, 1979. Based on advice received from the Agency's Section 8(e) Notice Coordinator, we are hereby converting these FYI notifications to a formal Section 8(e) Notification. These reports are described as follows:
 - Inhalation toxicity study in rats on trimethyl tin chloride, 99% CAS No. 1066-45-1. Study performed by Wells Laboratories, Inc. and identified as Laboratory No. F-1810.
 - Inhalation toxicity in rats of trimethyl tin isooctyl thioglycolate. Study performed by Wells Laboratories and identified as Laboratory No. G-463.

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- Inhalation toxicity in rats of dibutyl tin bis(isooctyl thioglycolate), CAS No. 25168-24-5. Study performed by Wells Laboratories and identified by Laboratory No. G-1177.
- Inhalation toxicity in male rats of dibutyl tin dichloride, CAS No. 693-18-1. Study performed by Hazleton Laboratories America, Inc. and identified as project number M452-112.
- 13 week dietary administration in rats of Advastab TM-180, Advastab TM-181, and Thermolite 831. Study performed by Hazleton Laboratories, Project No. 452-105.
- 13 week dietary administration in rats of Advastab TM-181FS and Advastab T-270. Study performed by Hazleton Laboratories, Project No. 452-106.
- 13 week dietary administration in rats of Advastab TM-185, Advastab TM-286, and Advastab TM-387. Study performed by Hazleton Laboratories, Project No. 452-109.
- Sub-chronic (90 day) toxicity studies with trimethyl tin isooctyl thioglycolate in rats. Study performed by Central Institute For Nutrition And Food Research (Netherlands), Report. No. R-4530.

The submission to EPA dated May 31, 1979 was a supplementary submission for the Agency's Identity No. FYI-OTS-0279-0023.

2. A preliminary report from the Occupational Safety & Health Administration was submitted by Cincinnati Milacron to EPA on February 6, 1978 as "TSCA Section 8(e) Information." This report concerned manifestation of neurological effects believed to be caused by employee exposure to dimethyl tin dichloride. This submission was given the reference number FYI-OTS-029-0023. Based on the recommendation from the TSCA Section 8(e) coordinator, we hereby notify the EPA that this submission is a formal Section 8(e) Notice.
3. Oral and dermal toxicity of glycidyl acrylate, CAS No. 106-91-1. We present the following studies as a Section 8(e) Notice on the toxicity of glycidyl acrylate:
 - Oral toxicity in rats study performed by Bio-Toxicology Laboratories, Inc. for Thiokol Chemical Corporation.

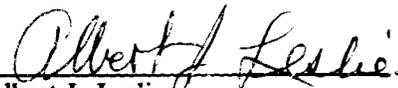
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- Acute dermal toxicity in rabbits study performed by Foster D. Sneil Division, Booz Allen & Hamilton, Inc., Project No. 2528 for Thiokol Corporation.

Thiokol Corporation produced for commercial purposes less than 10,000 pounds of this substance, all of which was made in calendar year 1978. Production was permanently discontinued in December of that year. Additional information on the production and uses of this material by Thiokol Corporation will be found in their submission to EPA under a Section 8(e) Notice which was given the identity number 8EHQ-0179-0270.

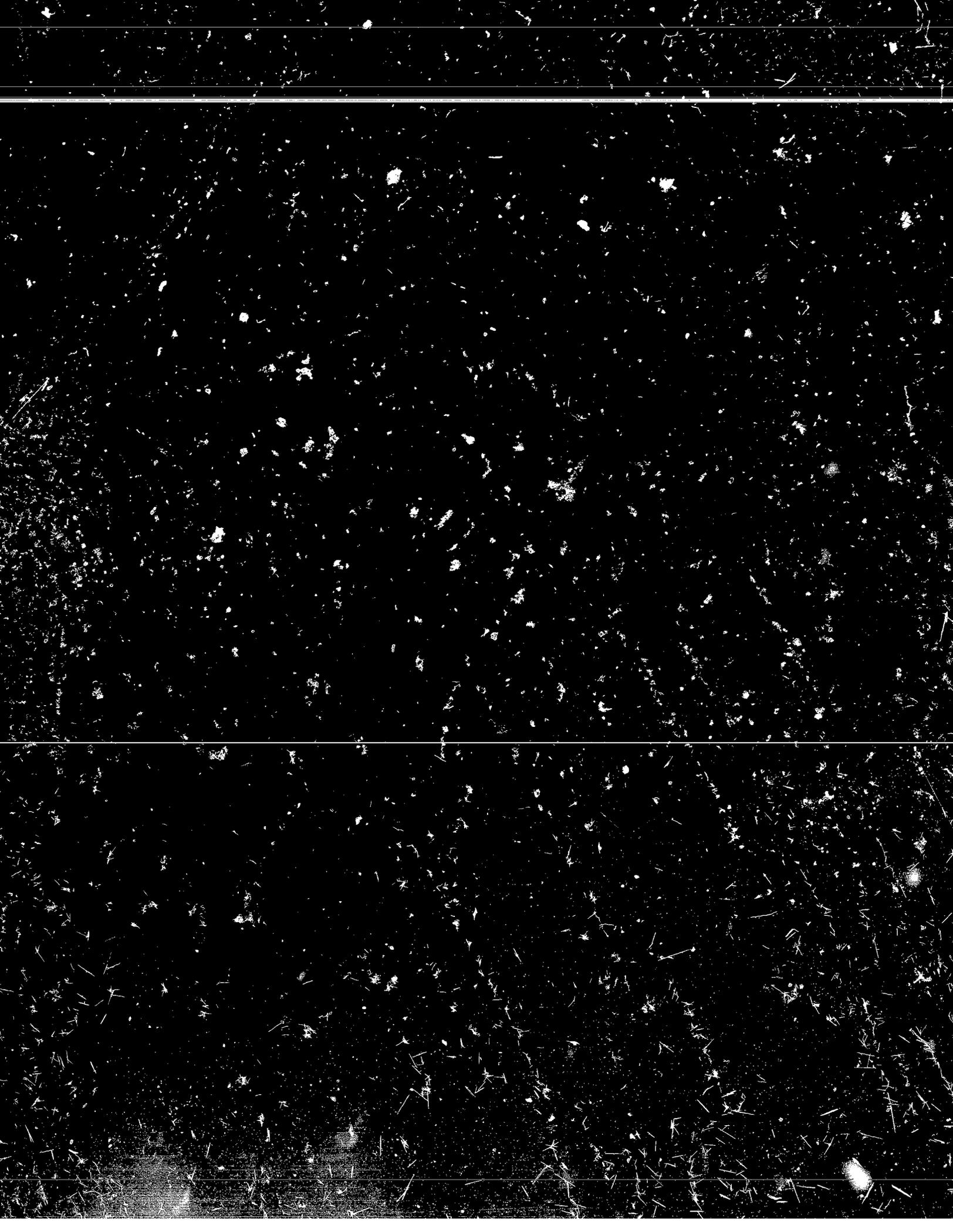
4. Short term feeding study with a methyl tin stabilizer identified as Advastab TM-121FS in rats. This study was performed by the Central Institute for Nutrition and Food Research in The Netherlands. The report is identified only as CIVO 71. The toxicity report is attached. Additional comments on the test article will be sent separately.
5. Sub-chronic (90 day) toxicity study with a methyl tin stabilizer 1097-27 in rats. This study was performed by the Central Institute for Nutrition and Food Research in The Netherlands, Report Number R4737. The toxicity report is attached. Additional comments on the test article will be sent separately.
6. Sub-chronic (90 day) toxicity study with a methyl tin stabilizer 1087-103 in rats. This study was performed by the Central Institute for Nutrition and Food Research in The Netherlands, Report Number R4740. The toxicity report is attached. Additional comments on the test article will be sent separately.

Please note that the studies referred to in this 8(e) CAP submission were performed on behalf of either Thiokol Corporation, Inc. or Cincinnati Milacron Chemicals, Inc. The chemical operations of these two companies which produced the materials described in this letter have since been acquired by Morton International, Inc.



Albert J. Leslie
Director, Product Documentation

AJL/g
(AJL2480)



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CENTRAL INSTITUTE FOR NUTRITION AND FOOD RESEARCH

RAPPORT NR. R 4740

Title: Sub-chronic (90-day) toxicity study
with a methyltin stabilizer (087-103)
in rats

Authors: Dr. H.P. Til
Drs. F.G.J. Reuzel

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

Approved by: Dr. A.P. de Groot

Date: July 1975

Gehele of gedeeltelijke publicatie van dit rapport is zonder schriftelijke toestemming verboden.
Total or partial publication of this report without written assent is not allowed.

23-15.000-574

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S U M M A R Y

1. The toxicity of a methyltin stabilizer, coded 1087-103, was examined in a sub-chronic (90-day) study by feeding the test substance to groups of ten male and ten female weanling rats at levels of 0, 30, 100, 300 or 1000 ppm in stock diet.
2. General condition, behaviour and survival were not adversely affected at any dietary level of the test substance.
3. Slight growth depression and decreased food intake occurred at 1000 ppm in both sexes and at 300 ppm in females only. Females also showed diminished food intake at 100 ppm. Food efficiency was slightly increased in females of the 1000 ppm group.
4. Haematological data showed several abnormalities in females of the top-dose group.
5. Biochemical blood studies in the top-dose group showed slightly increased values of alkaline phosphatase activity in both sexes and of fasting blood glucose in males.
6. Specific gravity of the urine was decreased in both sexes of the top-dose group, while the volume of the urine was increased in males.
7. The water content of the brain did not show significant differences between the various groups.
8. In the top-dose group the relative weight of the kidneys was increased in both sexes. The weight of the liver was slightly increased in males, while in females the thymus weight was decreased and the adrenal weight was increased.
9. At gross examination no treatment-related pathological changes were observed.
At microscopical examination degenerative and regenerative renal changes were observed both in male and female rats of the highest dose group.
10. It was concluded that the no-toxic effect level of the methyltin stabilizer 1087-103 was 300 ppm in the diet of rats for three months.

Sub-chronic (90-day) toxicity study of
a methyltin stabilizer 1087-103 in rats

1. INTRODUCTION

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

The present study included chemical, haematological and pathological observations during a three-months feeding period.

2. EXPERIMENTAL

2.1. Material

A 500 ml sample of the test substance, coded 1087-103, was received from Cincinnati Milacron Chemicals Inc. on 6th September 1974. The material, which was stated to be a methyltin compound for use as a stabilizer, was a clear, slightly grey-brown coloured, viscous liquid.

An infrared spectrum of the test substance is given in figure 1 (page 14).

2.2. Diets

The test material was thoroughly mixed into stock diet by means of a meat cutter (Stephan) at levels of 0, 30, 100, 300 or 1000 ppm. 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 diet containing 1000 mg compound 1087-103 per kg was prepared first. The other three test diets were obtained by further diluting the 1000 ppm diet with stock diet.

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

2.3. Animals

Fifty male and 50 female weanling albino rats from the CIVO-colony (Wistar derived) were divided according to body weight into

five groups of ten males and ten females each and fed the various diets (see 2.2).

The rats were housed in screen-bottomed cages (five to a cage) at 24-26° C in a well-ventilated room of constant temperature. Diets and tap water were constantly available.

2.4. Experimental design and conduct

General appearance, condition and behaviour of the rats were checked regularly during the 13-week period.

Individual body weights were recorded weekly. The food intake of each group was measured during week 1-4 and 10-12.

At week 12 blood samples were collected from the tip of the tail of ten rats/sex/group. All samples were examined for haemoglobin concentrations, packed cell volume and counts of erythrocytes and of total and differential leucocytes.

Fasting blood sugar and blood urea nitrogen (BUN) were determined at week 13, using the Technicon AutoAnalyzer method N 9a for glucose and the automated phenazone/diacetyl monoxime technique of Ceriotti and Spadario (1965) for urea. These analyses were also conducted upon tail-tip blood of ten rats/sex/group.

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 Lab stick from Ames Laboratories. Kidney function was examined in all rats by determinations of specific gravity and volume in urine samples collected during the last 16 hours of a 24-hour period of deprivation of food and water in week 13.

At autopsy in week 14 blood samples collected from all rats at decapitation were 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, 1948). Total serum protein determinations (biuret method) and serum albumin determinations (De Leeuw-Israel, Arp-Heofjes and Hollander, 1967) were also carried out in these blood samples.

In week 14 all rats were killed by decapitation and examined grossly for pathological changes. The following organs were weighed: heart, kidneys, liver, spleen, brain, gonads, thymus, thyroid and adrenals. Samples of these organs and of a wide range of other organs were fixed in 10% neutralized formaldehyde solution.

Detailed microscopic examination was performed on all male and female rats of the highest dosage group and on all control rats.

Haematoxylin-eosin stained paraffin sections of the organs weighed and also of the following organs were examined: lung, trachea, salivary glands, prostate, epididymis, uterus, urinary bladder, skeletal muscle, thoracic aorta, esophagus, gastro-intestinal tract (six levels), pancreas and axillary and mesenteric lymph nodes.

In addition histological examination was carried out on the kidneys of the rats in the intermediate groups.

After weighing, appropriate samples of the brain of five rats/sex/group were taken for determinations of the water content by drying at 60° C till constant weight (24 hours).

3. RESULTS

3.1. General appearance, growth and food intake

During the course of the experiment no deaths occurred and no abnormalities of condition or behaviour were observed.

Mean body weights are shown in table 1.

Table 1. Mean body weights

Group nr.	1087-103 in the diet (ppm)	mean body weights (in g) at end of week									
		0	1	2	3	4	6	8	10	12	13
males											
7677	0	59	89	123	148	176	220	247	272	292	296
7678	30	59	86	122	151	178	226	258	281	304	309
7679	100	59	86	122	152	178	223	252	274	294	298
7680	300	59	86	120	150	176	217	243	267	289	296
7681	1000	59	76***	103***	134*	158*	204	231	252	277	281
females											
7677	0	55	78	103	121	132	152	167	179	193	195
7678	30	55	79	106	126	135	150	163	173	186	188
7679	100	55	76	101	119	128	145	160	168	183	184
7680	300	55	71*	95*	113	123	142	156*	167	178*	181*
7681	1000	55	68*	91*	114	126	145	162	174	186	186

*P < 0.05; ***P < 0.001

Slight growth depression occurred in male and female rats receiving 1000 ppm of the test substance in their diet and in female rats receiving 300 ppm. The differences with the controls were statis-

tically significant in the first few weeks of the study and also in females of the 300 ppm group in the last few weeks of the study.

In the first 1-4 weeks food intake was diminished in the 1000 ppm group in both sexes and in the 100 and 300 ppm groups in females (table 2).

Food efficiency figures were comparable in all groups (table 2) except for a slight increase in females receiving diets containing 1000 ppm.

Table 2. Mean food intake and food efficiency figures

1087-103 in the diet (ppm)	food intake in g/rat/day in week						food efficiency during week 1-4		
	1	2	3	4	11	12	gain	food	gain food
males									
0	9.9	13.6	15.1	15.1	16.6	15.8	117	376	0.31
30	9.5	13.0	14.3	15.1	16.1	16.3	119	363	0.33
100	9.6	13.2	14.8	15.2	17.1	16.0	119	370	0.32
300	9.2	12.8	15.1	15.4	16.9	16.0	117	368	0.32
1000	6.8	10.4	13.5	14.7	16.5	15.9	99	318	0.31
females									
0	9.0	11.4	12.1	12.0	12.0	12.1	77	314	0.25
30	9.0	11.0	12.5	11.9	11.9	11.1	60	315	0.25
100	8.5	10.7	11.9	11.5	11.7	11.2	73	299	0.24
300	6.9	10.2	11.3	11.1	11.1	10.8	60	277	0.25
1000	6.0	9.0	11.7	10.9	11.2	11.3	71	256	0.28

3.2. Haematology

Haemoglobin content, packed cell volume and erythrocyte counts were decreased in females of the 1000 ppm group (table 3).

The other statistically significant differences in haematological values between the test groups and the controls did not suggest any relationship with the feeding level of the test compound and are therefore not considered to be of toxicological significance, with the possible exception of the lower percentage of eosinophils in females of the 1000 ppm group.

3.3. Biochemical blood parameters

Fasting blood glucose levels were slightly increased in males fed 1000 ppm (table 4).

Table 3. Haematological findings recorded at week 12

1087-103 in the diet (ppm)	haemo- globin g/100 ml	packed cell volume %	erythro- cytes $\times 10^6/\text{mm}^3$	leucocytes				
				total $\times 10^3/\text{mm}^3$	differential count %			
					Lymph	neutr	eosin	mono
males								
0	17.2	51.6	8.6	14.6	75.3	22.7	0.6	0
30	16.6*	49.8	8.4	13.0	74.3	25.0	0.5	0
100	16.3***	50.2	8.7	12.2*	75.4	22.2	1.4**	0
300	16.9	50.5	8.7	12.5	75.0	23.3	1.7*	0
1000	16.8	50.9	8.4	12.7	80.8	18.3	0.9	0
females								
0	18.3	53.6	8.8	11.2	61.5	16.4	2.1	0
30	18.6	53.8	9.0	10.0	72.1	25.6	2.3	0
100	18.3	52.0	9.1	12.9	64.6*	33.9**	1.5	0
300	19.0	54.1	9.2	11.0	74.9	23.2	1.9	0
1000	17.7**	49.9**	8.4**	11.1	70.6*	29.1**	0.3**	0

*P < 0.05; **P < 0.01

Table 4. Mean blood biochemical values recorded terminally

1087-103 in the diet (ppm)	sugar mg%	BUN mg%	SGOT R-F units	SGPT R-F units	SAP B-L units	TSP g%	albumin %
0	75	19	177	28	8.6	6.3	3.9
30	75	19	190	20	8.8	8.0	3.9
100	80	19	174	29	8.5	7.9	3.8
300	76	19	191	29	8.5	6.1	3.7
1000	86*	20	174	27	11.1*	6.9	3.9
females week 13							
0	72	18	205	28	6.8	7.6	4.0
30	72	20*	183	27	7.2	7.3	4.0
100	68	22*	184	25	9.7*	7.4	3.9
300	71	21*	183	25	8.1	7.1	3.8
1000	77	18	184	24	10.1*	7.2	3.9

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

*P < 0.05

Table 5. Results of urine analyses recorded at week 11

1087-103 in the diet (ppm)	appear- ance	pH	sugar	protein	occult blood	ketones	100 times epith anoma	epith casts per 100 spm	microscopic uridiage
males									
0	yellow	6-7	-	+++	-	-	-	+	+
30	yellow	6-7	-	+++	-	-	-	+	++
100	yellow	6	-	++	-	-	-	+	++
300	yellow	6-7	-	+++	-	-	-	+	++
1000	yellow	7	-	++	+	-	-	+	+++
females									
0	yellow	7	-	+++	-	-	-	+	+
30	yellow	7	-	+++	-	-	-	+	+++
100	yellow	6-7	-	++++	-	-	-	+	+
300	yellow	6-7	-	++	-	-	-	+	+++
1000	yellow	8-9	-	++	+	-	-	+	++

Grading system: - = negative

+ = slight

++ = moderate

+++ = high

++++ = very high

RBC = red blood cells

WBC = white blood cells

W = worm casts

Alkaline phosphatase activity in the serum was slightly increased in the 1000 ppm group in both sexes.

The slight increases in blood urea nitrogen levels in the intermediate groups did not occur in the highest dose group. Therefore, these increases are considered as fortuitous and unrelated to treatment.

3.4. Urine analyses

There were no changes in the composition of the urine which could be attributed to the ingestion of the test compound (table 5). The pH-value for the urine of females was relatively high at 1000 ppm.

Table 6. Mean specific gravity and volume values of the urine

1087-103 in the diet (ppm)	males		females	
	specific gravity	volume	specific gravity	volume
0	1.0539	2.5	1.0713	1.2
30	1.0609*	2.5	1.0662	1.1
100	1.0605	2.2	1.0694	1.2
300	1.0678**	2.1	1.0682	1.0
1000	1.0434*	4.3**	1.0502***	1.5

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

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

The specific gravity values were distinctly decreased at 1000 ppm. The slight increases in specific gravity values in males of the 30 and 300 ppm groups did not suggest any relationship with the feeding of the test substances and are therefore not considered to be of toxicological significance.

The volume of the urine was significantly increased in the 1000 ppm group in males only.

3.5. Water content of the brain

There were no significant differences in mean water content of the brain amongst the various groups (table 7).

Table 7. Mean water content of the brain

1087-103 in the diet (ppm)	water content (%)	
	males	females
0	78.6	79.1
30	78.7	75.7
100	77.1	77.9
300	76.4	76.8
1000	76.7	76.7

3.6. Organ weights

Mean relative organ weights are shown in table 8.

The relative weights of the kidneys were distinctly increased in the 1000 ppm group. The weights of the liver were slightly increased in the 1000 ppm group in males only. In females the weights of the thymus were distinctly decreased and the weights of the adrenals were slightly increased at 1000 ppm.

The relative organ weights were not materially affected by lower dosages.

3.7. Pathology

Gross examination did not reveal pathological changes that could be ascribed to the ingestion of the test compound.

At microscopical examination (table 9), renal changes were observed in nearly all male and in all female rats of the highest dose group. These changes consisted of varying numbers of accumulations of epithelial nuclei in the distal convoluted tubules, indicating epithelial regeneration. This regeneration was strictly localized in the intercortico/medullary layer. Epithelial cells of the papillary collecting tubules were swollen in most of the affected kidneys. Moreover, one female rat of the highest dose group showed swollen epithelial cells in the intercortico/medullary layer and another female rat of the same group showed cystically dilated, colloid-filled collecting tubules. The frequency and degree of the normally occurring tubular nephrosis was higher in female rats of the top-dose group than in controls.

The slight changes in the weights of the liver, thymus and adrenals which occurred either in males or in females of the top-dose group were not accompanied with treatment-related histological changes.

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

Group no.	p.p.s	1087-103	testicle/									
			body weight	heart	kidney	liver	spleen	brains	ovary	thymus	thyroid	adrenal
MALES												
7677	0	294.	.359	.67	3.47	.197	.59	.95	.081	.0064	.0147	
		(8.)	(.015)	(.02)	(.09)	(.006)	(.02)	(.05)	(.008)	(.0006)	(.0012)	
7678	30	307.	.357	.69	3.42	.185	.59	.89	.056	.0051	.0132	
		(7.)	(.009)	(.01)	(.12)	(.004)	(.01)	(.04)	(.007)	(.0005)	(.0010)	
7679	100	297.	.349	.70	3.45	.184	.57	.82	.097	.0049	.0141	
		(9.)	(.006)	(.01)	(.15)	(.005)	(.02)	(.04)	(.007)	(.0005)	(.0008)	
7680	300	294.	.348	.72	3.50	.185	.61	.96	.091	.0046	.0147	
		(2.)	(.005)	(.02)	(.08)	(.007)	(.01)	(.03)	(.004)	(.0005)	(.0006)	
7681	1000	290.	.343	.79***	3.1*	.203	.50	.93	.083	.0072	.0169	
		(7.)	(.006)	(.02)	(.07)	(.008)	(.01)	(.03)	(.025)	(.0007)	(.0007)	
FEMALES												
7677	0	186.	.386	.70	3.16	.232	.59	.0282	.155	.0078	.0221	
		(4.)	(.008)	(.01)	(.09)	(.005)	(.02)	(.0022)	(.007)	(.0009)	(.0010)	
7678	30	181.	.400	.75	3.30	.228	.99	.6326	.157	.0077	.0267*	
		(3.)	(.009)	(.02)	(.07)	(.003)	(.02)	(.0035)	(.009)	(.0009)	(.0013)	
7679	100	179.	.387	.72	3.30	.212	.91	.0284	.140	.0075	.0223	
		(2.)	(.007)	(.02)	(.08)	(.010)	(.01)	(.0019)	(.008)	(.0017)	(.0012)	
7680	300	176.*	.383	.70	3.29	.219	.88	.0296	.142	.0085	.0250	
		(4.)	(.011)	(.02)	(.08)	(.015)	(.01)	(.0016)	(.009)	(.0009)	(.0015)	
7681	1000	182.	.392	.85***	3.33	.213	.89	.0293	.113***	.0110	.0275*	
		(6.)	(.010)	(.03)	(.06)	(.011)	(.03)	(.0033)	(.006)	(.0026)	(.0022)	

* 0.01 ≤ P < 0.05

** 0.001 ≤ P < 0.01

*** P < 0.001

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

The renal abnormalities not mentioned above and the lesions found in other organs and tissues examined occurred either in a single animal, or they were about equally distributed between the different groups. Generally they are common findings in the strain of rats used.

Table 9. Histopathology and the number of animals showing the observed lesions

abnormalities	males					females				
	ppm 1000-10000 in the diet									
	0	30	100	300	1000	0	30	100	300	1000
number of animals examined	10	10	10	10	10	10	10	10	10	10
<u>Kidney</u>										
1. SLIGHT TO MARKED REGENERATION OF TUBULAR EPITHELIUM IN THE INTERCORTICO/MEULLARY LAYER, FREQUENTLY ACCOMPANIED WITH SWOLLEN EPITHELIUM OF THE PAPILLARY COLLECTING TUBULES	0	0	0	0	3	0	0	0	0	10
2. SWOLLEN EPITHELIAL CELLS IN THE INNER MEDULLA	0	0	0	0	0	0	0	0	0	1
3. CYSTICALLY DILATED, COLLOID-FILLED, COLLECTING TUBULES	0	0	0	0	0	0	0	0	0	1
4. TUBULAR NEPHROSIS (THICKENED BASEMENT MEMBRANE, LARGE PALE NUCLEI, NARROWED LUMEN):										
a. SLIGHT	1	1	0	1	2	0	0	0	3	6
b. MODERATE	0	0	0	0	0	0	0	0	0	3
5. Nephrocalcinosis (intercortico/meullary):										
a. slight	1	2	0	0	1	7	5	4	5	3
b. moderate	0	0	0	0	0	0	2	0	4	0
c. severe	0	0	0	0	0	0	0	0	1	0
<u>Liver</u>										
1. Foci of RES cells, occasionally accompanied by a single necrotic hepatocyte	3	- ¹⁾	-	-	6	4	-	-	-	0
2. A few foci of necrotic hepatocytes	1	-	-	-	2	1	-	-	-	0
3. Small subcapsular accumulation of round cells	1	-	-	-	0	0	-	-	-	0
4. Chronic proliferative perivasculitis	1	-	-	-	0	0	-	-	-	0
<u>Lung</u>										
1. Slight to heavy peribronchial, peribronchiolar and perivascular cuffs of lymphocytes (murine pneumonia)	10	-	-	-	10	6	-	-	-	8

Table 9. Continued

a b n o r m a l i t i e s	males					females				
	ppm 1087-103 in the diet									
	0	30	100	300	1000	0	30	100	300	1000
<u>Lung (continued)</u>										
2. Focal chronic interstitial pneumonia	1	-	-	-	5	3	-	-	-	0
3. Medial hypertrophy of medium sized arteries	1	-	-	-	0	0	-	-	-	0
4. Lobular subchronic interstitial pneumonia	1	-	-	-	1	0	-	-	-	0
<u>Thyroid</u>										
1. Activated appearance seen as small follicles lined by cuboidal epithelium:										
a. little activity	7	-	-	-	9	6	-	-	-	10
b. moderate activity	3	-	-	-	1	2	-	-	-	0
2. Ultime-bronchial tissue	0	-	-	-	0	0	-	-	-	1
3. Proliferation of interstitial cells	0	-	-	-	1	0	-	-	-	0
4. Ectopic lymphoid tissue	1	-	-	-	0	0	-	-	-	0
<u>Heart</u>										
Small focal chronic myocarditis	1	-	-	-	0	0	-	-	-	1
<u>Adrenal</u>										
Colloid filled cyst in the zona fasciculata	0	-	-	-	1	0	-	-	-	0
<u>Urinary bladder</u>										
Proteinaceous plug	0	-	-	-	1	0	-	-	-	0
<u>Testis</u>										
Unilateral atrophy	1	-	-	-	0					
<u>Epididymis</u>										
Mass of stagnant sperm cells	1	-	-	-	0					
<u>Prostate</u>										
1. Granular colloid debris	2	-	-	-	1					
2. Lymphocytic prostatitis	2	-	-	-	2					
<u>Striated muscle</u>										
Small necrotic focus	1	-	-	-	0	0	-	-	-	0
<u>Small intestine</u>										
Parasite	1	-	-	-	0	0	-	-	-	0

Remarks: '-' = not examined.

The organs examined histologically which are not mentioned in this table, did not show histopathological changes at all.

The histopathological changes written in capitals are treatment-related.

4. DISCUSSION AND CONCLUSION

The continuous feeding of the methyltin stabilizer 1067-103 to young rats at various dietary levels up to 1000 ppm for three months resulted in distinct changes at the highest dose level. These included, decreased growth and food intake in both sexes, decreases in haemoglobin concentration, haematocrit values, red blood cell and eosinophil counts in females, increases in serum alkaline phosphatase activity in both sexes, increases in fasting blood sugar levels in males, changes in the relative weight of the adrenals and thymus in females and decreased specific gravity of the urine and increased relative weights of the kidneys in both sexes. The usual abnormalities also included degenerative and regenerative changes. Similar histological changes, but representing an earlier stage, were also seen in a previous two-week rat study at the same dietary level of 1000 ppm (SNI-Report Nr. R. 1030, 1975).

It is well-known that several organotin compounds may cause decreases in thymus weight accompanied with lymphocytic depletion of the thymic cortex. Although the decrease in thymus weight of females in the present study was not associated with histopathological changes, the phenomenon possibly reflects a toxic effect of the test substance.

The slight changes in growth and food intake in the 100, 300 and 1000 ppm groups, especially in females were not accompanied by an unfavourable effect on the food efficiency. Therefore, these changes are considered to be the result of unpalatability of the diets, rather than an expression of a toxic action of the test substance.

At the lowest dietary level of 30 ppm none of the criteria applied showed any changes attributable to treatment.

Apart from a transitory decrease in growth rate and/or food intake likely caused by unpalatability no other treatment-related changes occurred at 100 and 300 ppm.

In view of the above considerations the no-toxic effect level of the methyltin stabilizer 1067-103 is placed at 300 ppm in the diet of rats for three months, which is equivalent to 15 mg/kg body weight/day.

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CIVO-TNO
4.8.'75 AJ

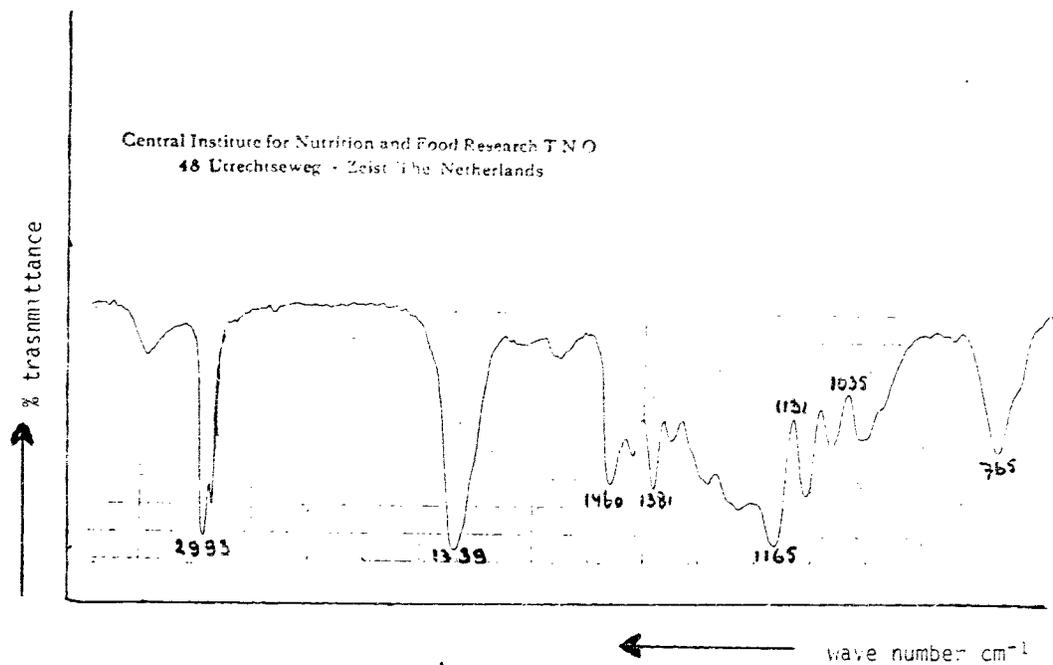


Fig. 1. Infrared spectrum of methyltin stabilizer 1087-103
Phase: Sandwich

0021

We, the undersigned, hereby declare that the work was performed under our supervision, according to the procedures herein described, and that this report provides a correct and faithful record of the results obtained.



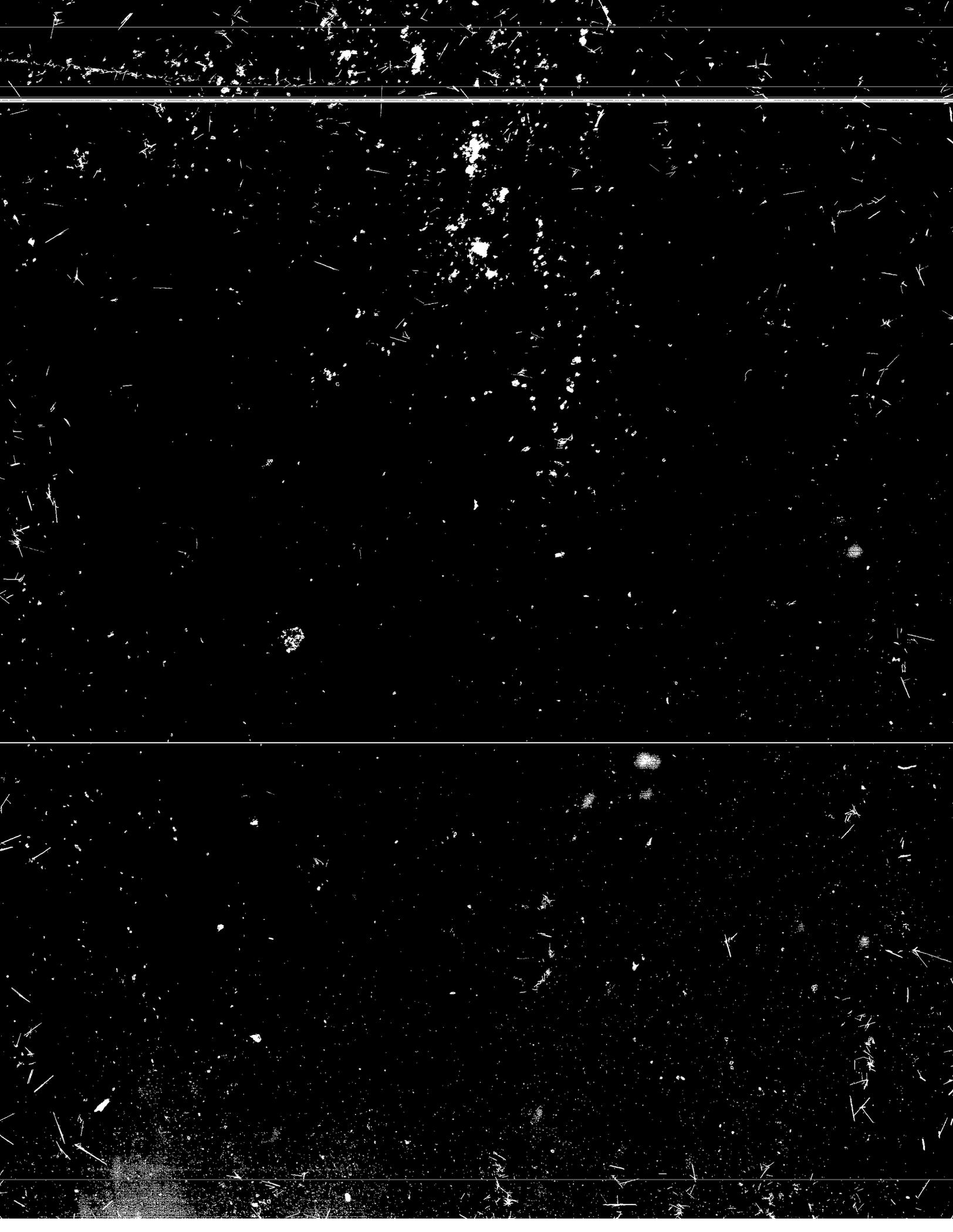
Dr. A.P. de Groot
Head of the Department of Biology and Toxicology



Dr. H.P. Til

Drs. P.G.J. Reuzel



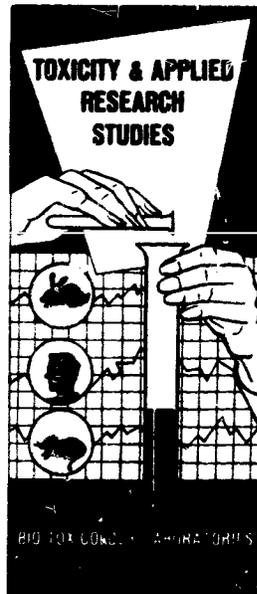


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0 0 2 3

ACUTE ORAL LD₅₀ TOXICITY STUDIES

FOR
THIOKOL CHEMICAL CORP.

COMPILED BY:
Jean M. Wallace



REPORTED:
December 4, 1975

REQUESTED BY:
Dr. S. Aronovic

0024

Bio-Toxicology Laboratories, Inc.

1000 Route 100, Suite 100
Trenton, New Jersey 08607
Telephone: (609) 391-1100

December 4, 1975

Dr. S. Aronovic
Thiokol Chemical Corp.
P. O. Box 1296, 930 Lower Ferry Road
Trenton, N. J. 08607

Dear Dr. Aronovic:

Following are the results of the experimental procedures conducted for Thiokol Chemical Corporation.

MATERIALS:

Cyanoethyl Acrylate
Glycidyl Acrylate
- Glycidyl Methacrylate
Pentaerythritol Tetra Triacrylate
Tetraethylene Glycol Diacrylate
Triethylene Glycol Diacrylate
Trimethylol Propane Triacrylate
Ethylene Cyanohydrin

RECEIVED:

November 12, 1975

EXPERIMENTAL PERIOD:

November 13 - December 4, 1975

EXPERIMENTAL PROCEDURES:

Acute Oral LD₅₀ Toxicity Study

The conclusions in this report are based upon the results of the studies completed December 4, 1975.

This report is submitted for the exclusive use of Thiokol Chemical Corp.

Very truly yours,

LAG/jmw



Lois A. Green
President

FDA Registration No. 24-20621

Toxicity and Applied Research Studies - Animal and Human

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ACUTE ORAL LD₅₀ TOXICITY STUDIES

Cyanoethyl Acrylate
Glycidyl Acrylate
Glycidyl Methacrylate
Pentaerythritol Tetra Triacrylate
Tetraethylene Glycol Diacrylate
Triethylene Glycol Diacrylate
Trimethylol Propane Triacrylate
Ethylene Cyanohydrin

0026

METHOD - ACUTE ORAL TOXICITY

A group of approximately 30 albino male and female rats, fasted for twenty-four hours were employed to establish an LD₅₀ range for each product under test.

Young adult rats which had not been used for previous test purposes were assigned to various dose levels at random. Both sexes were equally distributed.

The product under test was placed in a glass syringe and introduced through the esophagus into the stomach with a stainless steel catheter.

Animals on the same dosage level were then placed in a common cage with free access to food and water. The animals were observed daily for a two week period. No postmortem, or histopathology examinations were performed in this particular study.

EXPERIMENTAL DATA

Cyanoethyl Acrylate
Glycidyl Acrylate
Glycidyl Methacrylate
Pentaerythritol Tetra Triacrylate
Tetraethylene Glycol Diacrylate
Triethylene Glycol Diacrylate
Trimethylol Propane Triacrylate
Ethylene Cyanohydrin

ACUTE ORAL TOXICITY ASSAY

Glycidyl Acrylate

EXPERIMENTAL DATA

Doses: 50 mg./Kg.-2000 mg./Kg. Animals: fasted male and female albino rats
 Concentration: As received Weights: 200-300 grams

Group No.	No. Animals	Dose Level	Number and Day of Deaths														Total	
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	S*	D*
I	5	50	3														2	3
II	5	100	4		1												0	5
III	5	125	5														0	5
IV	5	250	5														0	5
V	5	500	5														0	5
VI	5	1000	5														0	5
VII	5	2000	5														0	5
VIII																		
IX																		
X																		

OBSERVATIONS:

Nasal hemorrhage, sluggish and impaired locomotion and unkempt coats were noted at 50 mg./Kg. and 100 mg./Kg.

Lethargy, nasal hemorrhage, and comas were evident at levels of 125 mg./Kg. and above.

Equally toxic to males and females.

LD₀ = Below 50 mg./Kg.

LD₅₀ = Below 50 mg./Kg. (95% Confidence limits = not established)

LD₁₀₀ = 100 mg./Kg.

* D = Deaths

* S = Survivals

SUMMARY AND CONCLUSION

Cyanoethyl Acrylate
Glycidyl Acrylate
Glycidyl Methacrylate
Pentaerythritol Tetra Triacrylate
Tetraethylene Glycol Diacrylate
Triethylene Glycol Diacrylate
Trimethylol Propane Triacrylate
Ethylene Cyanohydrin

**SUMMARY & CONCLUSIONS
OF TOXICITY DATA**

SAMPLE Glycidyl Acrylate

(See Individual Score Sheets
for Detailed Information)

STUDIES PERFORMED

- DRAIZE EYE IRRITATION
- PRIMARY IRRITATION
- X ACUTE ORAL TOXICITY

DRAIZE EYE IRRITATION STUDY						
STRUCTURE	eyes unwashed		eyes washed		eyes washed	
	Total	Mean	Total	Mean	Total	Mean
	Points	Value	Points	Value	Points	Value
Cornea						
Iris						
Conjunctivae						
Requires labeling under the Federal Hazardous Substances Act. Does not require labeling under the Federal Hazardous Substances Act. Requires labeling as an eye irritant.						

PRIMARY IRRITATION STUDY - F.H.S.L.A. Procedure	6 albino rabbits
Primary Irritation Index:	

PRIMARY IRRITATION STUDY - D.O.T. Procedure	6 albino rabbits			
Primary Irritation Index:				
Test Site	Evaluation of Skin Reaction	Ratio regarding six rabbits		
		4 hrs.	24 hrs.	48 hrs.
Intact				
Abraded				

ACUTE ORAL TOXICITY (single parenteral dose)	X Acute Oral LD ₅₀ Study - 30 albino rats
Acute Oral LD ₅₀ Study:	F.H.S.L.A. Procedure - 10 albino rats
<u>LD₅₀</u> <u>95% Confidence</u>	Federal Hazardous Substances
Below 50 mg./Kg. <u>Limits</u>	Act Procedure:
(Not established)	Dosage: 5.0 c.c. or 5.0 gms./Kg.
	Deaths:
X Requires labeling under the Federal Hazardous Substances Act. (Highly toxic)	
Does not require labeling under the Federal Hazardous Substances Act.	

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CENTRAL INSTITUTE FOR NUTRITION AND FOOD RESEARCH

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OK FBI

RAPPORT NR. R 4737

Title: Sub-chronic (90-day) toxicity study
with a methyltin stabilizer 1097-27
in rats

Authors: Dr. H.P. Til and Drs. P.G.J. Reuzel

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

Approved by: Dr. A.P. de Groot

Date: July 1975

Gehele of gedeeltelijke publicatie van dit rapport is zonder schriftelijke toestemming verboden.
Total or partial publication of this report without written assent is not allowed.

3-15.000-1174

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SUMMARY

1. The toxicity of a methyltin stabilizer, coded 1097-27, was examined in a sub-chronic (90-day) study by feeding the test substance to groups of ten male and ten female weanling rats at levels of 0, 30, 100, 300 or 1000 ppm in stock diet.
2. General condition, behaviour and survival were not adversely affected at any dietary level of the test substance.
3. Body weights, food intake and food efficiency were decreased in the 1000 ppm group in both sexes and in the 300 ppm group in males only, during the first few weeks. Food intake was also slightly decreased in females of the 300 ppm group in the first week only.
4. The differential leucocyte count showed slight changes in the top-dose group.
5. Fasting blood glucose levels were distinctly increased at 1000 ppm in both sexes and at 300 ppm in males only. Alkaline phosphatase activity in the serum of females was distinctly increased at 1000 ppm.
6. Specific gravity of the urine was distinctly decreased in the 1000 ppm group.
7. There were no significant differences in the water content of the brain between the various groups.
8. The relative weights of the kidneys and liver were distinctly increased and the thymus weight was decreased in the 1000 ppm group. The relative weight of the brain was decreased in females at 1000 ppm.
9. At gross examination no treatment-related changes were observed. Microscopical examination revealed both degenerative and regenerative changes in the kidneys of rats in the highest dose group.
10. It was concluded that the no-toxic effect level of the methyltin stabilizer 1097-27 was 100 ppm in the diet of rats for three months.

Sub-chronic (90-day) toxicity study with
a methyltin stabilizer 1097-27

1. INTRODUCTION

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

The present study included chemical, haematological and pathological observations during a three-month feeding period.

2. EXPERIMENTAL

2.1. Material

A 500 ml sample of compound 1097-27 was received from Cincinnati Milacron Chemicals Inc. on 6th September 1974. The material, which was stated to be a methyltin compound for use as a stabilizer in PVC bottles and films, was a clear, slightly yellow coloured, slightly viscous liquid.

An infrared spectrum of the test substance is given in figure 1 (page 14).

2.2. Diets

The test material was thoroughly mixed into stock diet by means of a meat cutter (Stephan) at levels of 0, 30, 100, 300 or 1000 ppm. 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 diet containing 1000 mg of compound 1097-27 per kg was prepared first. The other three test diets were obtained by further diluting the 1000 ppm diet with stock diet. All diets were freshly prepared once a fortnight and stored at room temperature.

2.3. Animals

Fifty male and 50 female weanling albino rats from the CIVO-colony (Wistar derived) were divided according to body weight into five groups of ten males and ten females each and fed the various diets (see 2.2).

The rats were housed in screen-bottomed cages (five to a cage) at 24-25° C in a well-ventilated room of constant temperature. Diets and tap water were constantly available.

2.4. Experimental design and conduct

General appearance, condition and behaviour of the rats were checked regularly during the 13-week period.

Individual body weights were recorded weekly. The food intake of each group was measured during weeks 1 to 4 and 10 to 12.

At week 12 blood samples were collected from the tip of the tail of ten rats/sex/group. All samples were examined for haemoglobin concentrations, packed cell volume and counts of erythrocytes and of total and differential leucocytes.

Fasting blood sugar and blood urea nitrogen (BUN) were determined at week 13 using the Technicon AutoAnalyzer method 11 9a for glucose and the automated phenazone/diacetyl condensing technique of Ceriotti and Spaniolio (1965) for urea. These analyses were also conducted upon tail-vein blood of ten rats/sex/group.

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 Labstix from Ames Laboratories. Kidney function was examined in all rats by determinations of specific gravity in urine samples collected during the last 16 hours of a 24-hour period of deprivation of food and water in week 13.

At autopsy in week 14 blood samples collected from all rats at decapitation were examined for serum enzyme activities, viz. glutamic-oxalacetic transaminase (Reitman and Frankel, 1957), glutamic-pyruvic transaminase (Reitman and Frankel) and alkaline phosphatase (Bessey, Lowry and Brock, 1946). Total serum protein determinations (biuret method) and serum albumin determinations (De Leeuw-Israel, Arp-Heefjes and Hollander, 1967) were also carried out in these blood samples.

In week 14 all rats were killed by decapitation and examined grossly for pathological changes. The following organs were weighed: heart, kidneys, liver, spleen, brain, 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.

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Detailed microscopic examination was performed on all male and female rats of the highest dosage group and on all control rats.

Haematoxylin-eosin stained paraffin sections of the organs weighed and also of the following organs were examined: lung, trachea, salivary glands, prostate, epididymis, uterus, urinary bladder, skeletal muscle, thoracic aorta, esophagus, gastro-intestinal tract (six levels), pancreas and axillary and mesenteric lymph nodes.

The kidneys of the intermediate dose groups were also examined microscopically.

After weighing, appropriate samples of the brain of two rats/sex/group were taken for determinations of the water content by drying at 80° C till constant weight (24 hours).

3. RESULTS

3.1. General appearance, growth and food intake

During the course of the experiment no deaths occurred and no abnormalities of condition or behaviour were observed.

The mean body weights, food intake and food efficiency figures are shown in the tables 1 and 2.

Table 1. Mean body weights

group nr.	1097-27 in the diet (ppm)	mean body weights (in g) at end of week									
		0	1	2	3	4	6	8	10	12	13
males											
7632	0	51.0	75	106	140	169	222	246	273	290	297
7633	30	51.0	75	107	141	171	218	239	263	276	286
7634	100	51.1	75	106	139	170	218	238	265	280	287
7635	300	51.1	71**	99*	131	158*	204*	230	256	272	282
7636	1000	51.0	67**	93**	119***	143***	196**	235	264	283	286
females											
7632	0	47.1	67	90	111	126	148	155	169	176	179
7633	30	47.1	67	89	109	124	145	156	168	177	178
7634	100	47.0	64	87	104	119	139	148	160	169	171
7635	300	47.1	63	85	107	120	141	154	166	176	176
7636	1000	47.1	61*	82*	99**	113*	142	165	161	168	187

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

0 0 3 6

Table 2. Mean food intake and food efficiency figures

group no.	1097-2 in the diet (ppm)	food intake in g/rat/day in week						food efficiency during week 1-4		
		1	2	3	4	11	12	gain food	gain food	
males										
7632	0	7.8	11.1	13.0	15.1	15.0	17.6	118	335	0.35
7633	30	7.9	11.1	13.9	15.0	14.2	11.3	120	335	0.36
7634	100	6.4	11.7	14.2	15.3	15.1	15.6	119	349	0.34
7635	300	7.2	10.6	13.5	14.5	15.1	15.4	107	325	0.33
7636	1000	6.2	9.7	11.4	13.0	16.5	16.0	92	262	0.33
females										
7632	0	7.1	9.5	10.9	11.5	9.6	9.8	70	273	0.29
7633	30	7.0	9.4	10.7	11.4	9.6	9.5	77	170	0.29
7634	100	6.5	8.0	9.9	10.5	9.7	10.1	72	250	0.29
7635	300	5.5	8.9	10.6	10.7	10.0	10.1	73	253	0.29
7636	1000	5.4	6.2	9.2	10.7	13.8	12.0	66	235	0.28

Body weights were distinctly decreased at 300 and 1000 ppm in males and at 1000 ppm in females. These effects, which were marked only in the first six weeks of the experiment, were accompanied by lower food intake in both sexes and decreased food efficiency only in males. In females receiving diets containing 300 ppm food intake was slightly diminished only in the first week. During weeks 11 and 12 food intake was increased at 1000 ppm in both sexes.

3.2. Haematology

Mean haematological values are shown in table 3.

In females of the 1000 ppm group the percentage of neutrophils was slightly decreased while the percentage of eosinophils was slightly increased.

3.3. Biochemical blood parameters

Mean biochemical blood values are given in table 4.

Table 3. Haematological findings recorded at week 12

1097-27 in the diet (ppm)	haemo- globin g/100 ml	packed erythro- cell volume %	erythro- cytes $\times 10^6/\text{mm}^3$	leucocytes				
				total $\times 10^3/\text{mm}^3$	differential count %			
				lymph	neutr	eosin	mono	
males								
0	16.4	48.7	8.5	16.6	66.5	12.1	1.4	0
30	16.7	47.4	8.6	14.7	64.4	14.6	1.0	0
100	16.3	48.4	8.9	15.9	67.6	11.0	1.4	0
300	16.3	49.1	8.6	16.2	67.7	9.9	2.4	0
1000	16.6	48.1	8.5	15.0	67.1	12.3	0.6	0
females								
0	16.5	47.7	7.7	14.2	64.5	14.7	0.6	0
30	16.3	47.5	7.7	14.3	64.0	14.2	1.8	0
100	16.9	46.2	7.8	15.0	65.6	12.5	1.9	0
300	16.4	49.1	7.5	15.9	64.0	14.5	1.5	0
1000	16.5	47.7	7.7	14.3	67.0	10.5*	2.5*	0

*P < 0.05.

Table 4. Mean biochemical blood values recorded terminally

1097-27 in the diet (ppm)	sugar mg%	BUN mg%	SGOT R-F units	SGPT R-F units	SAP B-L units	TSP %	albumin %
males							
0	75	20	199	32	9.5	6.9	3.6
30	74	18	191	31	11.3	6.9	3.5
100	77	19	186	31	11.0	7.0	3.7
300	82*	19	174	30	10.4	7.1	3.8
1000	94***	20	219	27	11.4	7.2	3.7
females							
0	74	20	210	26	8.7	7.5	4.1
30	76	19	209	29	9.2	7.3	4.0
100	69*	23	209	29	6.9	7.3	3.9
300	74	19	185	26	10.2	7.2	3.8
1000	79*	20	195	24	15.3***	7.6	3.9

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

*P < 0.05; *** P < 0.001.

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Table 5. Results of urine analyses recorded at week 13

1097-27 in the diet (ppm)	appearance	pH	sugar	protein	occult blood	ketones	microscopic findings						
							RBC	WBC	epith	cryst	casts	WBC	WBC
males													
0	yellow	6/7	-	++	-	-	-	-	±	+	++	-	+
30	yellow	7	-	+	-	-	-	-	+	+	+	++	+
100	yellow	7/8	-	+	-	-	-	-	±	++	++	-	+
300	yellow	7/8	-	++	-	-	-	-	±	++	++	-	+
1000	yellow	8	-	++	-	-	-	-	±	+++	+++	-	+
females													
0	yellow	8	-	++	-	-	-	-	±	+	++	-	++
30	yellow	7/8	-	++	-	-	-	-	±	+	++	-	++
100	yellow	7	-	++	-	-	-	-	±	+	++	-	++
300	yellow	7/8	-	++	-	-	-	-	±	+	++	-	++
1000	yellow	9	-	++	±	-	-	-	±	+	++	-	+++

Grading system: - = negative

± = minimal

+

++ = moderate

+++ = high

RBC = red blood cells

WBC = white blood cells

WBC = worm eggs

Fasting blood glucose levels were distinctly increased in males of the 300 and 1000 ppm group and in females of the 1000 ppm group. The slight decrease in females at 100 ppm did not suggest any relationship with the feeding of the test substance and is therefore considered an incidental finding.

The alkaline phosphatase activity in the serum of females at 1000 ppm was increased. This effect was noticed also at 300 ppm, but the difference with the controls was not statistically significant.

The other biochemical blood values did not show statistically significant differences between the test groups and the controls.

3.4. Urine analyses

There were no changes in the composition of the urine which could be attributed to the feeding of the test compound (table 5).

The specific gravity of the urine was distinctly decreased in the top-dose group in both sexes (table 6). The slight increases which were found in males at 30 and 100 ppm did not suggest any relationship with the feeding level of the test compound and are therefore not considered to be of toxicological significance.

Table 6. Mean specific gravity of the urine at week 13

1097-27 in the diet (ppm)	specific gravity	
	males	females
0	1.0641	1.0710
30	1.0738*	1.0756
100	1.0722*	1.0836
300	1.0680	1.0671
1000	1.0431***	1.0449***

*P < 0.05; ***P < 0.001.

3.5. Water content of the brain

There were no significant differences in mean water content of the brain amongst the various groups (table 7).

Table 7. Mean water content of the brain

1097-27 in the diet (ppm)	Water content %	
	males	females
0	80.2	80.0
30	78.4	79.5
100	78.7	79.1
300	77.6	77.3
1000	80.0	78.9

3.6. Organ weights

Mean relative organ weights are shown in table 8.

The weights of the kidneys and liver were increased and the weight of the thymus was decreased in the 1000 ppm group in both sexes. Brain weight was significantly decreased in females of the top-dose group.

The other slight changes in organ weights were probably fortuitous and unrelated to treatment.

3.7. Pathology

3.7.1. Gross examination

At autopsy gross examination did not reveal pathological findings that could be ascribed to the ingestion of the test compound.

3.7.2. Microscopic examination

At microscopical examination treatment-related changes were observed in the kidneys of male and female rats receiving 1000 ppm of the test compound in their diet (table 9). The changes observed consisted of small accumulations of nuclei of epithelial cells of the distal and proximal convoluted tubules indicating regeneration. This regenerative activity was mainly found in the interarcortico/modullary layer, but occurred also, though less frequently, in the cortex. In addition epithelial cells of the collecting tubules in the papil were strongly swollen and epithelial giant cells and dilatation of either distal tubules and collecting tubules were occasionally seen. Moreover, a markedly increased degree and incidence of normally occurring tubular nephrosis (thickened basal membrane, narrowed lumen, large pale nuclei) were found at the top-dose level in both males and females.

In spite of a significant increase of liver weights and a significant decrease of thymus and brain weights in rats of the highest

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 in the diet	body weight	heart	kidney	liver	spleen	brains	ovary	testicle/	thymus	thyroid	adrenal
MALES												
7632	0	293. (11.)	.347 (.012)	.70 (.01)	3.30 (.06)	.175 (.005)	.59 (.02)	.95 (.04)	.102 (.005)	.0064 (.0006)	.0152 (.0012)	
7633	30	285. (8.)	.365 (.008)	.71 (.02)	3.34 (.09)	.174 (.006)	.62 (.02)	.95 (.03)	.125* (.008)	.0075 (.0008)	.0150 (.007)	
7634	100	294. (13.)	.356 (.017)	.69 (.03)	3.30 (.14)	.174 (.008)	.59 (.02)	.95 (.04)	.101 (.006)	.0083 (.0006)	.0145 (.0008)	
7635	300	279. (9.)	.343 (.009)	.78 (.04)	3.29 (.06)	.184 (.004)	.62 (.02)	1.00 (.04)	.111 (.009)	.0078 (.0008)	.0110 (.0007)	
7636	1000	285. (7.)	.342 (.009)	.66*** (.03)	3.11** (.11)	.166 (.007)	.59 (.01)	.95 (.02)	.065*** (.007)	.0068 (.0008)	.0158 (.0008)	
FEMALES												
7632	0	177. (6.)	.407 (.012)	.71 (.02)	3.19 (.10)	.204 (.009)	.93 (.03)	.0320 (.0019)	.170 (.008)	.0099 (.0015)	.0253 (.0018)	
7633	30	177. (5.)	.408 (.012)	.69 (.02)	3.27 (.09)	.201 (.009)	.93 (.03)	.0285 (.0025)	.146 (.012)	.0091 (.0008)	.0213* (.0012)	
7634	100	168. (2.)	.411 (.014)	.73 (.01)	3.40 (.09)	.205 (.010)	.97 (.02)	.0335 (.0022)	.160 (.012)	.0109 (.0011)	.0246 (.0016)	
7635	300	175. (4.)	.398 (.012)	.72 (.02)	3.31 (.08)	.209 (.008)	.96 (.03)	.0334 (.0025)	.165 (.008)	.0105 (.0014)	.0259 (.0019)	
7636	1000	178. (6.)	.405 (.010)	1.00*** (.04)	3.81** (.14)	.216 (.007)	.83** (.02)	.0330 (.0016)	.126** (.008)	.0096 (.0007)	.0282 (.0018)	

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

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

dose group, no treatment-related histological changes were observed in these organs.

The other abnormalities found (table 9) are mainly common findings in the strain of rats used and occurred only in one or a few rats or were about equally distributed between the test groups and the controls.

Table 9. Histopathology and the number of animals showing the observed lesions

a b n o r m a l i t i e s	ppm 1097-27 in the diet									
	males					females				
	0	30	100	300	1000	0	30	100	300	1000
number of animals examined	10	10	10	10	10	10	10	10	10	10
<u>Kidney</u>										
1. SLIGHT TO SEVERE REGENERATION OF TUBULAR EPITHELIUM, MAINLY IN THE INTERCORTICO/MEDULLARY LAYER, FREQUENTLY ACCOMPANIED BY SWOLLEN EPITHELIUM OF THE COLLECTING TUBULES IN THE PAPIL	0	0	0	0	8	0	0	0	0	10
2. A FEW EPITHELIAL GIANT CELLS IN THE MEDULLA	0	0	0	0	0	0	0	0	0	2
3. DILATED DISTAL CONVOLUTED TUBULES	0	0	0	0	0	0	0	0	0	3
4. DILATED COLLECTING TUBULES	0	0	0	0	0	0	0	0	0	1
5. TUBULAR NEPHROSIS (THICKENED BASAL MEMBRANE, LARGE PALE NUCLEI, NARROWED LUMEN):										
a. SLIGHT	0	0	0	0	5	1	0	1	2	3
b. MODERATE	0	0	0	0	2	0	0	0	0	1
c. SEVERE	0	0	0	0	0	0	0	0	0	2
6. A few big proteinaceous droplets in the cytoplasm of tubular epithelial cells	0	1	0	0	1	0	0	0	0	0
7. Unilateral hydronephrosis	0	0	0	0	2	0	0	0	0	0
8. Nephrocalcinosis (intercortico-medullary area):										
a. slight	0	0	0	0	0	3	3	5	5	3
b. moderate	0	0	0	0	0	2	1	1	4	0
c. severe	0	0	0	0	0	1	0	0	0	0
9. Focal pyelitis (chronic)	0	0	0	0	0	1	0	0	0	0
10. Perivascular infiltrates of round cells	0	0	1	0	0	0	0	0	0	0
<u>Liver</u>										
1. A few foci of RDS cells, occasionally accompanied by a single necrotic hepatocyte	5	1	-	-	2	3	-	-	-	1
2. Slight periportal infiltrates of lymphocytes or plasma cells	0	-	-	-	2	1	-	-	-	0
3. A few small foci of necrotic hepatocytes	0	-	-	-	2	0	-	-	-	0

Table 9. Continued

a b n o r m a l i t i e s	males				females					
	ppm 1097-27 in the diet									
	0	30	100	300	1000	0	30	100	300	1000
<u>Lung</u>										
1. Slight to heavy peribronchial, peribronchiolar and perivascular cuffs of lymphocytes (murine pneumonia)	4	-	-	-	5	6	-	-	-	5
2. Focal chronic interstitial pneumonitis	0	-	-	-	2	2	-	-	-	0
3. Sub-acute broncho-pneumonia	0	-	-	-	0	0	-	-	-	0
<u>Mandibular salivary gland</u>										
A small focus of ectopic parotid tissue	0	-	-	-	0	0	-	-	-	1
<u>Thyroid</u>										
1. Activated appearance seen as small follicles lined by cuboidal epithelium:										
a. little activity	7	-	-	-	8	9	-	-	-	10
b. moderate activity	3	-	-	-	2	1	-	-	-	0
2. Ulcero-branchial tissue	0	-	-	-	2	1	-	-	-	0
3. A small proliferation of interstitial cells	1	-	-	-	0	0	-	-	-	0
<u>Urinary bladder</u>										
Parasite (Trichosomoides crassicauda)	1	-	-	-	0	1	-	-	-	0
<u>Stomach</u>										
A cystically dilated fundic gland, filled with cellular debris	1	-	-	-	0	0	-	-	-	0
<u>Ileum</u>										
A few foci of cellular debris in a Peyer's patch	0	-	-	-	0	1	-	-	-	0

Remarks ')- = not examined

The organs examined histologically which are not mentioned in this table did not show histopathological changes at all.

Treatment-related abnormalities are written in capitals.

4. DISCUSSION AND CONCLUSION

The continuous feeding of the methyltin stabilizer 1097-27 to young rats at various dietary levels up to 1000 ppm for three months resulted in distinct changes at the highest dose level. Those effects included decreased growth, food intake and food efficiency, slight changes in the differential leucocyte counts in females, increases in fasting blood glucose levels in males and in serum alkaline phosphatase activity in females, and decreased specific gravity of the urine and increased relative weights of the kidneys in both sexes. The renal changes also included degenerative and regenerative phenomena. Similar histological renal changes have been observed also in a previous two-week rat study at the same dietary level of 1000 ppm, although in that study they represented an earlier stage than that found in the present study (Report No. R. 4630, 1975).

The significant decreases in the relative weight of the thymus in the 1000 ppm group were not accompanied by histological changes. However, it is well-known that several organotin compounds may cause decreases in thymus weight associated with lymphocytic depletion of the thymic cortex. Therefore, the decreased thymus weights in the present study are likely caused by the ingestion of the test substance.

The feeding of organotin compounds sometimes gives rise to increased brain weights accompanied by an increase in the water content of the brain and histological brain lesions. In the present study, however, the brain weight was decreased in females of the highest dose group. This phenomenon was not associated with any histological abnormality or with an increase in the water content. There is at present no explanation for this finding.

At the 300 ppm dietary level the only treatment-related changes were slightly decreased growth, food intake and food efficiency and a slight increase in fasting blood glucose levels in males only.

At the lower dietary levels of 30 and 100 ppm none of the criteria applied showed any changes attributable to treatment.

On the basis of the present results the no-effect level of the methyltin stabilizer 1097-27 is 100 ppm in the diet of rats for three months, which is equivalent to 5 µg/kg body weight/day.

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CIVO-Report Nr. R. 4630 (1975).

We, the undersigned, hereby declare that the work was performed under our supervision, according to the procedures herein described, and that this report provides a correct and faithful record of the results obtained.



Dr. A.P. de Groot,
Head of the Department of Biology and Toxicology



Dr. H.P. Til



Drs. F.G.J. Reuzel

0 0 4 6

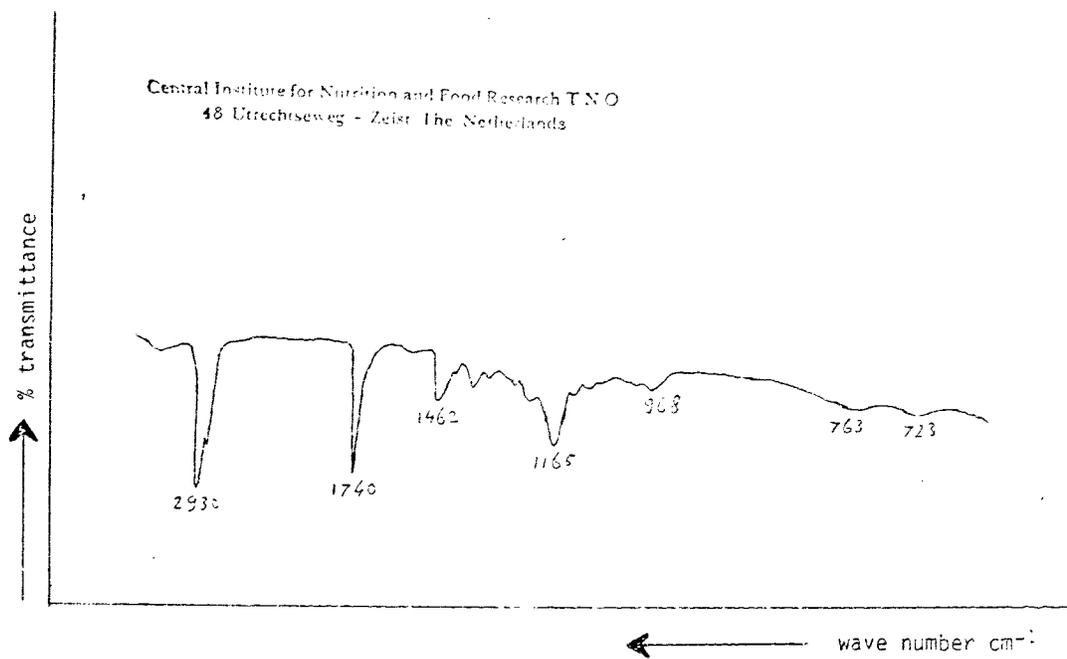


Fig. 1. Infrared spectrum of methyltin stabilizer 1097-27
Phase: Sandwich

0047

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Foster D. Snell Division

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September 28, 1979

Mr. S. Aronovic
Thiokol Corporation
Chemical Division
930 Lower Ferry Road
Trenton, NJ 08650

Subject: Snell Project No. 2528

Dear Mr. Aronovic:

Enclosed please find one copy of our final report on the above subject matter.

The unused portion of the test material is being retained in the Snell Division Archives.

If you have any questions regarding this study, please feel free to contact me at your convenience.

Sincerely,

Eunice J. Wakatama for

BOOZ, ALLEN & HAMILTON Inc.
Foster D. Snell Division

Richard A. Machi, B.S.
Study Director

RAM:sac
Encl.
cc: Archives

0048

EVALUATION OF:

Glycidyl Acrylate (Lot #125)

Acute Dermal LD50 (Rabbit)

Snell Project #2528

Submitted to:

Thiokol

Thiokol Corporation
Chemical Division
930 Lower Ferry Road
Trenton, New Jersey 08607

Submitted by:

BOOZ, ALLEN & HAMILTON Inc.
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September 28, 1979


Richard A. Machi, B.S.
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Michael A. Gallo, Ph.D.
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Myron S. Weinberg, Ph.D.
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Reviewed by John J. Gagliardi, B.S.
Director of Quality Assurance

0044

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SUMMARY

A sample of Thiokol Corporation Glycidyl Acrylate (Lot #125) was studied in the rabbit (Acute Dermal LD50). Under the conditions of this study Glycidyl Acrylate has an acute dermal LD50 of 170 (134 to 216) mg/kg body weight.

STUDY PREPARATION

The sample Glycidyl Acrylate was received from Thiokol Corporation at the Booz, Allen & Hamilton Inc., Foster D. Snell Division Life Sciences Laboratories on March 15, 1978. The sample was used as received.

The rabbits (New Zealand White) used for the Acute Dermal LD50 study were obtained from Summit View Farms, Belvidere, New Jersey, and from Vrana's Rabbit Farm, Millville, New Jersey.

The study was performed under Snell project assignment number 2528. For reference purposes, Glycidyl Acrylate was identified as Snell laboratory sample number 4087.

METHOD OF STUDY

Acute Dermal LD50 (Rabbit) -- Glycidyl Acrylate

A total of thirty six (36) healthy New Zealand White rabbits with body weights between 2.3 and 3.0 kg were used. The rabbits were uniquely numbered and identified by ear tags prior to study initiation. Each rabbit was individually housed and allowed Purina Rabbit Chow and water at all times.

The dorsal trunks of each rabbit were clipped free of hair prior to dosing. The trunks of half of the rabbits in each group were further prepared by abrading. Epidermal incisions every two or three centimeters were made longitudinally over the area of exposure. The incisions were sufficiently deep to penetrate the stratum corneum, but not disturb the derma or elicit bleeding.

The dermal applications were performed in three phases, as follows:

Phase I

Two groups of four (4) rabbits per group, (2 males and 2 females) were administered doses of 1760 and 200 mg/kg body weight respectively. 100% mortality occurred at both dose levels.

0 0 5 5

Phase II

Two groups of ten (10) rabbits per group, (5 males and 5 females) were administered doses of 40 and 80 mg/kg body weight respectively. No mortalities occurred at either dose level.

Phase III

Two groups of four (4) rabbits per group (2 males and 2 females) were administered doses of 120 and 160 mg/kg body weight respectively. One mortality occurred in each group.

The test material was held in contact with the skin for 24 hours by means of non-reactive heavy gauge plastic, covered with an opaque wrapping. At the end of the 24-hour exposure period, the wrappings were removed and the skin was gently wiped to remove any remaining test material.

Subsequent to receiving their assigned dose, animals were observed for mortality and overt signs of toxicity frequently during the day of dosing and at least once daily for 14 days thereafter. The primary irritation scores for the test skin sites observed at 24 hours and 14 days post dosing were determined according to the grading system suggested by Draize as presented in Exhibit 1 on the following page. Any animal failing to survive the observation period was given a necropsy examination for gross organ pathology. At the end of the post-dosing observation period, surviving animals were sacrificed and observed grossly for organ pathology. Body weight data were recorded initially, and for survivors, at termination of the study.

0-0-5-6

EXHIBIT 1

SCALE FOR SCORING SKIN REACTION

(1) <u>Erythema and Eschar Formation</u>	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
	<hr/>
Total possible erythema score	4
(2) <u>Edema Formation</u>	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
	<hr/>
Total possible edema score	4

Draize, H.J., in "Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics", Assoc. Food and Drug Officials of the U.S., Austin, Texas, 1959.

0053

The acute dermal LD50 was calculated according to the standard method of Litchfield and Wilcoxon¹ and is presented along with 95% confidence limits.

¹ Litchfield and Wilcoxon, ("A simplified method of evaluating dose effect experiments", Journal of Pharmacology and Experimental Therapeutics, 96, p. 99 (1949).

RESULTS

Acute Dermal LD50 (Rabbit) -- Glycidyl Acrylate

The data analysis in this section of the report was generated from Snell laboratory notebook pages DT-3-441, 466, 473, 480, 542 and 544. The studies were initiated on March 21, 1978 and terminated August 31, 1979.

Mortality response and signs of toxicity are presented in Tables 1, 3, 5, 7 and 8 and summaries of rabbit growth are presented in Tables 2, 4 and 6 at the end of this report.

Glycidyl Acrylate at 1760 mg/kg body weight -- (4 rabbits)

All four (4) rabbits died within 24 hours post dosing. Moderate erythema was observed at all test sites.

Glycidyl Acrylate at 200 mg/kg body weight -- (4 rabbits)

All four (4) rabbits died within 24 hours post dosing. Mild erythema and edema were observed on two of the four animals.

Glycidyl Acrylate at 160 mg/kg body weight -- (4 rabbits)

One male rabbit died on day 6 of the 14-day observation period. No erythema to severe erythema and slight to severe edema were observed at the test sites.

Glycidyl Acrylate at 120 mg/kg body weight -- (4 rabbits)

One female rabbit died within 24 hours post-dosing. Moderate to severe erythema and slight to severe edema were observed at the test sites.

Glycidyl Acrylate at 40 and 80 mg/kg body weight -- (20 rabbits)

No mortalities occurred during this phase of the study. Moderate to severe erythema and very slight to severe edema were observed at the test sites.

Under the conditions of this study, Glycidyl Acrylate has an Acute Dermal LD50 within 95% confidence limits of 170 (134 to 216) mg/kg body weight.

Table 1 . Mortality Response and Signs of Toxicity* of Rabbits Over the 14-day Observation Period Following Dermal Administration of Glycidyl Acrylate at a Dose of 40 mg/kg Body Weight

-----Hours-----		-----Observation Period-----				-----Days-----		Cumulative
0-1	1-3	2	3	4	5	6	7-14	Mortalities
10N	10N	10N	10N	10N	10N	10N	10N	0/10

*N=Normal

Signs of Toxicity

Eschar formation & subdermal bleeding (10/10)

Necropsy¹

No mortalities

Autopsy²

Apparently normal (10/10)

- (1) Findings on those animals which died during the 14-day observation period.
- (2) Findings on those animals which were sacrificed at the end of the 14-day observation period.

Source: Foster D. Snell Division Laboratory Notebook page DT-3-473.

Table 2. Summary of Rabbit Growth Over the 14-day Observation Period Following Dermal Administration of Glycidyl Acrylate at a Dose of 40 mg/kg Body Weight

<u>Rabbit Number</u>	<u>Sex</u>	<u>Initial Body Weight (kg)</u>	<u>Final Body Weight (kg)</u>	<u>Growth (kg)</u>
A6856	M	2.5	3.2	+ 0.7
A6864	M	2.9	2.7	- 0.2
A6866	M	2.4	2.6	+ 0.2
A6867	M	2.3	2.3	+ 0.0
A6901	M	2.5	2.7	+ 0.2
A6886	F	3.	3.0	+ 0.0
A6887	F	2.4	2.7	+ 0.3
A6899	F	2.9	3.0	+ 0.1
A6900	F	2.8	3.4	+ 0.6
A6907	F	2.3	2.6	+ 0.3
	Mean:	<u>2.60</u>	<u>2.82</u>	<u>+ 0.22</u>

Source: Foster D. Snell Division Laboratory Notebook page DT-3-473.

Table 1 Mortality Response and Signs of Toxicity* of Rabbits Over the 14-day Observation Period Following Dermal Administration of Glycidyl Acrylate at a Dose of 80 mg/kg Body Weight

<u>Hours</u>		<u>Observation Period--Days</u>				<u>Cumulative Mortalities</u>		
0-1	1-2	2	3	4	5	6	7-14	
10N	10N	10N	10N	10N	10N	10N	10N	0/10

*N=Normal

Signs of Toxicity

Lethargic, thin (1/10)

Necropsy¹

No mortalities

Autopsy²

Skins necrotic w/subdermal hemorrhages (10/10)

- (1) Findings on those animals which died during the 14-day observation period.
- (2) Findings on those animals which were sacrificed at the end of the 14-day observation period.

Source: Foster D. Snell Division Laboratory Notebook page DT-3-480.

Table 4. Summary of Rabbit Growth Over the 14-day Observation Period Following Dermal Administration of Glycidyl Acrylate at a Dose of 80 mg/kg Body Weight

<u>Rabbit Number</u>	<u>Sex</u>	<u>Initial Body Weight (kg)</u>	<u>Final Body Weight (kg)</u>	<u>Growth (kg)</u>
A7049	M	3.0	2.7	- 0.3
A7078	M	2.9	2.3	- 0.6
A7032	M	2.4	2.4	+ 0.0
A7033	M	2.8	2.9	+ 0.1
A7034	M	3.0	3.1	+ 0.1
A7048	F	2.9	2.9	+ 0.0
A7074	F	2.7	2.9	+ 0.2
A7075	F	2.5	2.7	+ 0.2
A7076	F	2.8	2.9	+ 0.1
A7077	F	2.3	2.5	+ 0.2
Mean:		<u>2.73</u>	<u>2.73</u>	<u>+ 0.00</u>

Source: Foster D. Snell Division Laboratory Notebook page DT-3-480.

0 0 5-4

Table 5 . Mortality Response and Signs of Toxicity* of Rabbits Over the 14-day Observation Period Following Dermal Administration of Glycidal Acrylate at Dosage Levels of 120 and 160 mg/kg Body Weight

Dose mg/kg	-----Observation Period-----						Cumulative Mortalities				
	Hours		Days		Days						
	0-1	1-3	3-6	6-24	2	3	4	5	6	7-14	
120	4N	4N	4N	2N 1S 1M	2N 1S	2N 1S	2N 1R	3N	3N	3N	1/4
	4N	4N	4N	2N 2S	1N 3S	1N 3S	1N 3S	1N 3S	1N 2S	3N	1/4

*N=Normal, S=Sign, R=Recovery, M=Mortality

Dose mg/kg	Signs of Toxicity	Necropsy ¹	Autopsy ²
120	None	Appears normal (1/4)	Apparently normal (2/4) 50% lungs covered with white substance & par- tially consolidated (1/4)
160	Muscles of hind quarters swollen (1/2)	Yellow fluid in intest- ines (1/4)	Apparently normal (3/4)

(1) Findings on those animals which died during the 14-day observation period.
 (2) Findings on those animals which were sacrificed at the end of the 14-day observation period.

Source: Foster D. Snell Division Laboratory Notebook page DT-3-542 and 544.

Table 6. Summary of Rabbit Growth Over the 14-day Observation Period Following Dermal Administration of Glycidyl Acrylate at Doses of 120 and 160 mg/kg Body Weight

<u>Dose</u> mg/kg	<u>Rabbit</u> <u>Number</u>	<u>Sex</u>	<u>Initial</u> <u>Body Weight</u> (kg)	<u>Final</u> <u>Body Weight</u> (kg)	<u>Growth</u> (kg)
120	A5023	M	2.7	3.0	+ 0.3
	A2589	F	2.6	X	X
	A5094	M	2.5	2.2	- 0.3
	A5151	F	2.6	2.0	- 0.6
		Mean ¹ :	<u>2.60</u>	<u>2.40</u>	<u>- 0.20</u>
160	A2585	M	2.4	X	X
	A2627	F	2.0	1.8	- 0.2
	A5095	M	2.6	2.7	+ 0.1
	A5150	F	2.6	2.6	+ 0.0
		Mean ¹ :	<u>2.40</u>	<u>2.37</u>	<u>+ 0.03</u>

¹ = Average of surviving animals.

X = Mortality occurred during the study.

Source: Foster D. Snell Division Laboratory Notebook page DT-3-542 and 544.

Table 7. Mortality Response and Signs of Toxicity* of Rabbits Over the 14-day Observation Period Following Dermal Administration of Glycidal Acrylate at a Dose of 200 mg/kg Body Weight

-----Hours-----		-----Observation Period-----							Cumulative
1-24		2	3	4	5	6	7	14	Mortalities
4M		--	--	--	--	--	--	--	4/4

*M=Mortality

<u>Animal No.</u>	<u>Signs of Toxicity</u>	<u>Necropsy¹</u>
A6074	None	50% lungs hemorrhagic, 90% liver hemorrhagic, stomach & large intestines green, subdermal blood vessels injected
A6075	None	Yellow mucous like material in chest cavity near stomach, stomach and large intestines green
A6092	None	Subdermal blood vessels injected, lungs 25% hemorrhagic, spleen atrophied.
A6093	None	Stomach and large intestines dark green, subdermal blood vessels injected, spleen atrophied.

(1) Findings on those animals which died during the 14-day observation period.
Source: Foster D. Snell Division Laboratory Notebook Page DT-3-466.

Table 8 . Mortality Response and Signs of Toxicity* of Rabbits Over the 14-day Observation Period Following Dermal Administration of Glycidyl Acrylate at a Dose of 1,760 mg/kg Body Weight

		-----Observation Period-----										
		-----Hours-----			-----Days-----				Cumulative			
		0-1	1-3	3-6	6-24	2	3	4	5	6	7-14	Mortalities
4S	4S	4S	4S	4M		--	--	--	--	--	--	4/4

*S=Sign, M=Mortality

<u>Animal No.</u>	<u>Signs of Toxicity</u>	<u>Necropsy</u>
A4581	Motor paralysis, dyspnea	Subdermal blood vessels injected, lungs grossly hemorrhagic, blood in chest cavity, liver 20% hemorrhagic, liver 80% tan, kidneys tan, dorsal muscle tissue of abdominal cavity hemorrhagic.
A4582	Motor paralysis, dyspnea	Lungs hemorrhagic, blood in chest cavity, liver and kidneys tan.
A4604	Motor paralysis, dyspnea	Lungs hemorrhagic, blood in chest cavity, dorsal muscle tissue of abdominal cavity shows blood vessels injected.
A4605	Motor paralysis, dyspnea	Lungs hemorrhagic, liver and kidneys tan, dorsal muscle tissue of abdominal cavity hemorrhagic, subdermal blood vessels injected.

(1) Findings on those animals which died during the 14-day observation period.
Source: Foster D. Snell Division Laboratory Notebook page DT-3-441.

% Mortality

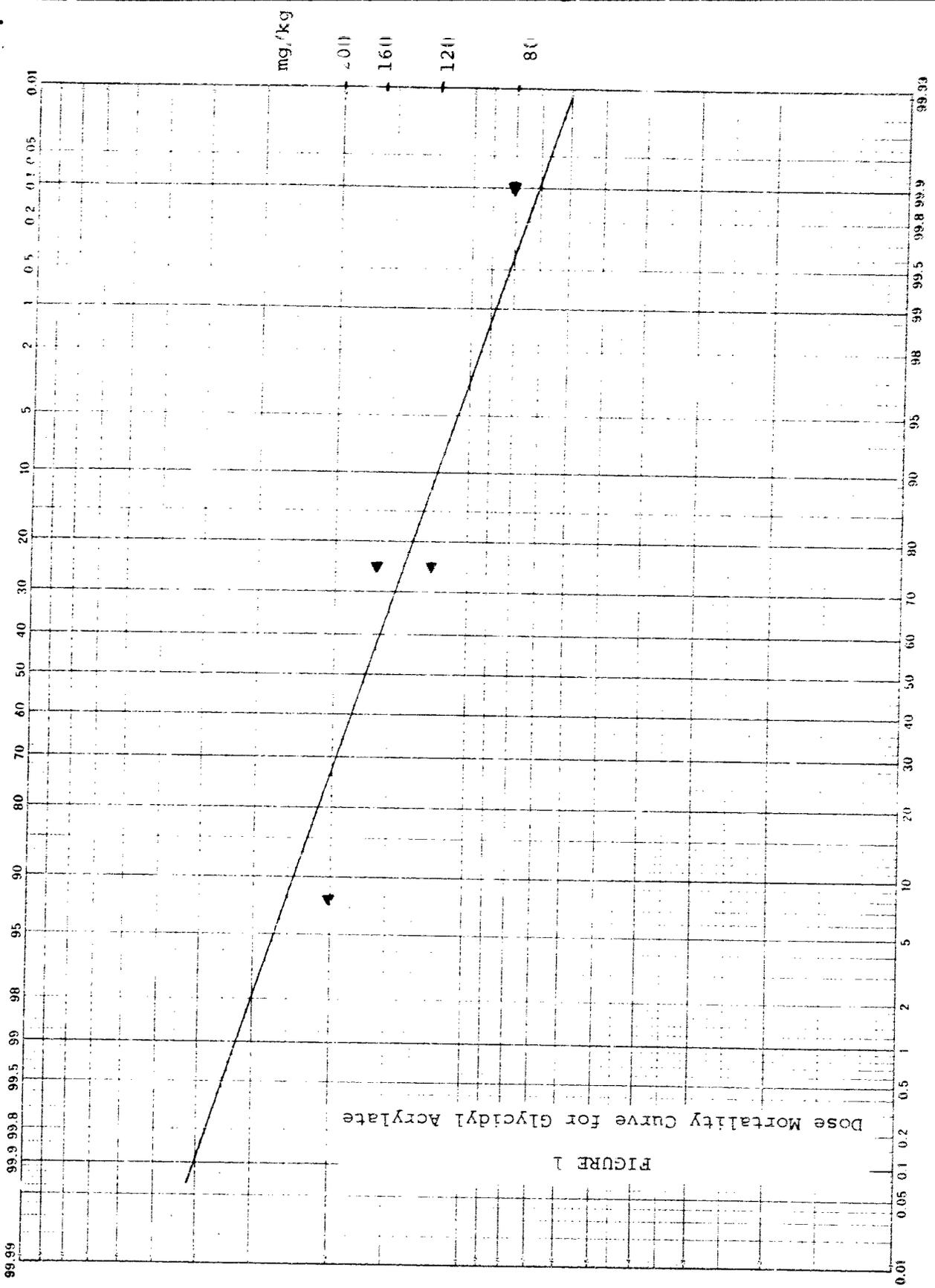


FIGURE 1
 Dose Mortality Curve for Glycidyl Acrylate

CALCULATIONS

Solution of the Dose-Mortality Curve of Glycidyl Acrylate

Dose mg/kg	Mortality/ Tested	Observed % Mortality	Expected % Mortality	Observed Minus Expected	Contribution to χ^2
40	0/10	0	--	--	--
80	0/10	0 (0.12)	0.4	0.28	0.002
120	1/4	25	11.0	14.00	0.200
160	1/4	25	42.0	17.00	0.110
200	4/4	100 (92.2)	72.0	20.20	0.200
1760	4/4	100	--	--	--

K = 4 $N^1 = 8$ n = 2 Total = 0.512

$$\sqrt{N^1} = 2.83$$

Animals/Dose = 6

LD 84	223				
50	170	=	1.31		$\chi^2 = 3.07$
16	127	=	1.34		$\chi^2 = 5.99$
			2.65		

Data not significantly heterogeneous

$$S = 2.56/2 = 1.28$$

$$f_{LD50} = S^2.77/2.83 = S0.98$$

$$f_{LD50} = 1.27$$

$$R = 200/80 = 2.5$$

$$A = 1.08$$

$$f_S = A10(3)/4(2.83) = (1.08)2.65$$

$$f_S = 1.23$$

$$LD50 = 170, (134 \text{ to } 216) \text{ mg/kg}$$

$$S = 1.28 (1.57 \text{ to } 1.04)$$

See key on following page

KEY

- K = the number of doses plotted
- $n = k - 2$ = degrees of freedom for χ^2
- $t = 4.3$, where $p = 0.05$
- LD50 = median lethal dose
- S = slope function
- f_{LD50} and f_S = factors for LD50 and S, respectively
- N^1 = total number of animals used between 16 and 84 percent
expected mortalities
- R = the ratio of largest to smallest dose plotted
- A = a value derived from S and R

Client Therokol Job # 2528 LS # 4027

Sample Biological Assay

Date started 3/21/78 Date completed 3/22/78

Kind

Animal #	Initial Wt.	Sex	1760 Dose ^{mg/kg}	Hours ³⁰⁰				Days						Final Wt		
				1	3	6	24	2	3	4	5	6	7-14			
455	29	♂	5.10	S	S	S	D									
452	29	♂	5.10	S	S	S	D									
454	28	♀	4.93	S	S	S	D									
455	26	♀	4.58	S	S	S	D									

ju Eu Eu ju

- Autopsy
- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10

Comments

4 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Therokol

Client Frankel Chemical Co. Job # 2528 LS# 4087

Sample used as received Sample Glycidyl Acrylate

Date started 6/22/78 Date completed 6/23/78
 spec grav = 1 ml

A = Abraded

Animal #	Initial Wt	Sex	Dose mg/kg	Hours		Days				Final Wt	
				1	3	1/2	1	2	3		7
A 6074	2.6	♂	0.52			M					
6075	2.7	♂	0.54			M					
A 6092	2.9	♀	0.58			M					
6093	2.9	♀	0.58			M					

Autopsies
 1 - 6074 - 24 hrs hemorrhage, 0.5 liter in stomach, stomach empty, testis
 2 - 6075 - 24 hrs hemorrhage, 0.5 liter in stomach, stomach empty, testis
 3 - 6092 - 24 hrs hemorrhage, 0.5 liter in stomach, stomach empty, testis
 4 - 6093 - 24 hrs hemorrhage, 0.5 liter in stomach, stomach empty, testis
 5 - 6092 - 24 hrs hemorrhage, 0.5 liter in stomach, stomach empty, testis
 6 - 6093 - 24 hrs hemorrhage, 0.5 liter in stomach, stomach empty, testis
 7 - 6092 - 24 hrs hemorrhage, 0.5 liter in stomach, stomach empty, testis
 8 - 6093 - 24 hrs hemorrhage, 0.5 liter in stomach, stomach empty, testis
 9 -
 10 -

Comments Sample Calc.) Rabbit wt. = 2.6 kg.
 dose = 200 mg/kg = 0.52g/kg (= 2.6 kg x 0.2g/kg = 0.52g)
 0.52g seen calculated with 0.2g/kg dose 1/2

Table 1 - 2

Client Thiokol Corp. Job # 2528 LS# 4087

Sample Chloral Acrylate

Date started 8/3/78

Date completed 8/17

Roll #

Animal #	Initial Wt.	Sex	40mg/kg Dose	Hours												Final Wt.
				1	3	6	24	48	72	96	120	144	168	192	216	
A 6856	2.5	♂	.100	N	N	N	N	N	N	N	N	N	N	N	N	3.2 +0.7
A 6864	2.9		.116	N	N	N	N	N	N	N	N	N	N	N	N	2.7 +0.2
6866	2.4		.096	N	N	N	N	N	N	N	N	N	N	N	N	2.6 +0.2
6867	2.3		.092	N	N	N	N	N	N	N	N	N	N	N	N	2.3 +0.0
6901	2.5	↓	.100	N	N	N	N	N	N	N	N	N	N	N	N	2.7 +0.2
A 6886	3.0	♀	.120	N	N	N	N	N	N	N	N	N	N	N	N	3.0 +0.0
A 6887	2.4		.096	N	N	N	N	N	N	N	N	N	N	N	N	2.7 +0.3
6899	2.9		.116	N	N	N	N	N	N	N	N	N	N	N	N	3.0 +0.1
6900	2.8		.112	N	N	N	N	N	N	N	N	N	N	N	N	3.4 +0.6
6907	2.3	↓	.092	N	N	N	N	N	N	N	N	N	N	N	N	2.6 +0.3

Mean: 2.60 CO CO CO SSF SSF SSF SSF EW EW SSF CO Ca 2.92 0.22

- Autopsy
- 1 Apparently normal 8/17/78 Chris Sauer
 - 2 "
 - 3 "
 - 4 "
 - 5 "
 - 6 "
 - 7 "
 - 8 "
 - 9 "
 - 10 "

Comments

8/17 20 hrs: skins: + 6886 edema-4 erythema-4; all other animals: erythema 3 edema 4

5/8 all animals Erythema 4 edema 2

8/17 All animals - Eschar formation & subdermal bleeding

0074

Client Thiokol Corp. Job # 2525 LS # 4087

Sample Blycidyl Acrylate

Date 8/17/78

Date completed 8/31

Tables 3 & 4

Animal #	Initial Wt.	Sex	Dose	8/17 8/18 Hours											Final Wt	
				1	3	6	24	2	3	4	5	6	7-14			
7049	3.0	♂	.24	N	N	N	N	N	N	N	N	N	N	N	2.7	-0.3
7078	2.9		.23	N	N	N	N	N	N	N	N	N	N	N	2.3	-0.6
7032	2.4		.19	N	N	N	N	N	N	N	N	N	N	N	2.4	0.0
7033	2.8		.22	N	N	N	N	N	N	N	N	N	N	N	2.9	+0.1
7034	3.0	↓	.24	N	N	N	N	N	N	N	N	N	N	N	3.1	+0.1
7048	2.9	♀	.23	N	N	N	N	N	N	N	N	N	N	N	2.9	0.0
7074	2.7		.22	N	N	N	N	N	N	N	N	N	N	N	2.9	+0.2
7075	2.5		.20	N	N	N	N	N	N	N	N	N	N	N	2.7	+0.2
7076	2.8		.22	N	N	N	N	N	N	N	N	N	N	N	2.9	+0.1
7077	2.3	↓	.18	N	N	N	N	N	N	N	N	N	N	N	2.5	+0.2

mean 2.73

Autopsy

- 1 7049 - All skins necrotic w/ subdermal hemorrhages - cs
- 2 7078 " "
- 3 7032 " "
- 4 7033 " "
- 5 7034 " "
- 6 7048 " "
- 7 7074 " "
- 8 7075 " "
- 9 7076 " "
- 10 7077 " "

Comments

- 8/17 All animals - Sauter - 4, Edema - 2 - cs
- 8/22 All animals as autopsied - 4, Edema - 1 - cs
- 8/30 - 7078 - 10 heads, then - cs

0075

Tables 5, 6, 7 + 8

Client Thiokol Job # 2528 LS # 4087

Sample Glycidal Acrylate

Date started 6/27/79 Date completed 7/1/79

Animal #	Initial Wt	Sex	Dose	Hours												7/11	
				1	3	6	24	2	3	4	5	6	7	8	9		
A5094	2.5	♂	.30	N	N	N	N	N	N	N	N	N	N	N	N	N	2-2
A5151	2.6	♀	.31	N	N	N	N	N	N	N	N	N	N	N	N	N	2-2
A5095	2.6	♂	.42	N	N	N	N	N	N	N	N	N	N	N	N	N	2-2
A5150	2.6	♀	.42	N	N	N	N	LE	2-6								

Autopsies A5094, A5151, A5095, A5150 - 7/1/79
 1. A5094 - apparently normal
 2. A5151 - " 50% lungs covered w/white subpt of partial necrosis
 3. A5095 - " apparently normal
 4. A5150 - " "

Comments: Erithema 4, Edema 4 A5094, A5151, A5095, A5150

7/11	Erithema	Edema
A5094	4	3
A5151	4	3
A5095	4	3
A5150	4	4



September 24, 1979.
(date)

TO: All personnel required to review
this report:

Richard A. Machi
John J. Gagliardi
Michael A. Gallo
Myron S. Weinberg

FROM: Eunice Wakatama Title: _____

SUBJECT: Status Corrections/Comments on Report # 2528

Please leave this form attached to the report until it goes to the client (dated 9-26-79); then send back to me.

<u>COMMENTS</u>	<u>DATE REVIEWED</u>	<u>SIGNATURE</u>	<u>DATE OF SIGNATURE ON REPORT</u>
Reviewed	9-24-79	Ejw.	N.A.
Reviewed	9/24/79	Rmj	
- 10 -	9/29/79	MAC	9/25/79
<i>All comments on attached sheet</i>	9/20/79	Ⓣ	9/23/79

0 0 7 8



"Contains NO CBI" CIVO 71

Short-term feeding study with a methyltin stabilizer
(Advastab TM-181 FS ¹⁾) in rats
H.P. Til and Marianne I. Willems

OK
Til

Central Institute for Nutrition and Food Research (CIVO) TNO
Zeist, The Netherlands

Running title: Toxicity of a methyltin stabilizer

1) Registered trade name of Cincinnati Milacron Chemicals Inc.,
Reading, Ohio, U.S.A.

1971

This was a preliminary report
which was never released.

0 0 7 9

Short-term feeding study with a methyltin stabilizer
(Advastab TM-181 FS) in rats

SUMMARY

A toxicity study was conducted with a methyltin compound (Advastab TM-181 FS) in weanling male and female rats which were fed the test substance at levels of 0 (control), 10, 30, 100 or 300 ppm in the diet for 13 wk.

Growth, food intake and food efficiency were slightly decreased in females receiving the highest dose level. In addition this level affected the kidneys as appeared from increased kidney-to-body weight ratios and proteinaceous casts in the urine of females, a fairly low specific gravity of the urine of males and histopathological renal alterations characterized by cellular debris in tubular lumens and necrosis and regeneration of tubular epithelial cells in both sexes.

An additional 3 wk study in rats fed diets containing 0, 100 or 500 ppm of the test compound did not produce convincing evidence of tin accumulation in the kidneys, liver, femur or brain. The tin content of the blood was distinctly increased at 500 ppm, but not at 100 ppm.

The no-toxic effect level in the diet of rats for 13 wk was 100 ppm, a level approximately equivalent to an intake of 5 mg/kg body weight/day.

INTRODUCTION

Alkyltin compounds are used as stabilizer for plastics, biocidal agents and catalysts. The organotin stabilizers and catalysts most commonly used are dibutyl- and dioctyltin compounds. Toxic properties of these compounds have been reviewed by Barnes and Stoner (1958), Barnes and Magos (1968) and Piver (1973).

Recently methyltin compounds have been introduced as stabilizers for polyvinyl chloride used in food packaging. Advastab TM-181 FS is one of these stabilizers and consists of a mixture of mainly mono- and dimethyltin compounds. Its acute oral toxicity (LD 50) in rats was found to be 1355 mg/kg (Personal communication, Dr. R.F. Lang, Cincinnati Milacron S.A., Dilsen, Belgium). The effects of the continuous feeding of Advastab TM-181 FS to rats over a period of 13 wk and the tin content in various tissues after a period of 3 wk were studied and the results are reported in this paper.

EXPERIMENTAL

Material

Advastab TM-181 FS (batch no. SW 81134, date 5/17/71) was supplied by Cincinnati Milacron Chemicals Inc., Reading, U.S.A. It was a clear, viscous, slightly yellow coloured liquid.

The supplier stated the following composition:

26.0 % monomethyltin tris (isooctylmercaptoacetate)
73.4 % dimethyltin bis (isooctylmercaptoacetate), and
0.6 % trimethyltin isooctylmercaptoacetate.

Animals

Male and female weanling rats from the Institute's Wistar-derived colony were housed in stainless steel cages fitted with wire mesh floors and fronts in groups of five of the same sex in a room maintained at 24 °C and 45 % humidity.

Experimental design and conduct

13 wk feeding study

Five groups of rats each consisting of ten males and ten females were given stock diet supplemented with 0 (control), 10, 30, 100 or 300 ppm Advastab TM-181 FS for a period of 13wk. Diets and tap water were constantly available. Individual body weights were recorded weekly and the food consumption of each group was measured in wk 1 - 4 and in wk 11 and 12.

Haematological studies were carried out on the blood from the tip of the tail of all rats in wk 12. Measurements were made of haemoglobin concentration and haematocrit value, counts of total red blood cells and of total and differential white blood cells.

Blood sugar levels (AutoAnalyzer method N-9a), urea nitrogen levels (Ceriotti and Spandrio, 1965), serum glutamic-oxalacetic and glutamic-pyruvic transaminases (Reitman and Frankel, 1957), serum alkaline phosphatase (Bessey, Lowry and Brock, 1946) total serum protein level (biuret method), serum albumin level (De Leeuw-Israel, Arp-Neefjes and Hollander, 1967) and bilirubin level (Ichida and Nobuoka, 1968) were determined.

The kidney function was assessed by the concentration test (Sharratt and Frazer, 1963) and by determining the activity of glutamic-oxalacetic transaminase (Reitman and Frankel, 1957) in the urine of the rats from the control and top-dose group at wk 13. Also in wk 13 pooled urine samples from ten rats of each sex and group were examined for pH, colour, sugar, protein, occult blood, ketones and microscopic constituents.

In wk 14 all rats were killed by decapitation and examined for gross changes. The heart, kidneys, liver, spleen, brain, gonads, thymus, thyroid and adrenals were weighed. Samples of these organs, and of the trachea, lungs, salivary glands, thoracic aorta, skeletal muscle, axillary and mesenteric lymph nodes, pancreas, urinary bladder, prostate, epididymis, uterus, oesophagus, and gastro-intestinal tract (6 levels) were preserved in 10 % buffered formalin. Detailed microscopic examination was performed on H.E. stained paraffin sections of the above mentioned organs of all rats in the top-dose group and of the controls. In the intermediate groups histopathology was restricted to the liver, kidneys and thyroid of males and females, whereas the adrenals were examined in females only.

Accumulation test

Three groups of ten male and ten female rats were given free access to diets containing 0, 100 or 500 ppm Advastab TM-181 FS for a period of 3 wk. Body weight and food intake were recorded weekly. At day 21 all rats were killed by decapitation. The weights of the liver and kidneys were recorded. Blood samples, and also appropriate tissue samples of the kidneys, liver, femur and brain of each rat were collected and pooled per group for males and females separately. The pooled samples were stored at - 20 °C until use. After thawing and subsequent homogenizing the samples were analyzed for tin by polarography according to the method described by Markland and Shenton (1957).

RESULTS

90-day study

During this study no test rats died and the rats showed no abnormalities of condition or behaviour. One female control animal died in wk 13 because of pneumonia.

There was a slightly reduced growth rate in females fed the diet containing 300 ppm Advastab TM-181 FS (Table 1). This phenomenon was associated with a slight decrease in food intake and food efficiency (Table 1).

The slight decreases in body weights of females receiving 10 ppm were considered incidental findings since they did not occur in females fed the 30 and 100 ppm diets. In males the body weights, food intake and food efficiency figures were comparable in all groups.

There were no changes in the cellular components of the blood that could be attributed to the feeding of the test compound. The haemoglobin concentration was relatively high in females receiving the 100 and 300 ppm diets (Table 2), but the differences with the controls were not statistically significant.

The albumin level in the serum of males and the activity of serum glutamic-oxalacetic transaminase in females were decreased, whereas the activity of serum alkaline phosphatase in females was increased in the top-dose group (Table 2). There were no other significant changes in the biochemical indices.

At the highest dose level proteinaceous casts were present in the urine of females and the specific gravity of the urine of males was decreased (Table 2). Otherwise, urinary findings were essentially normal.

The organ-to-body weight ratios for the kidneys and brain showed a significant increase at the highest dietary level in females (Table 2). The ratios for the thyroid were relatively high in all test groups in both sexes. However, the values were not related to the dose level of the test substance (Table 2). The other organ weights recorded were closely comparable in all groups.

No relevant pathology was revealed by gross examination. Occasional lesions, such as unilateral hydronephrosis, greyish areas in the lungs (bronchopneumonia) and proteinaceous plugs in the urinary bladder, were randomly distributed among the groups. Histopathological examination revealed treatment-related changes in the kidneys of males and females of the highest dose group (Table 2). The renal changes were localized to the outer medulla and mainly characterized by the presence of calcified cellular debris in the tubular lumens and signs of regeneration of tubular epithelial cells. In addition definite necrosis of tubular epithelium occurred in the inner cortex and the outer medulla of the kidneys of three females. This type of renal abnormalities was not visible at the lower test levels.

Tubular nephrosis, characterized by swollen basophilic cells with vesicular nuclei, occurred to a somewhat higher incidence in the 300 ppm group than in all other dose groups.

In the kidneys of females fed on 30 ppm and 100 ppm the degree and frequency of calcareous deposits in the intercortico medullary layer were higher than in all other groups, the highest dose-group included.

A marked individual cell necrosis was found in the adrenal of one female top-dose rat. This lesion was neither observed in the other nine females of this group nor in females of the lower dose groups. Otherwise, there were no differences between test and control animals in the findings in any of the tissues examined microscopically.

Accumulation test

Mean body weight and food intake were slightly decreased at 500 ppm in both sexes. At this feeding level food efficiency was relatively low in males only. Both the absolute and relative kidney weights were increased (8 to 20 %) at 500 ppm in both sexes.

The tin content of the kidneys, liver, femur and brain was distinctly increased at 500 ppm, that of the kidneys also at 100 ppm (Table 3). The tin content of the blood was considerably increased at the 500 ppm level.

DISCUSSION

The slight reduction in growth rate of females which occurred in the top-dose group was associated with a decrease in food consumption and food efficiency, and is therefore considered the reflexion of a toxic effect of the test compound.

The increase in the relative weight of the kidneys, together with the presence of casts in the urine of females, the decrease in the specific gravity of the urine of males and histopathological renal changes in both sexes point to a nephrotoxic effect of Advastab TM-181 FS at the top-dose level.

The degree and incidence of nephrocalcinosis were increased in females fed 30 and 100 ppm Advastab TM-181 FS. From analysis of data on nephrocalcinosis of ten comparable 13 wk feeding studies in the same strain of rats and comprising a total of 100 female control rats, it appeared that the incidence in groups of ten female rats was as follows: slight 2 - 6 (mean 4.1); moderate 0 - 4 (mean 2.2) and severe 0 - 2 (mean 0.3). Comparing these results to those of the present study (Table 2) leads to the conclusion that the degree and incidence found in the present study is within the normal range for the strain of rats used. Since, moreover, it is known that minimal dietary changes may influence the occurrence of nephrocalcinosis i.a. by affecting the availability of Ca and/or P (Mackay and Oliver, 1935; Forbes, 1963; Woodard, 1971) it does not seem justified to consider the frequency and degree of the phenomenon in the present study the expression of a toxic effect of Advastab TM-181 FS.

The slight changes in SAP-activity, SGOT-activity and albumin level in the top-dose group occurred in only one of the sexes and in all cases the values were within the normal range. Therefore, these slight changes were considered of minor, if any, toxicological significance.

The increase in the relative weight of the brain in females fed 300 ppm of the test compound showing growth depression is not considered of any toxicological importance, because of the well-known inverse relationship between the organ-to-body weight ratio of this organ and body weight (Feron, De Groot, Spanjers and Til, 1973).

The increase in relative thyroid weight found in all test groups was neither dose-related nor accompanied by any treatment-related histopathological changes in this organ. Therefore, this observation was not regarded as being of toxicological significance.

It is known that many types of organotin compounds effect the immunological system (Verschuuren et al, 1966, Seinen and Willems, 1976). It may be mentioned, however, that in the present study no evidence was obtained of an effect of Advastab TM-181 FS on the thymus or any other tissue involved in the immunological system.

From the accumulation study it appeared that the tin content in the kidneys, liver, femur and brain increased only slightly with increasing levels of tin in the diet. This finding indicates no storage of tin in these organs. The tin level of the blood was clearly increased at 500 ppm which means that the tin compound is actually absorbed from the gut.

This study has shown that the no-toxic effect level of Advastab TM-181 FS in the diet of rats for 13 wk is 100 ppm. As compared to other organotin compounds it appears that the oral toxicity of the test compound is less than that found for the trialkyltin and pentin compounds (Stoner, Barnes and Duff, 1955; FAO/WHO, 1971) and in the same order of magnitude as that of tributyl and dioctyltin compounds (Barnes and Stoner, 1958, Gaunt et al, 1968).

This dietary concentration of 100 ppm is equivalent to an intake of approximately 5 mg/kg body weight/day.

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ACKNOWLEDGEMENTS

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Table 1. Mean values of body weight, food consumption and food efficiency of rats fed Advestab TW-181-FS at dietary levels of 0 - 300 ppm for 13 wk

Dietary level (ppm)	Body weight (g) at wk				Food consumption (g/rat/day) during wk			Efficiency of food utilization † during wk 1-4	
	0	2	4	8	12	1+2	3+4		11+12
	MALES								
0	61	128	194	282	316	11.4	15.0	15.9	0.36
10	61	131	203	283	320	12.0	16.1	16.7	0.36
30	61	126	188	278	312	10.9	14.6	16.1	0.36
100	61	127	185	276	321	11.4	15.8	16.4	0.33
300	61	124	191	280	314	11.0	15.6	16.3	0.35
	FEMALES								
0	59	109	143	185	205	9.7	11.6	11.8	0.28
10	59	107	140	174 *	192 *	9.7	11.4	11.6	0.28
30	59	106	138	180	194	9.3	11.3	11.7	0.28
100	59	108	140	181	199	9.9	11.6	11.6	0.27
300	59	100 **	131 **	171 *	187 *	8.5	11.1	10.9	0.26

Values are means for groups of ten rats. Those marked with asterisks differ significantly (Wilcoxon test) from the control values:

* P < 0.05; ** P < 0.01.

† Weight gained (g) / food consumed (g)

TABLE 1. Mean results in rats fed Advastab TM-101 FS at 0 - 300 ppm of the diet for 7 wk, showing differences of possible toxicological significance between test and control animals

Parameters effected	Values for males receiving diets containing Advastab TM-101 FS at levels (ppm) of				Values for females receiving diets containing Advastab TM-101 FS at levels (ppm) of				
	0	10	30	300	0	10	30	100	300
Haemoglobin concentration (g/100 ml)	15.8	15.9	15.1	15.5	15.6	16.1	16.2	16.4	16.9
Serum: GOT (R-FU)	157	162	146	152	140	159	154	155	142
AP (B-LU)	9.0	8.4	8.5	7.3	9.4	6.2	6.8	7.3	6.4
Albumin (g %)	2.4	2.6	2.3	2.5	2.1	2.5	2.5	2.7	2.7
Kidney weight (g/100 g b.w.)	0.64	0.65	0.64	0.63	0.67	0.62	0.65	0.64	0.63
Brain weight (g/100 g b.w.)	0.54	0.54	0.54	0.53	0.53	0.77	0.83	0.80	0.81
Thyroid weight (mg/100 g b.w.)	4.4	5.2	4.8	5.3	5.2	6.3	8.0	7.2	7.3
Casts in urine †	-	-	-	-	-	-	-	-	-
Specific gravity of urine	1.0607	NE	NE	NE	1.0529	1.0583	NE	NE	1.0545
Kidney pathology									
1. Regeneration and/or calcified cellular debris in medullary tubules	0	0	0	0	9	0	0	0	6
2. Distinct necrosis of tubular epithelial cells in cortex and medulla	0	0	0	0	0	0	0	0	3
3. Slight to moderate tubular nephrosis	4	3	4	4	7	2	4	4	8
4. Nephrocalcinosis slight	0	0	0	0	0	2	4	3	4
moderate	0	0	0	0	0	1	1	3	4
severe	0	0	0	0	0	0	0	1	0

GOT = Glutamic-oxalacetic transaminase AP = Alkaline phosphatase NE = Not examined

R-FU = Reitman-Frankel units B-LU = Bessey-Lowry units

† = Grading system: - = negative; + = slight

‡ = No. of rats affected/group

Values are the means for groups of ten rats. Those marked with asterisks differ significantly (Student's test)

Table 3. Levels of tin in the kidneys, liver, femur, brain and blood of rats fed Advastab TM-181 FS at dietary levels of 0 - 500 ppm for 3 wk

Sex and dietary level (ppm)	Level of tin (ppm) [†]				
	kidneys	liver	femur	brain	blood
MALES					
0	1.0	< 1.0	2.0	< 1.0	< 1.0
100	4.5	1.5	2.0	1.5	2.5
500	8.0	5.5	5.5	4.5	45
FEMALES					
0	1.0	< 1.0	< 1.0	< 1.0	< 1.0
100	3.5	2.5	1.0	1.5	5.0
500	3.5	7.5	9.0	2.5	91

† Determined in pooled samples from ten males and ten females of each group separately

0.0 9.5

Table 3. Levels of tin in the kidneys, liver, femur, brain and blood of rats fed Advastab TM-181 FS at dietary levels of 0 - 500 ppm for 3 wk

Sex and dietary level (ppm)	Level of tin (ppm) [†]				
	kidneys	liver	femur	brain	blood
MALES					
0	1.0	< 1.0	2.0	< 1.0	< 1.0
100	4.5	1.5	2.0	1.5	2.5
500	8.0	5.5	5.5	4.5	4.5
FEMALES					
0	1.0	< 1.0	< 1.0	< 1.0	< 1.0
100	3.5	2.5	1.0	1.5	5.0
500	3.5	7.5	9.0	2.5	9.0

[†] Determined in pooled samples from ten males and ten females of each group separately