MONSANTO COMPANY

IBT # B-5313
CLOSED OUT

IBT No. B5313 - 90-Day Subacute Oral Toxicity of Aroclor 5460 - Albino Rats

Three copies of the above report dated October 18, 1967 were handed to Dr. Hunt while visiting the office October 18, 1967.

Adele Rose

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DEPOSITION EXHIBIT
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REPORT TO

MONSANTO COMPANY

90-DAY SUBACUTE ORAL TOXICITY OF
AROCHLOR 5460 - ALBINO RATS

BTL-67-12

IBT NO. B5313

I. Introduction

A sample identified as Aroclor 5460, Lot No. AI-43 was received from Monsanto Company on May 5, 1967 for the purpose of conducting a 90-day subacute oral toxicity study employing albino rats as test animals. The study was initiated on May 15, 1967 and terminated on August 18, 1967. This report presents the results of this investigation.

II. Procedure

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A. Experimental Animals

Eighty rats* (40 male and 40 female) were selected for the experiment, ear-punched with the animal numbers assigned and housed individually in standard, wire-bottomed, steel rat cages. Each cage bore a color-coded card identifying the rat with respect to project number, dose level assignment, individual animal number and sex.

* Charles River Breeding Labs., North Wilmington, Massachusetts.

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B. Organisation of Groups

A structural outline of the experiment is given in Table I.

TABLE I

Outline of Experiment

Group	Dietary Level of Aroclor 5460 (ppm)	Number of Animals Male	Female
Control	No Test Material Administered	10	10
I	100	10	10
II	300	10	10
III	1000	10	10

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C. Diets, Feeding and Food Consumption

All diets were prepared in the central diet room of this laboratory. The basic ration from which all diets were constructed was a standard, pulverized, stock rat ration*. The diet for any given test group was prepared by blending the calculated weight of the Aroclor 5460 with a pre-weighed portion of the stock diet in a Hobart mixer.

The amount of food allotted per week to each rat was sufficient for ad libitum feeding. Checks were made daily to ensure that the food jars were not empty.

Food consumption measurements were conducted weekly throughout the investigation.

D. Body Weights and Weight Gains

Initially, the body weight of each rat in every group was determined and recorded. Thereafter, individual weighings were made weekly and the data recorded as an index to growth.

Total weight gains were computed and subjected to statistical analysis. An Analysis of Variance was conducted first and significant effects disclosed by that treatment were further studied by "t"-tests.

E. Mortality and Reactions

Checks for mortality and abnormal behavioral reactions were made daily throughout the test period.

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* Wayne Lab-Blox, pulverized; Allied Mills, Chicago, Illinois. During the last five weeks of feeding, the animals were maintained on pulverized Purina Labena, Ralston-Purina Company, St. Louis, Mo.

F. Hematologic Studies and Urine Analyses

Blood studies, including determinations of hemoglobin concentration, erythrocyte count, hematocrit value, and both total and differential leukocyte counts, were conducted prior to inception of the study, after 33 days of feeding and just prior to the conclusion of the test (89 days). Urine analyses for glucose, albumin and microscopic elements (as well as determinations of urinary pH and specific gravity) were also done at these time intervals.

Blood and urine studies were done individually on five males and five females in the control group and five males and five females in the 1000 ppm group.

G. Clinical Blood Chemistry Studies

Clinical blood chemistry studies, including determinations of blood urea nitrogen concentration (BUN) and serum alkaline phosphatase activity (SAP) were conducted at the same time intervals and on the same animals as the hematologic studies.

H. Pathologic Studies

Whenever an animal succumbed during the test period, a gross autopsy was performed. In those instances where post-mortem changes were not advanced, representative tissues were taken for microscopic study.

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Following 90 days of testing, all surviving test and control animals were sacrificed and subjected to gross pathologic examinations.

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At the time of sacrifice, a complete set of tissues and organs was removed from each rat for histopathologic study. Also, the body weight of each rat at necropsy was recorded along with the weight of the liver, kidneys, spleen, gonads, heart and brain.

Statistical analyses were conducted on the absolute organ weights and upon their corresponding ratio to the weight of their body and brain. An Analysis of Variance was conducted first and significant effects disclosed by that treatment were further studied by "t"-tests.

Microscopic examinations of the following tissues taken from five animals of each sex in the control group and the 1000 ppm group were conducted: heart, trachea, lung, liver, pancreas, esophagus, stomach (cardia, fundus and pylorus), small intestine (duodenum, jejunum and ileum), caecum, colon, spleen, lymph node, thymus, kidney, urinary bladder, testis, ovary, seminal vesicle, prostate gland, uterus, pituitary gland, adrenal gland, salivary gland (submaxillary), thyroid gland, parathyroid gland, intercostal muscle, bone marrow, peripheral nerve, spinal cord, optic nerve, eye and brain (cerebrum, cerebellum and pons).

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III. Results

A. Body Weights and Weight Gains

Mean male and female body weight data are assembled in Table II and shown graphically in Figures 1 and 2. The data in this table also include mean total weight gains for the entire testing period.

Animals in the 1000 ppm group exhibited slight growth depressions during the study. This depression however was not confirmed statistically at the conclusion of the investigation.

Animals in lower dose groups exhibited growth patterns comparable to those of control animals.

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TABLE II

Body Weight and Weight Gain Data

Summary of Mean Values

Dietary Level of Aroclor 5460 (ppm)	Sex	Body Weight (grams) Day: 0	7	14	21	28	35	42	49	56	63	70	77	84	91	95	95-Day Weight Gains (grams)
Control	M	109	163	218	280	311	341	372	394	431	444	452	488	503	510	516	407
	F	107	146	171	200	205	223	227	239	251	257	254	274	280	276	282	175
100	M	110	171	222	286	312	353	365	400	424	440	442	476	487	496	501	391
	F	107	148	170	198	206	219	224	242	247	259	263	279	283	285	289	182
300	M	109	166	218	269	292	327	343	374	396	423	433	462	480	491	494	385
	F	107	143	163	190	203	216	221	234	240	256	258	267	272	270	278	171
1000	M	110	159	200	254	280	309	328	357	387	406	417	446	463	463	474	364
	F	107	143	161	189	196	208	214	221	230	238	243	252	257	259	262	155

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Figure 1

MALE GROWTH CURVES

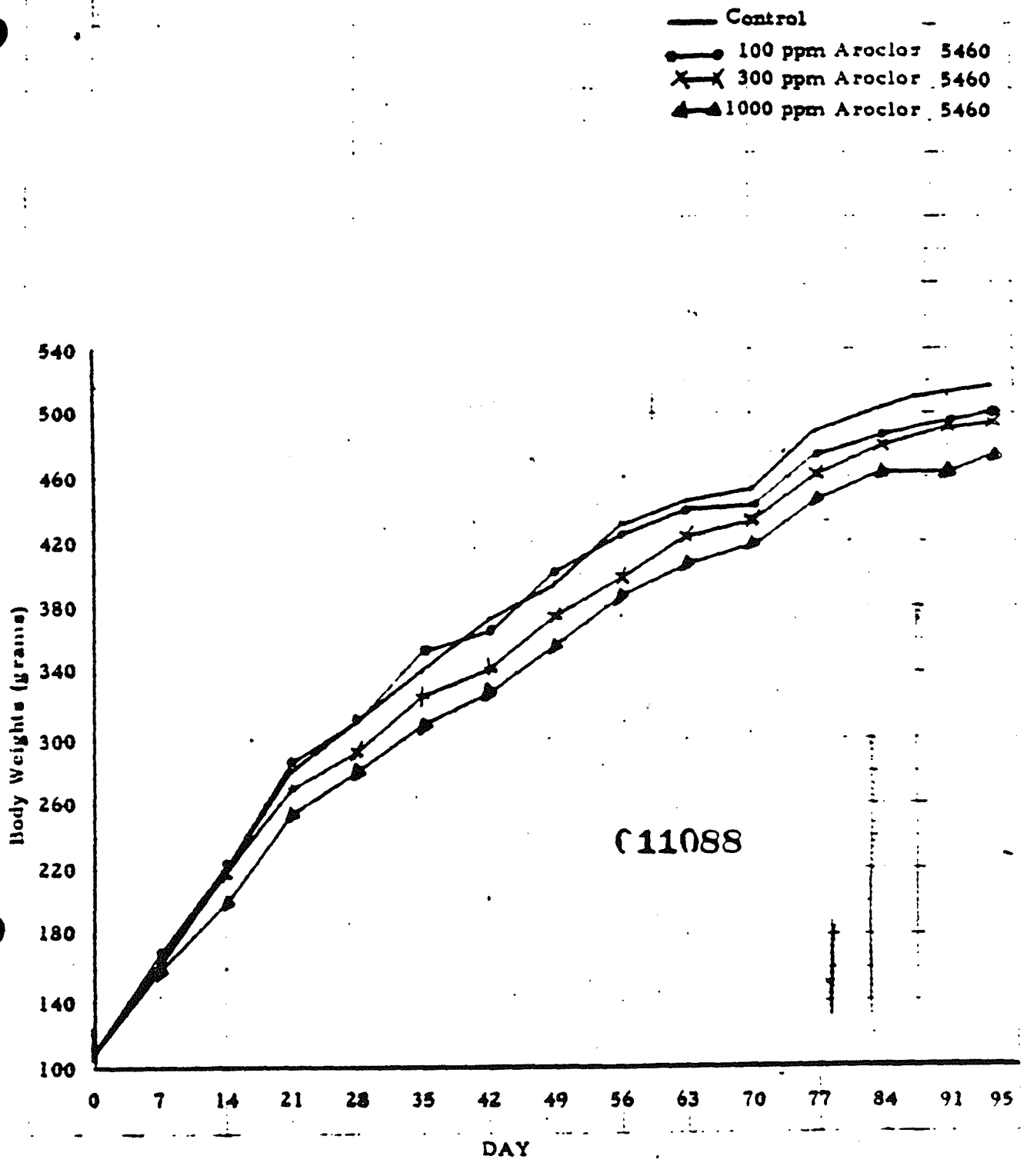
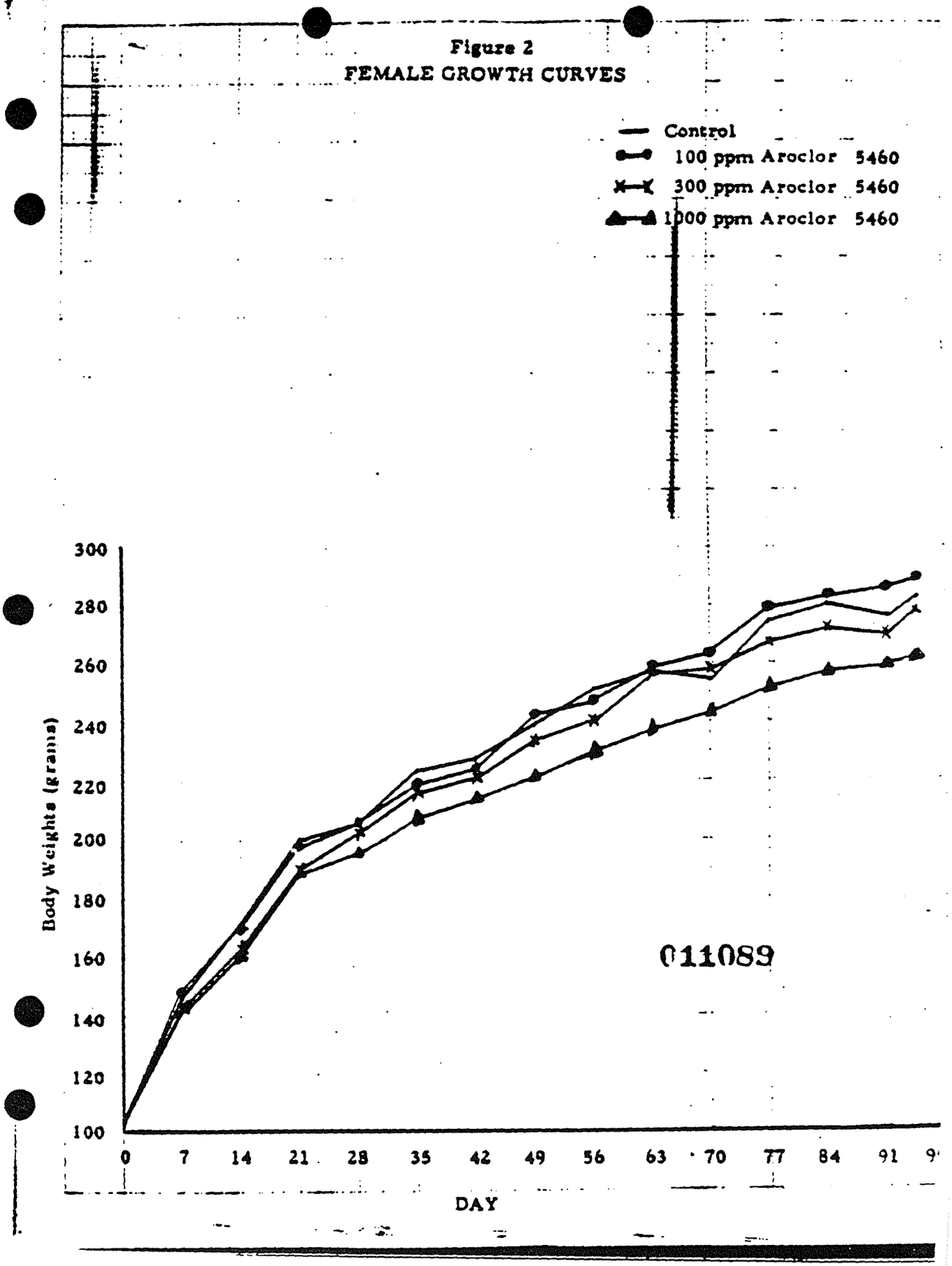


Figure 2
FEMALE GROWTH CURVES



B. Food Consumption

Mean male and female food consumption data are presented in Table III.

Food consumption among animals in the 1000 ppm group was somewhat lower than that of control animals during the study.

Animals in the other test groups ate amounts of food essentially comparable to that eaten by control rats.

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TABLE III

Food Consumption Data

Summary of Mean Values

Dietary Level of Aroclor 5460 (ppm)	Sex	Food Consumed (g/rat/week) Week: 1	2	3*	4**	5***	6	7	8	9	10	11****	12	13	Total Food Consumption (g/rat)
Control	M	127	153	215	174	82	229	209	221	213	234	146	198	195	2393
	F	99	112	177	138	62	139	138	134	133	157	93	120	115	1617
100	M	130	158	231	182	109	199	184	170	184	213	132	179	177	2248
	F	104	124	164	125	70	121	133	141	144	169	98	133	127	1653
300	M	135	158	218	178	105	182	181	190	187	231	144	188	186	2283
	F	101	117	158	121	72	112	122	129	134	161	91	121	116	1555
1000	M	97	126	181	151	72	142	177	163	185	218	131	173	173	1989
	F	100	113	154	119	54	143	114	108	124	149	86	116	104	1484

* Values represent a nine-day period.
** Values represent an eight-day period.
*** Values represent a four-day period.
**** Values represent a six-day period.

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TABLE IV

Hematologic Data

Summary of Mean Values

Dietary Level of Aroclor 5460 (ppm)	Sex	Total Leukocyte Count (thousands/mm^3) Day: 0	33	89	Erythrocyte Count (millions/mm^3) Day: 0	33	89	Hemoglobin Concentration (g/100 ml) Day: 0	33	89	Hematocrit Value (%) Day: 0	33	89
Control	M	15.6	18.7	16.5	5.90	6.66	7.73	12.5	14.2	14.4	47	48	50
	F	14.5	14.6	8.1	5.78	6.78	6.94	12.9	14.2	14.4	47	47	47
1000	M	13.6	21.2	16.3	6.16	6.34	6.87	12.8	12.4	12.8	48	43	44
	F	13.6	21.4	13.5	6.46	6.09	6.27	14.5	12.2	12.7	49	42	43

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TABLE V

Hematologic Data

Summary of Mean Values

Dietary Level of Aroclor 5460 (ppm)	Sex	Differential Leukocyte Count (Number of Cells per Hundred)														
		Lymphocytes Day:			Neutrophils Day:			Monocytes Day:			Eosinophils Day:			Basophils Day:		
		0	33	89	0	33	89	0	33	89	0	33	89	0	33	89
Control	M	87.6	92.8	85.0	9.8	6.6	14.4	2.4	0.2	0.4	0.2	0.4	0.2	0.0	0.0	0.0
	F	90.0	94.4	92.8	6.2	4.8	6.2	3.2	0.0	0.2	0.4	0.6	1.0	0.2	0.2	0.0
1000	M	87.6	79.0	84.2	8.8	18.4	15.0	3.2	0.2	0.4	0.4	2.0	0.4	0.0	0.4	0.0
	F	84.8	93.6	81.6	11.6	4.6	17.4	3.0	0.0	1.0	0.6	1.6	0.0	0.0	0.2	0.0

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E. Clinical Blood Chemistry Studies

The results of the clinical blood chemistry studies conducted during the study are presented in Table VI.

Values obtained for test animals were comparable to those of control animals for all parameters investigated.

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C. Mortality and Reactions

Five animals died during the investigation. A control male died on day 15 of acute respiratory infection. A control female succumbed on day 30. No cause of death was determined for this animal. Two 300 ppm group males died of pneumonia on days 55 and 63 respectively. One female in the 1000 ppm group died on day 89 as a result of trauma incurred during the collection of blood samples.

No untoward behavioral reactions were noted among any of the animals employed in the study.

D. Hematologic Studies

The results of hematologic studies conducted during the study are presented in Tables IV and V.

No outstanding differences in results between test and control rats were noted with respect to any of the hematologic parameters investigated.

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TABLE VI

Clinical Blood Chemistry Data

Summary of Mean Values

Dietary Level of Aroclor 5460 (ppm)	Sex	Serum Alkaline Phosphatase Activity (King-Armstrong Units) Day: 0	33	89	Blood Urea Nitrogen Concentration (mg Urea N/100 ml) Day: 0	33	89
Control	M	39	40	12	18	19	17
	F	40	29	12	24	23	21
1000	M	28	36	13	18	20	21
	F	27	25	12	18	21	26

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F. Urine Analyses

The results of the urine examinations conducted periodically during the study are presented in Table VII.

No difference between the urine of test animals as compared to control animals was seen at any of the examination periods.

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TABLE VII

Urine Analyses Data

Summary of Mean Values

Dietary Level of Aroclor 5460 (ppm)	Sex	Glucose Concentration Day: 0	33	89	Albumin Concentration Day: 0	33	89	Specific Gravity Day: 0	33	89	pH* Day: 0	33	89	Examination of Microscopic Elements Day: 0	33	89
Control	M	n	n	n	n	n	t	1.015	1.031	1.037	6	7	7	N	N	N
	F	n	n	n	n	n	n	1.020	1.034	1.033	6	7	6	N	N	N
1000	M	n	n	n	n	n	t	1.026	1.027	1.022	7	7	7	N	N	N
	F	n	n	n	n	n	t	1.015	1.035	1.028	6	7	6	N	N	N

Symbols: n = negative
N = normal
t = trace: less than 10 mg albumin/100 ml
* determinations conducted with pH paper (combistix)

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G. Pathologic Studies

1. Gross Pathologic Findings

Gross pathologic findings among test rats were comparable to those of control rats.

2. Organ Weight and Ratio Data

Organ weight and ratio data are presented in Tables VIII through XIII.

Statistically significant differences between a test group and either the control group or the treated control group are represented by asterisks following the test value.

A few inter-group differences were noted upon statistical examination of organ weight and ratio data.

Liver weights and ratios were elevated among animals in the 1000 ppm group as was the liver to body weight ratio of males in the 300 ppm group.

Females in the 100 ppm group exhibited a dimimution in spleen to body and spleen to brain weight ratios.

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TABLE VIII

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Liver

Dietary Level of Aroclor 5460 (ppm)	Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
Control	22.6	11.7	4.39	4.16	11.8	5.98
100	22.7	12.4	4.52	4.29	11.1	6.08
300	24.8	11.7	5.02*	4.23	12.3	6.07
1000	29.1**	13.6*	6.14**	5.16**	15.5**	7.06**

* = Statistically significant at the 95 per cent level.
** = Statistically significant at the 99 per cent level.

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TABLE IX

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Kidneys

Dietary Level of Aroclor 5460 (ppm)	Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
Control	3.95	2.17	0.766	0.770	2.06	1.10
100	3.70	2.21	0.738	0.767	1.81	1.09
300	3.87	2.36	0.785	0.848	1.92	1.22
1000	3.70	2.19	0.782	0.833	1.97	1.14

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TABLE X

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Spleen

Dietary Level of Aroclor 5460 (ppm)	Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
Control	0.773	0.627	0.151	0.222	0.402	0.320
100	0.684	0.498	0.137	0.172**	0.336	0.240**
300	0.695	0.546	0.140	0.196	0.344	0.282
1000	0.701	0.563	0.148	0.214	0.373	0.293

** = Statistically significant at the 99 per cent level.

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TABLE XI

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Gonads

Dietary Level of Aroclor 5460 (ppm)	Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
Control	3.35	0.125	0.651	0.0444	1.74	0.0638
100	3.48	0.126	0.698	0.0438	1.70	0.0622
300	3.53	0.110	0.719	0.0398	1.75	0.0571
1000	3.36	0.130	0.713	0.0494	1.80	0.0675

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TABLE XII

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Heart

Dietary Level of Aroclor 5460 (ppm)	Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
Control	1.54	1.00	0.301	0.357	0.803	0.513
100	1.56	0.981	0.313	0.341	0.767	0.485
300	1.57	0.965	0.318	0.348	0.778	0.499
1000	1.55	0.930	0.328	0.355	0.827	0.485

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TABLE XIII

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Brain

Dietary Level of Aroclor 5460 (ppm)	Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)	
	Males	Females	Males	Females
Control	1.92	1.96	0.375	0.699
100	2.04*	2.13	0.410	0.742
300	2.02	1.94	0.411	0.699
1000	1.88	1.92	0.399	0.735

* = Statistically significant at the 95 per cent level.

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3. Microscopic Pathologic Findings

The results of the histopathologic examination of tissues taken from animals in the control group and the 1000 ppm group are presented in Tables XIV and XV.

Findings among animals in the 1000 ppm group were comparable to those noted among control animals.

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TABLE XIV

Histopathologic Changes

Group: Control

Number of Animals Examined	Organ	Findings	Incidence	Average Grade
5 Males	Trachea	Chronic Tracheitis	1	1.0
	Lung	Hyperemia	5	3.5
	Colon	Intestinal Tract Parasite	1	1.0
5 Females	Trachea	Chronic Tracheitis	1	1.0
	Lung	Hyperemia	5	3.0
		Acute and Chronic Bronchitis	1	1.0

All other tissues and organs, as listed on page 5, were normal histologically.

Grading System
0.0 = negative
0.5 = minimal
1.0 = slight
2.0 = mild
3.0 = moderate
4.0 = severe
5.0 = extreme

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