REVIEWER

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

006331

SEP 28 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Transmittal of 90-Day Chlordane Inhalation Study Conducted in Rats and Monkeys (Acc.# 254322).

Caswell No.: 174
TOX Br. Proj. No.: 0531

FROM: Henry Spencer, Ph.D., Pharmacologist
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9/17/87
9/21/87

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THRU: Albin Kocialski, Ph.D., Supervisory Pharmacologist
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ABK 9/22/87
9/27/87

Background

A 90-day subchronic inhalation study, EPA Accession No. 254318, completed by Huntingdon Research Centre, England, dated June 16, 1984, was submitted and reviewed.

Conclusions

Exposure to aerosols of 0.1, 1, or 10 mg/m^3 of technical chlordane for 8 hr/day, 5 days/week for 13 weeks in rats and cynomolgus monkeys showed effects in thyroids and livers of both sexes of both species.

The NOEL for liver and thyroid changes in rats was 0.1 mg/m^3 and the LEL was 1.0 mg/m^3. The NOEL of 0.1 mg/m^3 in monkeys was based on liver weight changes, while the LEL was 1.0 mg/m^3.

NOTE: A NOEL was absent for increased levels of P450 enzymes of the liver and increased serum calcium levels in rats at 0.1 mg/m^3 using a limited number of animals (2). The study is classified as Core Minimum.

The study DER was previously transmitted in the Chlordane Standard, under Acc. # 254318.

006331

EPA: 68-01-6561
TASK: 87
February 7, 1985

DATA EVALUATION RECORD

CHLORDANE

Subchronic Inhalation Toxicity Study in the Rat and Monkey

CITATION: Hardy, C.J., et al. "Chlordane: A 90-day inhalation toxicity study in the rat and monkey." (Unpublished Study No. VCL 28 conducted by Huntingdon Research Centre for Velsicol Chemical Company; dated June 16, 1984.)

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returned 2/8/85
pp 8
pp 10

DATA EVALUATION RECORD

STUDY TYPE: Subchronic inhalation toxicity study in the rat and monkey.

CITATION: Hardy, C.J., et al. "Chlordane: A 90-day inhalation toxicity study in the rat and monkey." (Unpublished Study No. VCL 28 conducted by Huntingdon Research Centre for Velsicol Chemical Company; dated June 16, 1984.)

ACCESSION NUMBER: 254318.

LABORATORY: Huntingdon Research Centre, Huntingdon, England.

QUALITY ASSURANCE STATEMENT: Present, signed, and dated May 31, 1984.

TEST MATERIAL: Chlordane technical 100% pure, batch B-8113. Supplied as an amber viscous liquid and stored at room temperature.

PROCEDURES:

1. One hundred and sixty-one male and 161 female weanling Wistar rats were obtained from Charles River, UK. The rats were housed 5 per cage during an acclimation period. After acclimation, 152 males and 152 females were assigned to 4 groups: the control, mid-dose, and high-dose contained 35 rats of each sex while the low-dose group contained 47 rats of each sex. All rats were housed up to 4 per cage throughout the study. Twelve males and 12 females in the low-dose group served as a recovery group and were held for 17 days after the final exposure before being sacrificed. Twenty-eight male and 28 female cynomolgus monkeys were obtained from Shamrock Farms, Limited. The monkeys were housed singly and, after acclimation, 24 males and 24 females were assigned to 4 groups consisting of 6 male and 6 female monkeys.

2. Target levels of chlordane exposure were 0, 0.1, 1.0, and 10 mg/m^3. Aerosols of chlordane were generated using stainless steel concentric jet atomizers heated to 70° C with an airflow of 12.5 LPM at 50 psi. The aerosol was passed through an elutriation column supplied with an additional airflow of 38 LPM. [This process enhanced the proportion of chlordane present as a vapor.] The aerosol/vapor mixture entered the exposure chamber at the inlet duct at the top of the chamber. Total flow through the chamber was maintained between 1150 and 1300 LPM throughout the exposures. Temperature, humidity, airflow, and pressure were recorded for each chamber at approximately 30 minute intervals throughout each exposure period.

Chlordane concentration in the exposure chambers was determined at least 3 times during each 8-hour exposure period. Samples were collected using a sintered glass bubbler that contained absolute alcohol as the trapping agent. Sample flows of 1 or 2 LPM were used to collect 10 or 100 liters of test atmosphere. The contents of the bubbler were transferred quantitatively to a volumetric flask for analysis by gas chromatography. In addition to chamber concentration, samples were collected for particle size analysis by a May Multistage liquid impinger. For the low-dose chamber, a Royco Model 218 optical size analyzer was used to determine the particle size distribution in the test atmosphere.

Exposures were 8 hours/day, 5 days/week for 13 weeks except for the 5 days of exposure on which rats or monkeys were bled. Each chamber was of stainless steel and glass with a volume of approximately 6 m^3. Rats were exposed in individual cages and the monkeys in cages holding 2 animals.

3. Rats were provided with a weighed quantity of food (Spratt's Laboratory Diet No. 1) and a weighed quantity of water, and allowed free access to food and water except during exposure and urine collection. Each monkey was offered, daily, 200 g of Mazuri primate diet and tapwater ad libitum except during exposure and urine collection. In addition, each monkey was provided a slice (34 g) of whole meal bread and fresh fruit or vegetable produce on week-days. Each monkey was also provided Vitamin B12 weekly; given an intrapalpebral tuberculine test at 6 week intervals; and a one-time chest X-ray.

4. Animals were examined twice daily for clinical signs and mortality. Body weights were determined weekly. Food consumption was determined weekly for each cage of rats and daily for individual monkeys. Ophthalmology was conducted on 10 male and 10 female rats per group and each monkey prior to the first exposure and during the last week of exposure. For 5 male and 5 female rats and all monkeys in each group, rectal temperature was recorded before exposure and during weeks 1, 4, and 13 of the study. Pulmonary function studies were conducted on monkeys only during week 12 of the study. Hematology, blood chemistry and urinalysis were conducted on 10 male and 10 female rats and all monkeys per group during weeks 5 and 13. Hematology determinations included: packed cell volume, hemoglobin, red cell indices, red cell counts, white cell counts, and platlet counts. Blood chemistry determinations included: glucose, BUN, protein, SAP, SGPT, SGOT, creatinine, cholesterol, Na, K, Cl, Ca, P, GDH, LDH, and bilirubin. Urinalysis determinations included: volume, pH, protein, glucose, ketones, bile pigments, urobilogen, heme pigments, and microscopic evaluation of the sediments.

An interim sacrifice of 5 male and 5 female rats from each was was conducted during week 9. All other rats (except recovery animals) were terminated over a 3 day period during week 14 and all monkeys were terminated over a 6 day period. Animals were killed by exsanguination under sodium pentobarbitone anesthesia. All rats were

subjected to a complete necropsy and subjected to a detailed microscopic examination of approximately 50 organs and tissues. All monkeys were subjected to a complete necropsy and tissues from the high dose and control groups were examined microscopically. The following organs were weighed after dissection of extraneous tissue: adrenals, brain, heart, kidneys, liver, lung, ovaries, pituitary, spleen, testes, thymus (where present), thyroids, and uterus.

5. Analyses of variance was followed by Student's "t" test and Williams test for body weight, and food consumption. For other parameters, Bartlett's test was applied to test for heterogeneity of the variance. If no significant heterogeneity was detected, a one-way analysis of the variance was conducted using the Kruskal-Wallis method.

RESULTS:

Chamber Analysis: The mean overall analytical concentration of chlordane in the exposure chambers was 0.10 ± 0.025, 0.98 ± 0.277, and 9.23 ± 1.493 mg/m^3 for the 69 exposure days.

The particle size distribution analyses revealed that 82.9 and 91.8% of the mass of particles were less than 5.5 micrometers for the mid- and high-dose groups, respectively.

Mortality: One control male rat died under anesthesia prior to bleeding during week 9 and one mid-dose female rat was sacrificed following blood collection during week 13 because one eye was damaged during the collection process. No other animals died on study.

Body Weight: Body weight data at selected intervals are presented in Table 1. No statistically significant differences were noted for either sex of either species.

Food Consumption: The male rats from the 0.1 and 1.0 mg/m^3 groups consumed more food (4-9%) than controls throughout the study. No other differences in food consumption patterns were noted. Food consumption was not measured for monkeys.

Laboratory Studies: No consistent significant treatment-related differences in either sex or species were noted in the following data sets: ophthalmoscopy; pulmonary function; rectal temperature; hematology; blood chemistry except for calcium, cholesterol, and glutamic dehydrogenase (GDH) in rats; and urinalysis. The data for blood levels of Ca, cholesterol, GDH, and cytochrome P_{450} for rats are presented in Table 2.

Organ Weight: Individual and group mean absolute organ weight data were presented for each sex for the rats and for combined sexes for the monkeys. Selected organ weight data are given in Table 3.

Pathology: Individual pathology data were available for each animal on study including antimortum, macroscopic, and histopathology findings. The incidence of selected liver and thyroid lesions is given in Table 4.

TABLE 1. Selected Body Weight Data for Animals Exposed to Chlordane for 13 Weeks

Exposure Group (mg/m^3)	Mean Body Weight (g ± S.D.) at Week					Mean Weight Gain (g ±S.D.)
	-2	0	1	7	13	
Male Rats[a]						
0	111±4	202±9	263±12	483±36	563±51(29)	452±51
0.1	112±4	208±12	274±12	502±35	581±48(30)	470±46
1.0	112±4	209±8	271±12	499±32	579±42(30)	468±41
10.0	112±4	205±8	266±12	487±33	560±45(30)	448±46
Female Rats[a]						
0	103±5	160±8	183±10	271±17	298±19(30)	196±19
0.1	103±5	161±8	190±11	278±20	300±24(30)	197±21
1.0	103±5	158±8	189±12	278±20	298±21(29)	196±20
10.0	103±6	160±10	189±14	278±21	297±23(30)	194±20
Male Monkeys[b]						
0	2304±321	2200±320	2188±318	2329±400	2388±481	83±244
0.1	2217±196	2096±253	2096±238	2425±429	2571±558	354±424
1.0	2271±174	2171±197	2208±186	2404±372	2454±480	183±340
10.0	2229±410	2192±431	2225±412	2458±501	2438±520	208±153
Female Monkeys[b]						
0	2421±290	2300±286	2325±293	2363±247	2371±226	-50±204
0.1	2463±233	2333±220	2322±246	2333±191	2354±205	-108±139
1.0	2483±258	2388±274	2446±269	2463±213	2488±246	4±112
10.0	2404±463	2304±411	2317±387	2354±390	2338±322	-67±221

[a] Number rats/group = 35, unless specified ( ).
[b] Number monkeys/group = 6.

TABLE 2. Mean Calcium, Cholesterol, Glutamic Dehydrogenase (GDH) and Cytochrome P450 Values for Rats Exposed to Chlordane for 13 Weeks

Exposure Level (mg/m^3)	Calcium (mEq/l ±S.D.) at Week			Cholesterol (mg/dl ±S.D.) at Week				GDH Activity (mU/mL ±S.D.) at Week				Liver Cytochrome P_{450} at termination (only 2 rats/group)	
	-1	5	13	-1	5	9	13	-1	5	9	13	.nmoles/g Liver	Total mg Microsomal Protein in Liver
Males													
0	5.4±0.2 (3)[a]	5.5±0.1 (10)	5.2±0.1 (9)	61±6 (3)	56±11 (10)	60±16 (4)	55±12 (9)	1±0 (3)	9±3 (10)	11±7 (4)	15±5 (9)	5.15 5.59	370 509
0.1	5.4±0.1 (3)	- -	5.4±0.2** (10)	59±3 (3)	- -	59±7 (5)	49±10 (10)	3±1 (3)	- -	9±6 (5)	17±13 (10)	7.99 5.85	683 554
1.0	5.4±0.1 (2)	- -	5.4±0.1** (10)	58±10 (2)	- -	66±10 (5)	53±9 (10)	1±0 (2)	- (10)	23±18 (5)	17±5 (10)	9.64 9.09	728 684
10.0	5.4±0.2 (2)	5.5±0.1 -	5.8±0.2** (10)	64±5 (2)	64±11 (10)	71±7 (5)	61±21 (10)	1±0 (2)	13±3* (10)	21±9 (5)	17±4 (10)	14.67 15.83	929 873
Females													
0	5.3±0.1 (2)	5.2±0.1 (10)	5.3±0.2 (10)	61±7 (2)	60±10 (10)	51±6 (5)	45±12 (10)	3±0 (2)	5±1 (10)	6±3 (5)	6±2 (10)	3.86 4.53	188 264
0.1	5.5±0.0 (2)	- -	5.2±0.1 (10)	69±1 (2)	- -	59±9 (5)	51±15 (10)	4±0 (2)	- -	6±2 (5)	6±5 (10)	5.65 5.43	294 294
1.0	5.7±0.1 (3)	- -	5.4±0.1 (10)	54±10 (3)	- -	59±5 (5)	54±8 (10)	5±2 (3)	- -	6±2 (5)	5±1 (10)	7.62 5.17	435 280
10.0	5.3±0.1 (3)	5.4±0.2** (10)	5.6±0.2** (10)	54±7 (3)	77±10** (10)	83±19** (5)	71±19** (10)	5±1 (3)	5±1 (10)	7±2 (5)	6±1 (10)	9.56 12.60	400 436

* Significantly different from control value ($p \leq 0.05$).
** Significantly different from control value ($p \leq 0.01$).
[a]Number in parentheses is the number of samples analyzed.

TABLE 3. Selected Organ Weight Data for Animals Exposed to Chlordane for 13 Weeks

Exposure Level (mg/m^3)	Mean Organ Weight at Week														
	Brain (g ±S.D.)			Liver (g ±S.D.)			Kidneys (g ±S.D.)			Thyroids (mg ±S.D.)			Adrenals (mg ±S.D.)		
	9	14	27	9	14	27	9	14	27	9	14	27	9	14	27
Male rats	(5)[a]	(15)	(9)	(5)	(15)	(9)	(5)	(15)	(9)	(5)	(15)	(9)	(5)	(15)	(9)
0	2.0 ±0.1	2.0 ±0.1	2.0 ±0.1	18.5 ±2.6	20.9 ±2.0	20.2 ±2.7	3.0 ±0.4	3.4 ±0.3	3.6 ±0.4	24 ±9	27 ±5	32 ±5	72 ±13	67 ±11	64 ±10
0.1	2.0 ±0.1	2.1 ±0.1	2.1 ±0.1	19.1 ±2.3	21.5 ±2.3	20.6 ±3.2	3.5 ±0.2	3.5 ±0.3	3.9 ±0.4	25 ±5	32 ±5	31 ±8	80 ±16	69 ±9	61 ±9
1.0	2.0 ±0.1	2.0 ±0.1	2.1 ±0.1	20.0 ±1.5	21.8 ±2.6	22.1 ±3.5	3.4 ±0.5*	3.5 ±0.2	4.0 ±0.3	28 ±4	31 ±7	32 ±8	76 ±7.5	67 ±7	62 ±10
10.0	2.0 ±0.1	2.1* ±0.1	2.1 ±0.1	22.6** ±1.7	25.9** ±2.9	19.6 ±3.3	3.4* ±0.2	3.7** ±0.4	3.7 ±0.4	28 ±8	37 ±7	33 ±6	68 ±5.7	69 ±15	57 ±7
Female rats	(5)	(15)	(9)	(5)	(15)	(9)	(5)	(15)	(9)	(5)	(15)	(9)	(5)	(15)	(9)
0	1.8 ±0.1	1.9 ±0.1	1.9 ±0.1	9.7 ±0.89	11.1 ±1.3	10.6 ±1.4	1.8 ±0.1	1.9 ±0.1	2.2 ±0.2	19 ±3	22 ±6	24 ±5	86 ±10	89 ±14	88 ±10
0.1	1.8 ±0.1	1.7 ±0.1	1.9 ±0.1	9.4 ±1.3	11.0 ±1.5	10.0 ±1.5	1.8 ±0.2	1.9 ±0.2	2.1 ±0.2	22 ±6	23 ±4	26 ±7	88 ±11	90 ±10	85 ±10
1.0	1.9 ±0.04	1.9 ±0.1	1.8 ±0.1	10.0 ±1.1	11.6 ±1.8	10.3 ±1.5	2.0 ±0.3	1.9 ±0.2	2.1 ±0.2	22 ±6	22 ±4	25 ±6	89 ±19	90 ±12	87 ±13
10.0	1.8 ±0.1	1.9 ±0.1	1.9 ±0.1	13.3** ±0.81	14.8** ±1.7	11.2 ±1.3	2.0 ±0.1	2.1** ±0.1	2.2 ±0.2	24 ±3	25 ±4	26 ±6	81 ±12	85 ±9	76* ±6
Monkeys[b]															
0	-	61.7±5.2	-	-	66.0±12.7	-	-	10.8±2.6	-	-	290±63		-	460±82	-
0.1	-	59.3±5.0	-	-	63.2±6.8	-	-	10.3±1.9	-	-	320±125	-	-	460±126	-
1.0	-	60.3±5.2	-	-	66.6±11.8	-	-	9.9±2.2	-	-	340±125	-	-	480±114	-
10.0	-	59.1±7.1	-	-	70.1±7.5	-	-	9.2±3.3	-	-	400±187	-	-	510±91	-

[a] Number in parentheses is the number of animals sampled.
[b] Data for both sexes (12 animals) were combined for organ weight analyses.
* Significantly different from control value ($p \leq 0.05$).
** Significantly different from control value ($p \leq 0.01$).

TABLE 4. Incidence of Selected Liver and Thyroid Lesions in Animals Exposed to Chlordane for 13 Weeks

Exposure Level (mg/m^3)	Incidence at Week								
	LIVER						THYROID		
	Hepatocellular enlargement or vacuolation			Fatty Deposition			Increase in height of follicular epithelium		
	9	14	27	9	14	27	9	14	27
Male Rats									
0	0/5	0/15	0/9	0/5	4/15	0/9	1/5	0/15	0/9
0.1	0/5	0/15	0/9	0/5	0/15	0/9	0/5	0/15	0/9
1.0	0/5	5/15*	2/9*	0/5	0/15	0/9	1/5	1/15	0/9
10.0	5/5*	15/15*	3/9*	0/5	2/15	3/9	3/5	11/15*	0/9
Female Rats									
0	0/5	0/15	0/9	0/5	0/15	0/9	0/5	0/15	0/9
0.1	0/5	0/15	1/9	0/5	0/15	0/9	0/5	0/15	0/9
1.0	0/5	5/15*	1/9	0/5	0/15	0/9	0/5	0/15	0/9
10.0	5/5*	15/15*	2/9	0/5	1/15	0/9	0/5	0/15	0/9
Male Monkeys									
0	-	1/6	-	-	1/6	-	-	0/6	-
0.1	-	NE[a]	-	-	NE	-	-	NE	-
1.0	-	NE	-	-	NE	-	-	NE	-
10.0	-	0/6	-	-	2/6	-	-	0/6	-
Female Monkeys									
0	-	0/6	-	-	3/6	-	-	0/6	-
0.1	-	NE	-	-	NE	-	-	NE	-
1.0	-	NE	-	-	NE	-	-	NE	-
10.0	-	2/6	-	-	3/6	-	-	0/6	-

*Significantly different from control value ($p < 0.05$).
[a]NE = Not examined as per protocol.

DISCUSSION:

A. According to the report:

Exposure Conditions: The authors noted that the measured exposure levels of 0.1 ± 0.025, 0.98 ± 0.277, and 9.23 ± 1.493 compared favorably with the target levels of 0.1, 1.0, and 10.0 mg/m^3, respectively. There were 6 major components in chlordane technical. The contribution of the 6 components varied with the dose level, with the more volatile components contributing slightly more at the lower concentration of chlordane. No explanation was given for this variation other than the possibility that a greater percentage of vapors may have been trapped at the lower concentration of chlordane. This same explanation was given for the differences in the percent respirable particles, 92% and 83%, in the mid- and high-dose chambers, respectively.

Rats: The authors concluded that no exposure-related effects were noted for mortality, clinical signs, body weight, food consumption, ophthalmoscopy, rectal temperature, urinalysis, and hematology. The effects noted for serum calcium levels, serum cholesterol levels, serum GDH levels, and liver cytochrome P_{450} levels were related to exposure to chlordane. In addition, microscopic changes were noted (Table 4) in the liver and thyroids. Based on the liver lesions and early changes in GDH levels, the NOEL for rats exposed to chlordane was 0.1 mg/m^3 and the LEL was 1.0 mg/m^3.

Monkeys: According to the authors, there were no findings that were considered to be exposure-related. The organ weight analyses for increased thyroid and liver weights were skewed toward increasing exposure; however, none of the values were statistically significant. Based on these data, the NOEL for monkeys exposed to chlordane was 10.0 mg/m^3 (highest dose tested) and LEL was not established.

B. According to this review:

Exposure Conditions: Although the mean exposure levels in this study were close to the target levels, no mention was made regarding the large standard deviation of the means. State-of-the-art exposure technology is available for producing much better data than those reported in this study. In addition, the variable contribution of the 6 components of chlordane technical indicates that the technology utilized in this study was out dated. No data from preliminary studies were reported to document the stability of chlordane technical at 70° C and/or the variable contribution from its 6 components. Furthermore, the particle size analyses did not adequately characterize the aerosol produced in the chamber. The aerodynamic mass median diameter and geometric standard deviation could not be calculated using the methods presented. However, from the analytical data that were reported, it appears that the animals were exposed to sufficiently high levels of respirable chlordane technical.

Rats

The increase in liver cytochrome P_{450} levels appeared to be exposure-related. However, since there were only 2 animals in each analysis group, the results were not statistically significant. The exposure-related effects were not resolved within 45 days after exposure to chlordane ceased. Based on dose-related changes in the liver and thyroids, the NOEL for rats exposed to chlordane technical is 0.1 mg/m^3 and the LEL is 1.0 mg/m^3.

Monkeys: The wide variation in body weight within each group of monkeys for both sexes may have precluded achieving statistical significance in this study. When the organ weight data for monkeys was subdivided according to sex (Table 5), there was an exposure-related increase in liver weight; an exposure-related decrease in kidney weight; and an exposure-related increase in thyroid weight for each sex. The differences were not statistically significant even for calculated organ-to-body weight or organ-to-brain weight ratios as shown in Table 6. However, the differences in liver weight appear to be biologically significant and justify establishing an effect level. For monkeys exposed to chlordane, the LEL is 10 mg/m^3 and the NOEL is 1.0 mg/m^3.

CONCLUSIONS:

Wistar rats and cynomologus monkeys exposed to aerosol/vapors of 0, 0.1, 1.0, or 10.0 mg/m^3 chlordane technical 8 hrs/day, 5 days/week for 13 weeks showed exposure-related effects in the liver and thyroids of both sexes of each species. The overall NOEL for rats, based liver and thyroid data, and for monkeys, based of liver weight data, is 0.1 mg/m^3 and the LEL is 1.0 mg/m^3.

CLASSIFICATION: Core Guideline.

TABLE 5. Weight Data For Monkeys Exposed to Chlordane for 13 Weeks

Exposure Level (mg/m^3)	Mean Body Weight (g ±S.D.)	Mean Absolute Organ Weight (g ±S.D.)				
		Brain	Liver	Kidneys	Thyroids	Adrenals
Males[a]						
0	2483±536	63.6±6.3	69.3±16.2	11.0±3.7	0.30±0.067	0.49±0.11
0.1	2663±521	62.2±3.9	63.6± 7.6	11.7±1.2	0.24±0.034	0.42±0.11
1.0	2488±527	63.1±4.8	70.8±13.3	10.4±2.7	0.34±0.13	0.43±0.074
10.0	2463±474	63.9±7.0	71.5± 9.2	10.0±1.8	0.35±0.11	0.49±0.10
Females[a]						
0	2425±301	59.8±3.4	62.8±8.3	10.5±0.97	0.29±0.064	0.44±0.033
0.1	2371±179	56.5±4.5	62.7±6.7	8.9±1.2	0.40±0.13	0.50±0.14
1.0	2500±241	57.6±4.4	62.4±9.3	9.4±1.5	0.34±0.13	0.52±0.14
10.0	2350±280	54.3±2.3	68.6±6.0	9.9±1.9	0.45±0.24	0.53±0.079

[a] Six animals per exposure group.

TABLE 6. Relative Organ Weight Data for Monkeys Exposed to Chlordane for 13 Weeks

Exposure Level (mg/m^3)	Liver		Kidney		Thyroid		Adrenal	
	Body (%)	Brain	Body (%)	Brain	Body (%)	Brain	Body (%)	Brain
Males[a]								
0	2.82±0.47	1.09±0.20	0.441±0.092	0.172±0.050	0.013±0.005	0.005±0.001	0.020±0.005	0.008±0.001
0.1	2.47±0.54	1.06±0.17	0.453±0.094	0.194±0.024	0.009±0.002	0.004±0.001	0.016±0.005	0.007±0.002
1.0	2.94±0.75	1.12±0.17	0.418±0.057	0.164±0.036	0.013±0.004	0.005±0.002	0.018±0.006	0.007±0.001
10.0	2.98±0.58	1.13±0.18	0.408±0.049	0.157±0.029	0.014±0.004	0.005±0.001	0.020±0.004	0.008±0.002
Females[a]								
0	2.68±0.28	1.06±0.16	0.437±0.042	0.177±0.020	0.012±0.003	0.005±0.001	0.018±0.002	0.007±0.001
0.1	2.67±0.42	1.12±0.18	0.374±0.042	0.158±0.030	0.017±0.005	0.007±0.002	0.021±0.005	0.009±0.003
1.0	2.52±0.45	1.09±0.22	0.375±0.051	0.163±0.025	0.014±0.005	0.006±0.002	0.021±0.007	0.009±0.003
10.0	2.94±0.35	1.27±0.14	0.423±0.064	0.184±0.039	0.019±0.010	0.008±0.005	0.023±0.005	0.010±0.002

[a] Six animals per exposure group.

TABLE 4. Incidence of Selected Liver and Thyroid Lesions in Animals Exposed to Chlordane for 13 Weeks

Exposure Level (mg/m^3)	Incidence at Week								
	LIVER						THYROID		
	Hepatocellular enlargement or vacuolation			Fatty Deposition			Increase in height of follicular epithelium		
	9	14	27	9	14	27	9	14	27
Male Rats									
0	0/5	0/15	0/9	0/5	4/15	0/9	1/5	0/15	0/9
0.1	0/5	0/15	0/9	0/5	0/15	0/9	0/5	0/15	0/9
1.0	0/5	5/15*	2/9*	0/5	0/15	0/9	1/5	1/15	0/9
10.0	5/5*	15/15*	3/9*	0/5	2/15	3/9	3/5	11/15*	0/9
Female Rats									
0	0/5	0/15	0/9	0/5	0/15	0/9	0/5	0/15	0/9
0.1	0/5	0/15	1/9	0/5	0/15	0/9	0/5	0/15	0/9
1.0	0/5	5/15*	1/9	0/5	0/15	0/9	0/5	0/15	0/9
10.0	5/5*	15/15*	2/9	0/5	1/15	0/9	0/5	0/15	0/9
Male Monkeys									
0	-	1/6	-	-	1/6	-	-	0/6	-
0.1	-	NE[a]	-	-	NE	-	-	NE	-
1.0	-	NE	-	-	NE	-	-	NE	-
10.0	-	0/6	-	-	2/6	-	-	0/6	-
Female Monkeys									
0	-	0/6	-	-	3/6	-	-	0/6	-
0.1	-	NE	-	-	NE	-	-	NE	-
1.0	-	NE	-	-	NE	-	-	NE	-
10.0	-	2/6	-	-	3/6	-	-	0/6	-

*Significantly different from control value ($p < 0.05$).
[a]NE = Not examined as per protocol.

Rats

The increase in liver cytochrome P_{450} levels appeared to be exposure-related. However, since there were only 2 animals in each analysis group, the results were not statistically significant. The exposure-related effects were not resolved within 45 days after exposure to chlordane ceased. Based on dose-related changes in the liver and thyroids, the NOEL for rats exposed to chlordane technical is 0.1 mg/m^3 and the LEL is 1.0 mg/m^3.

Monkeys: The wide variation in body weight within each group of monkeys for both sexes may have precluded achieving statistical significance in this study. When the organ weight data for monkeys was subdivided according to sex (Table 5), there was an exposure-related increase in liver weight; an exposure-related decrease in kidney weight; and an exposure-related increase in thyroid weight for each sex. The differences were not statistically significant even for calculated organ-to-body weight or organ-to-brain weight ratios as shown in Table 6. However, the differences in liver weight appear to be biologically significant and justify establishing an effect level. For monkeys exposed to chlordane, the LEL is 10 mg/m^3 and the NOEL is 1.0 mg/m^3.

CONCLUSIONS:

Wistar rats and cynomologus monkeys exposed to aerosol/vapors of 0, 0.1, 1.0, or 10.0 mg/m^3 chlordane technical 8 hrs/day, 5 days/week for 13 weeks showed exposure-related effects in the liver and thyroids of both sexes of each species. The overall NOEL for rats, based liver and thyroid data, and for monkeys, based of liver weight data, is 0.1 mg/m^3 and the LEL is 1.0 mg/m^3.

CLASSIFICATION: Core Guideline.