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REPORT ON CARCINOGENESIS BIOASSAY OF TECHNICAL GRADE CHLORDECONE (KEPONE)

CARCINOGENESIS PROGRAM, DIVISION OF CANCER CAUSE AND PREVENTION

NATIONAL CANCER INSTITUTE

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CONTRIBUTORS: This report presents a synopsis of results of a carcinogenesis bioassay conducted by the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. This research was conducted at the Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to the NCI and from November 1, 1974, as a subcontract to Tracor Jitco, Incorporated, Prime Contractor for the NCI Carcinogenesis Bioassay Program.

The results of this study were reviewed and this report was prepared by Drs. C. Cueto, Jr.[1], N. P. Page[1] and U. Saffiotti[1]. The experimental design, including dose levels were determined by Drs. R. R. Bates[1] and T. E. Shellenberger[3,4] with the assistance of Drs. J. H. Weisburger[1,2] and E. K. Weisburger[1]; Principal Investigator for the contract and supervisor of the experiments was Dr. H. P. Burchfield[3]; chemical analysis was performed by Dr. E. E. Storrs[3]; animal treatment and observations were supervised by Dr. W. E. Greer[3] with the technical assistance of Mr. G. J. Eldrige[3], Ms. D. H. Monceaux[3] and Ms. D. Broussard[3]; the pathology was conducted by Drs. E. E. Bernal[3] and B. Burrato[3]; pathology was reviewed by Drs. R. M. McCully[5], C. N. Barron[5] and R. A. Squire[1]; statistical analyses were performed by Dr. K. C. Chu[1].

A detailed technical report is in preparation which will provide details of the design, materials and methods used, conduct and results of the study.

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Summary: A carcinogenesis bioassay of technical grade chlordecone (Kepone) was conducted using Osborne-Mendel rats and B6C3F1 mice. Chlordecone was administered in the diet for 80 weeks at two dose levels, with the rats sacrificed at 112 weeks and the mice at 90 weeks. The starting dose levels were 15 and 30 ppm for male rats, 30 and 60 ppm for female rats, 40 ppm for male mice and 40 and 80 ppm for female mice. As these dose levels were not well tolerated, the dose levels were reduced during the course of the experiment such that the average dose levels were as follows: 8 and 24 ppm for male rats, 18 and 26 ppm for female rats, 20 and 23 ppm for male mice and 20 and 40 ppm for female mice. Clinical signs of toxicity were observed in both species, including generalized tremors and dermatologic changes. A significant increase ($P < .05$) was found in the incidence of hepatocellular carcinomas of high dose level rats and of mice at both dose levels of chlordecone. The incidences in the high dose groups were 7% and 22% for male and female rats (compared with 0 in controls for both sexes) and 88% and 47% for male and female mice (compared with 16% for male room controls and 0 in females); for the low dose groups of mice the incidences were 81% for males and 52% for females. In addition, the time to detection of the first hepatocellular carcinoma observed at death was shorter for treated than control mice and, in both sexes and both species, it appeared inversely related to the dose. In chlordecone-treated mice and rats extensive hyperplasia of the liver was also found. The incidence of tumors other than in the liver for chlordecone-treated groups did not appear significantly different from that in controls.

I. INTRODUCTION:

Chlordecone is the common name for the chlorinated insecticide, decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one, which is commercially available under the trade name of Kepone. The compound, first introduced in 1958, has been used as an insecticide against leaf-eating insects, ants and cockroaches, and as a larvicide against flies.

The testing of chlordecone is a part of the carcinogenesis bioassay of a series of halogenated chemicals, including many pesticides, present in the general and occupational environment of humans. Chlordecone was selected for inclusion in this series because of its chemical structure, its use, and its stability.

II. MATERIALS AND METHODS:

Chemical - The material used was technical grade chlordecone, in the hydrate form. The compound was purchased as a single lot from City Chemical Company, New York, New York, and was manufactured by Allied Chemical Company, Houston, Texas. The purity of the product was determined by the Gulf South Research Institute (GSRI) Chemistry Department. Other than chlordecone, the other major material was determined to be water involved in the hydration of the

carbonyl group. The GSRI gas chromatographic analysis (electron capture detector) showed chlordecone as roughly 92% of the total peak area which agrees with the manufacturer's assay of the batch used. With a flame ionization detector, the chlordecone peak represented about 98-99% of the total peak area. Gas chromatographic analysis with either electron capture or flame ionization detector showed at least two small unidentified contaminants, together totalling 1.5-1.8% of the total peak area. Chlordecone readily hydrates on exposure to room temperature and humidity, and is normally used as a mono- to tri-hydrate (1). Further analysis and purification of the technical material was not attempted.

Dietary Preparation - All diets were formulated using finely-ground Wayne rat laboratory feed to which was added the required amount of chlordecone for each dietary level. Small amounts of acetone were used as an aid to uniformly disperse the test compound in the feed. The diets were mechanically mixed to assure homogeneity and to allow for evaporation of the acetone. Each final formulated diet, including the control, contained 2% corn oil, purchased from a commercial distributor and produced by Opelousas Refinery Company, Opelousas, Louisiana, added primarily as a dust suppressant. No chemical analysis was made of the corn oil. Water and the formulated diets were made available ad libitum to the experimental animals and were replaced three times per week.

Animals - The Osborne-Mendel rat, procured from Battelle-Memorial Institute, Columbus, Ohio, and the B6C3F1 hybrid mouse (C57B1/6 female x C3H/He male), procured from Charles River Breeding Laboratories, Incorporated, Cambridge, Massachusetts, were used in this study. Upon receipt, both species were quarantined for 7-10 days, determined to be free from observable disease or parasites, randomly assigned to experimental groups, and started on treatment at approximately 6 weeks of age.

Animal Husbandry - All animals were housed in air-conditioned, temperature and humidity-controlled rooms. Chlordecone was the only compound under test in the room where the rats were housed, while the mice were housed in a room where toxaphene, chlordane and chlordecone were concurrently under test. Rats were maintained in individual suspended wire cages, and mice were housed in plastic cages with filter caps, five per cage for female, two-three per cage for males. Clean cages for both species and filter caps for mouse cages were provided weekly. Absorbent sheets under the rat racks were changed three times per week. Cages on individual racks as well as racks within the room were rotated on a weekly basis to minimize potential position effects.

Clinical and Pathology Examinations - All animals were observed for signs of toxicity twice daily and weights were recorded on a monthly basis. Those appearing moribund at time of clinical examination

were sacrificed and necropsied. In the chronic study, the following tissues were taken from sacrificed animals and, where possible, from animals found dead: brain, pituitary, lymph nodes (cervical and mesenteric), thyroid, parathyroid, salivary glands, lung, heart, diaphragm, stomach (pylorus and fundus), duodenum, jejunum or ileum, large intestine, pancreas, adrenal gland, kidney (longitudinal and transverse), liver, skin, entire gonads, bladder, prostate or uterus, and femur with marrow. Tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and microscopically examined.

Histopathological examination and diagnosis were conducted at GSRI. A review of the pathology findings was conducted by pathologists at Tracor Jitco, Inc., with special attention given to liver lesions. National Cancer Institute pathologists also reviewed several of the liver lesions.

Data Recording and Statistical Analysis - Pertinent data on this experiment were recorded in an automatic data processing system known as the Carcinogenesis Bioassay Data System (2). The data elements, as recommended by the International Union Against Cancer (UICC) (3), include details on the chemical, the animals, experimental design, clinical observations, survival, monthly weights, and individual pathology results. Data

tables were generated for statistical analysis and inclusion in the report following pathology review and verification of data transcription. The statistical analysis of tumor incidence reported in Table II was performed using the Fisher Exact Test (4a) to compare the controls to each dose level. A correction for simultaneous comparison of controls was made using the Bonferroni inequality (5). Thus, a corrected P value < 0.05 was deemed significant. In addition, the Armitage test for linear trend in proportions (4b) was used. This analysis determines if the slope of a dose-response plot is statistically different from zero ($P < 0.05$), assuming a linear trend. If the associated statistic, which detects departure from linear trend, was not significant ($P > 0.05$) and the Armitage statistic was significant ($P < 0.05$), the latter P value was reported in Table II.

Design of Chronic Studies - Preliminary toxicity studies were conducted to obtain an estimated maximum tolerated dose (MTD) for the long-term (80 weeks) administration of chlordecone in the diet. These studies consisted of treating the animals for 6 weeks with various dose levels of chlordecone and observing them for an additional 2 weeks. Based primarily upon survival and weight gain (as compared to controls) the estimated MTD's were calculated as 30 ppm for male rats, 60 ppm for female rats and 40 and 80 ppm for male and female mice respectively. As can be seen from Table I, these dose levels were overestimated and they were found not to

be adequately tolerated, necessitating reductions at least once in all groups. Actual dose levels and days on treatment at each level are presented in Table I. A "time weighted average dose" has also been calculated for each group and is included in Table I. Treatment with chlordecone was for 80 weeks with sacrifice of all survivors by 90 weeks in the case of mice and 112 weeks for rats.

III. RESULTS:

A. Rats

1. Survival - As presented in Table II, the survival at terminal sacrifice (112 weeks) for both males and females at the high dose levels is considerably less than controls and it appears treatment-related. Survival at other time intervals during the study are also presented in Table II.

2. Clinical Signs - During the first 4 months of the study the appearance and behavior of the low level animals were generally comparable with the controls. Some high level males during this period experienced epistaxis and bleeding of the eyes, and 4 animals had died or were sacrificed. At week 5 a majority of the high level females experienced generalized tremors along with a slight drop in food

consumption. Many of the treated animals also showed a loss of body weight. At week 28 many low level females were experiencing generalized tremors. Body weights of this group increased slightly during this period but food consumption was normal. Adverse clinical signs in all treatment groups were noted at a low or moderate incidence during the remainder of the first year, with a gradually increasing frequency in treated animals during the second year of the study. These signs included rough hair coats, dermatitis, anemia and tremors. Some treated females showed evidence of vaginal bleeding. Surviving animals at termination of study generally exhibited a very poor physical condition.

3. Pathology - In the rats, two types of tumors were found: neoplastic nodules and hepatocellular carcinomas. The neoplastic nodules were composed of altered cell populations appearing to arise de novo in the liver without evidence of necrosis or fibrosis. There was compression of adjacent parenchyma along at least part of the border of the nodule. Within the nodule, there was abnormal plate arrangment although cell plates were usually only one cell layer thick. The cells within the nodule ranged from basophilic to eosinophilic or clear, with one type predominating or occasionally a mixture. Mitotic figures were occasionally present.

The hepatocellular carcinomas were large, poorly circumscribed masses. There were isolated islands of hepatocytes enveloped by sinusoidal lining cells, abnormal liver plates, two or more cells in thickness and arranged in bizarre histologic patterns. On occasion, pseudoglandular formation was observed. The cells were generally basophilic with varying degrees of nuclear atypia and some mitotic figures. All carcinomas were well-differentiated; no vascular invasion nor metastases were observed in the material examined. Table II gives the incidence of hepatocellular carcinomas and their statistical analysis.

For female rats, a significant hepatocellular carcinoma induction was found 10/45 at high dose, compared with 0/100 controls). For male rats, 3/44 high dose rats had hepatocellular carcinomas as compared to 0/10 matched controls, and the difference was not statistically significant at the 95% confidence level. However, hepatocellular carcinomas are rare in Osborne-Mendel rats and when the pooled control group is used (0/105) the difference is statistically significant ($P < 0.05$). These data are displayed in Figure 1.

Neoplastic nodules were diagnosed in 2 low dose male rats, with none in controls nor in the high dose group, and in

2 high dose female rats, with 1 in the matched controls and none in the low dose group. Extensive liver hyperplasia, fatty infiltration and degeneration were also found in rats of both sexes in both dose groups. No liver hyperplasia was seen in the matched control groups.

With the exception of liver tumors, the tumors in treated and control groups did not differ significantly in type and incidence. Table III presents all tumors by anatomic site.

B. Mice

1. Survival - A reduction in survival occurred in treated male mice as compared to the controls (Table II). In contrast, the survival of treated females was comparable to that of controls with most liver tumors found at terminal sacrifice.

2. Clinical Signs - During the first year of the study, the appearance and behavior of the low level males and females and the control mice were generally comparable. Alopecia (generalized and/or localized), sores on the tail and rough hair coats were evident, especially among the males, apparently due to fighting. In contrast, the high level female group

developed generalized tremors during the first week of the study which persisted until terminal sacrifice; however, the intensity decreased in the majority of animals toward the end of the study. Some individual mice in the high male group had severe tremors which did not appear to affect body weight or food intake. Approximately 20% of this high male group were highly excitable during the second year. Bloating or abdominal distention was noted first in the high level males at week 45 and in the high level females beginning at week 68. Also during the second year several high level males and a few low level males had palpable masses (nodules) in the abdominal area.

3. Pathology - The hepatocellular tumors in mice were all well differentiated. They varied from well demarcated nodules which compressed adjacent parenchyma to large masses which both compressed and extended into adjacent liver. Within the tumors, there were abnormal plate arrangements including, in some, trabecular patterns several cell layers thick. The tumor cells were usually basophilic, sometimes with hyperchromatic polymorphic nuclei. There was little cellular anaplasia and mitotic figures were variable in number. No vascular invasion nor metastases were observed in the material examined.

All these tumors were classified as hepatocellular carcinomas. Their incidence and statistical analysis are given in Table II. They were detected in 39/48 male mice at the lower dose and in 43/49 males at the higher dose, as well as in 26/50 female mice at the low dose and in 23/49 females at the high dose. An abnormally high incidence was found in the matched control group of male mice (6/19). In the 30 other control male mice, kept in the same room, only 2 hepatocellular carcinomas (8%) were found, the usual rate observed for this strain of mouse. Pooling all these control groups results in an overall incidence of 8/49 (16%). These data are displayed in Figure 2. In addition, decrease in the time to first tumor detection was noted in male mice at necropsy in both dose groups as compared to matched or room controls (Table II). Statistical analysis indicated a significant incidence of hepatocellular carcinomas at both dose levels of both male and female mice.

In addition to hepatocellular carcinomas, extensive liver hyperplasia was found in male and female mice in both high and low dose groups. A few matched controls of each sex also had liver hyperplasia although the incidence was quite low as compared to the treated groups.

Other than liver tumors, no other tumor type appeared in significant numbers as illustrated in Table IV.

IV. DISCUSSION:

The results of this study clearly suggest that technical grade chlordecone, as administered under the test conditions described, induced hepatocellular proliferative lesions, including hepatocellular carcinomas, in both sexes of rats and mice.

The term "hepatocellular carcinoma" was used to diagnose proliferative lesions of the livers in mice which, in the judgment of the pathologists, had the potential or the capacity for progressive growth, invasion, metastasis and for causing death of the host. This judgment was based upon the cytologic and histologic features of the neoplasms and the knowledge that lesions with the same morphologic characteristics as those observed have exhibited malignant biologic behavior.

The terms "neoplastic nodule" and "hepatocellular carcinoma" used to diagnose proliferative liver lesions in rats were based upon the morphologic criteria and nomenclature recently reported from a workshop on the classification of specific hepatocellular lesions in rats (6).

The schedule of treatment and sacrifice involved administration of the test compound for only 80 weeks followed by an observation period of 10 weeks in mice and 32 weeks in rats. The tumors found at terminal sacrifice were therefore observed well after

termination of treatment, but their potential spread and dissemination during the natural lifespan of the animals could not be evaluated because the observations were cut off at 90 weeks for mice and 112 weeks for rats.

In regard to the animal models, the Osborne-Mendel rat was chosen because of the experience gained by the Food and Drug Administration where this strain has been used for many years as a general purpose test animal. In addition, it was found sensitive to the carcinogenicity of CCl_4 by subcutaneous injection (7). However, the Osborne-Mendel rat was refractory to the induction of liver cancer by N-2-Fluorenylacetamide (FAA) (8). Data on susceptibility of various rat strains have been reviewed (9). The B6C3F1 strain of mice has been extensively used by NCI for carcinogenesis bioassays. Current experience in the NCI Program indicates an overall incidence of hepatocellular carcinomas reported in control mice of 7-10% in males and approximately 1% in females. For male mice, the matched controls, but not the other room controls, showed an abnormally high incidence. Although with the strict procedures used for diet preparation, a mixup in feed appears highly improbable, the possibility of environmental contamination of the controls cannot be ruled out. Even so, the increase in hepatocellular carcinomas in male mice at both dose levels was statistically significant ($P < .01$) using either pooled or matched controls. As we expected, no spontaneous hepatocellular carcinomas were

seen in rat controls of either sex nor in the female mouse controls. The significant response in the female mouse and both male and female rats is consistent with and reinforces the findings in the male mice.

The material used was considered adequately pure with no more than 2% impurities other than water. Chlordecone is normally available and used in a hydrated form. It is conceivable that a minor impurity could contribute to the carcinogenic response observed for the technical product but only further studies with a more purified material could settle this question.

A concern in any testing program is the possible influence of extraneous factors. As two other compounds were on test with mice in the same room the possibility of a low level exposure in the air must be considered. As all of the compounds are low in volatility, the use of filtered, fully-enclosed animal cages restricted the potential for cross-contamination. As rats were maintained in a room restricted only to the chlordecone experiment, such potential cross-contamination from other test compounds should not be of concern in this case.

The methodology used in these studies varied somewhat from current NCI procedures (10) in that: (a) the subchronic toxicity testing period was for 42 rather than 90 days; (b) the treatment period

was for 18 months rather than 24 months; and (c) the number of matched controls was 10-20 rather than 50 as is currently used. It is felt that in spite of these differences this experiment remains useful as a screening test for carcinogenicity. The shorter subchronic toxicity test did not accurately predict the maximum tolerated doses and as a result, dose levels had to be reduced during the course of the experiment. A 24-month exposure period might have induced an even greater response, especially in rats, than was found in this experiment. The use of pooled controls, and particularly room controls, compensates for the small numbers of matched controls. The response in all groups but the male rat was significant ($P < .05$) even using the small matched control groups.

Changes in dosage of chlordecone during the study were required to avoid toxic effects. For this reason, and because the basic design includes only two dose levels, a quantitative assessment of dose response relationships is not possible.

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Table I. Dosage Schedule - Concentration of Chlordecone in Feed

SPECIES	SEX	DOSAGE GROUP	DOSE	CONCENTRATION IN FEED (PPM)	TREATMENT PERIOD (DAYS)	TIME WEIGHTED AVERAGE DOSE[1] (PPM)
Rat (OM)	M	Low	Initial	15	147	--
			Final	5	413	8
	M	High	Initial	30	386	--
			Intermediate	10	99	--
			Final[2]	10	75	24
	F	Low	Initial	30	220	--
			Intermediate	15	166	--
			Final	5	174	18
	F	High	Initial	60	42	--
			Intermediate	30	344	--
			Final	10	174	26
Mice (B6C3F1)	M	Low	Initial	40	134	--
			Intermediate	20	161	--
			Final	10	265	20
	M	High	Initial	40	90	--
			Final	20	470	23
	F	Low	Initial	40	134	--
			Intermediate	20	161	--
			Final	10	265	20
	F	High	Initial	80	134	--
			Intermediate	40	161	--
			Final	20	265	40

NOTES: 1 Time-weighted average dose = Σ (dose concentration x treatment period in days)/ Σ (no. days receiving each dose
2 This group received Chlordecone on alternate weeks only during the final 75 days of treatment. Time-weighted average dose was calculated using only the days an animal received a dose.

TABLE II. Carcinogenesis Bioassay of Chlordecone (Technical Grade - Kepone)

SPECIES	SEX	DOSE[1]	EFFECTIVE[2] NUMBER	PERCENT SURVIVAL WEEKS 52	78	TERM.[3]	ANIMALS WITH HEPATOCELLULAR CARCINOMAS: TIME TO[4] TUMOR (WEEKS)	NUMBER	PERCENT[5]	P VALUES[6] MATCHED CONTROLS	POOLED CONTROLS	NUMBER[7] OTHER TBA
Rat	M	Control[8]	105	--	--	63	--	0	0	--	.0034*	NA**
(OM)	M	Control[9]	10	100	90	90	--	0	0	--	--	3
	M	Low	50	96	90	60	112	1	2	1.000	.6452	21
	M	High	44	84	60	42	• 108	3	7	1.000	.0490#	14
	F	Control[8]	100	--	--	61	--	0	0	--	--	NA**
	F	Control[9]	10	100	90	70	--	0	0	--	--	6
	F	Low	49	86	78	56	87	1	2	1.000	.6577	25
	F	High	45	84	72	40	83	10	22	.2183	.0000#	20
Mouse	M	Control[10]	49	--	--	92	87	8	16	--	.0600*	NA**
(B6C3F1)	M	Control[9]	19	100	95	90	87	6	32	.0000*	--	0
	M	Low	48	96	80	58	70	39	81	.0004#	.0000#	1
	M	High	49	90	54	50	62	43	88	.0000#	.0000#	0
	F	Control[10]	40	--	--	85	--	0	0	--	--	NA**
	F	Control[9]	10	100	100	90	--	0	0	--	--	0
	F	Low	50	98	94	84	87	26	52	.0031#	.0000#	0
	F	High	49	96	92	84	76	23	47	.0081#	.0000#	2

NOTES: 1 See TABLE 1 for actual dosage and for schedule of dosage changes.
2 Total number of animals initially placed on test minus number missing or autolyzed.
3 Termination of study: 112 weeks for rats and 90 weeks for mice.
4 Time to detection of first hepatocellular carcinoma at necropsy.
5 Percent of animals with hepatocellular carcinoma based on EFFECTIVE NUMBER of animals used.
6 One-tail P value determined by the Fisher Exact Test for 2 x 2 contingency table of control versus dose level with correction for use of simultaneous comparison of control unless otherwise stated. # - Statistically significant (P < .05). * - One-tail P value from Armitage test for linear trend in proportion is highly significant, and P > .05 for departure from linearity.
7 Animals with tumors other than liver.
8 Pooled controls with birthdate within 3 months of matched controls and maintained in different rooms from treated animals during the study.
9 Matched controls for females; pooled controls for males with 1/2 matched for each dose.
10 Pooled controls with birthdate within 4 months of matched controls, and maintained in same room as treated animals.

NA** Exact number not available at present.

TABLE III. Number of *Rats* with Tumors by Anatomic Site (Chlordecone)

(Percentages by System and by Organ Are Based on the Effective Number of Animals)

	MALES			FEMALES		
	CONTROLS	LOW DOSE	HIGH DOSE	CONTROLS	LOW DOSE	HIGH DOSE
EFFECTIVE NUMBER OF ANIMALS	10(100%)	50(100%)	44(100%)	10(100%)	49(100%)	45(100%)
ANIMALS WITH TUMORS	3(30%)	24(48%)	16(36%)	7(70%)	29(59%)	31(69%)
INTEGUMENTARY SYSTEM		1(2%)*				1(2%)
SUBCUT. TISSUE		1(2%)				
LEIOMYOSARCOMA		1				
SKIN						1(2%)
FIBROMA						1
RESPIRATORY SYSTEM			1(2%)			
LUNG			1(2%)			
ALVEOLAR/BRONCHIOLAR CARCINOMA			1			
DIGESTIVE SYSTEM		4(8%)	5(11%)	1(10%)	5(10%)	19(42%)
LIVER		4(8%)	3(7%)	1(10%)	3(6%)	15(33%)
HEPATOCELLULAR CARCINOMA		1	3		1	10
NEOPLASTIC NODULE		2		1		2
HEMANGIOMA					2	1
SARCOMA, NOS						2
MYELOMA		1				
LIVER/BILE DUCT			2(5%)		2(4%)	4(9%)
HAMARTOMA			1		1	4
PAPILLARY ADENOMA (BILE DUCT ONLY)					1	
BILE DUCT ADENOMA (BILE DUCT ONLY)			1			
CECUM			1(2%)			
LEIOMYOSARCOMA			1			
URINARY SYSTEM			2(5%)			
KIDNEY			1(2%)			
MIXED TUMOR MALIG.			1			
URINARY BLADDER			1(2%)			
PAPILLOMATOSIS			1			
ENDOCRINE SYSTEM	2(40%)	20(40%)	7(16%)	3(30%)	16(33%)	9(20%)
PITUITARY	2(40%)	12(24%)	6(14%)	3(30%)	13(27%)	4(9%)
CHROMOPHOBE ADENOMA	2	12	5	3	13	4
ADENOCARCINOMA			1			
THYROID		9(18%)			3(6%)	3(7%)
FOLLICULAR-CELL CARCINOMA		3				1
FOLLICULAR-CELL ADENOMA		2			1	
C-CELL ADENOMA		3			2	1
C-CELL CARCINOMA		1				1
PARATHYROID			1(2%)			
ADENOMA			1			
PANCREATIC ISLETS		1(2%)	1(2%)		1(2%)	
ISLET-CELL ADENOMA		1	1		1	
ADRENAL		1(2%)				2(4%)
CORTICAL ADENOMA		1				2
HEMATOPOIETIC SYSTEM		1(2%)	2(5%)		1(2%)	2(4%)
SPLEEN			1(2%)		1(2%)	
HEMANGIOMA			1		1	
BONE MARROW		1(2%)				
MYELOMA		1				
MULTIPLE ORGAN			1(2%)			2(4%)
LEUKEMIA GRANULOCYTIC			1			1
RETICULUM-CELL SARCOMA						1

* COLUMNS ARE OFFSET ACCORDING TO ORGAN SYSTEM, SPECIFIC ORGAN AND TUMOR TYPE.

TABLE III. Number of *Rats* with Tumors by Anatomic Site (Chlordecone) (Continued)

(Percentages by System and by Organ Are Based on the Effective Number of Animals)

	MALES			FEMALES		
	CONTROLS	LOW DOSE	HIGH DOSE	CONTROLS	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM	1(20%)*	1(2%)	2(5%)	5(50%)	13(27%)	5(11%)
MAMMARY GLAND	1(20%)	1(2%)	2(5%)	5(50%)	7(14%)	2(4%)
FIBROADENOMA		1	1	4	4	1
ADENOMA			1	2	1	
FIBROMA	1					
ADENOCARCINOMA					2	
FIBROLIPOMA						1
UTERUS					4(8%)	1(2%)
ENDOMETRIAL/STROMAL POLYP					3	1
MALIG. LYMPHOMA					1	
UTERUS/MYOMETRIUM						1(2%)
SQUAMOUS-CELL CARCINOMA						1
OVARY					1(2%)	1(2%)
ARRHENOBLASTOMA					1	
GRANULOSA-CELL TUMOR						1
CERVIX UTERI					1(2%)	
SQUAMOUS-CELL CARCINOMA					1	
NERVOUS SYSTEM				1(10%)		
PERIPHERAL NERVE				1(10%)		
NEURILEMOMA				1		
MUSCULOSKELETAL SYSTEM					1(2%)	
SKELETAL MUSCLE					1(2%)	
SARCOMA					1	
SPECIAL SENSE ORGANS					1(2%)	
EYE					1(2%)	
NEURILEMOMA MALIG.					1	
ALL OTHER SYSTEMS						1(2%)
MULTIPLE ORGAN						1(2%)
SQUAMOUS-CELL CARCINOMA						1

* COLUMNS ARE OFFSET ACCORDING TO ORGAN SYSTEM, SPECIFIC ORGAN AND TUMOR TYPE.

TABLE IV. Number of Mice with Tumors by Anatomic Site (Chlordecone)

(Percentages by System and by Organ Are Based on the Effective Number of Animals)

	MALES			FEMALES		
	CONTROLS	LOW DOSE	HIGH DOSE	CONTROLS	LOW DOSE	HIGH DOSE
EFFECTIVE NUMBER OF ANIMALS	19(100%)	48(100%)	49(100%)	10(100%)	50(100%)	49(100%)
ANIMALS WITH TUMORS	6(31%)	39(81%)	43(88%)	0(0%)	27(54%)	25(51%)
RESPIRATORY SYSTEM			2(4%)*			
LUNG			2(4%)			
ALVEOLAR/BRONCHIOLAR ADENOMA			2			
DIGESTIVE SYSTEM	6(31%)	39(81%)	43(88%)		26(52%)	24(49%)
LIVER	6(31%)	39(81%)	43(88%)		26(52%)	23(47%)
HEPATOCELLULAR CARCINOMA	6	39	43		26	23
CECUM						1(2%)
HEMANGIOMA						1
URINARY SYSTEM		1(2%)				
URINARY BLADDER		1(2%)				
TRANSITIONAL-CELL CARCINOMA		1				
HEMATOPOIETIC SYSTEM					1(2%)	
MULTIPLE ORGAN					1(2%)	
ACUTE LYMPHOCYTIC LEUKEMIA					1	
REPRODUCTIVE SYSTEM						1(2%)
OVARY						1(2%)
CYSTADENOMA						1

* COLUMNS ARE OFFSET ACCORDING TO ORGAN SYSTEM, SPECIFIC ORGAN AND TUMOR TYPE.

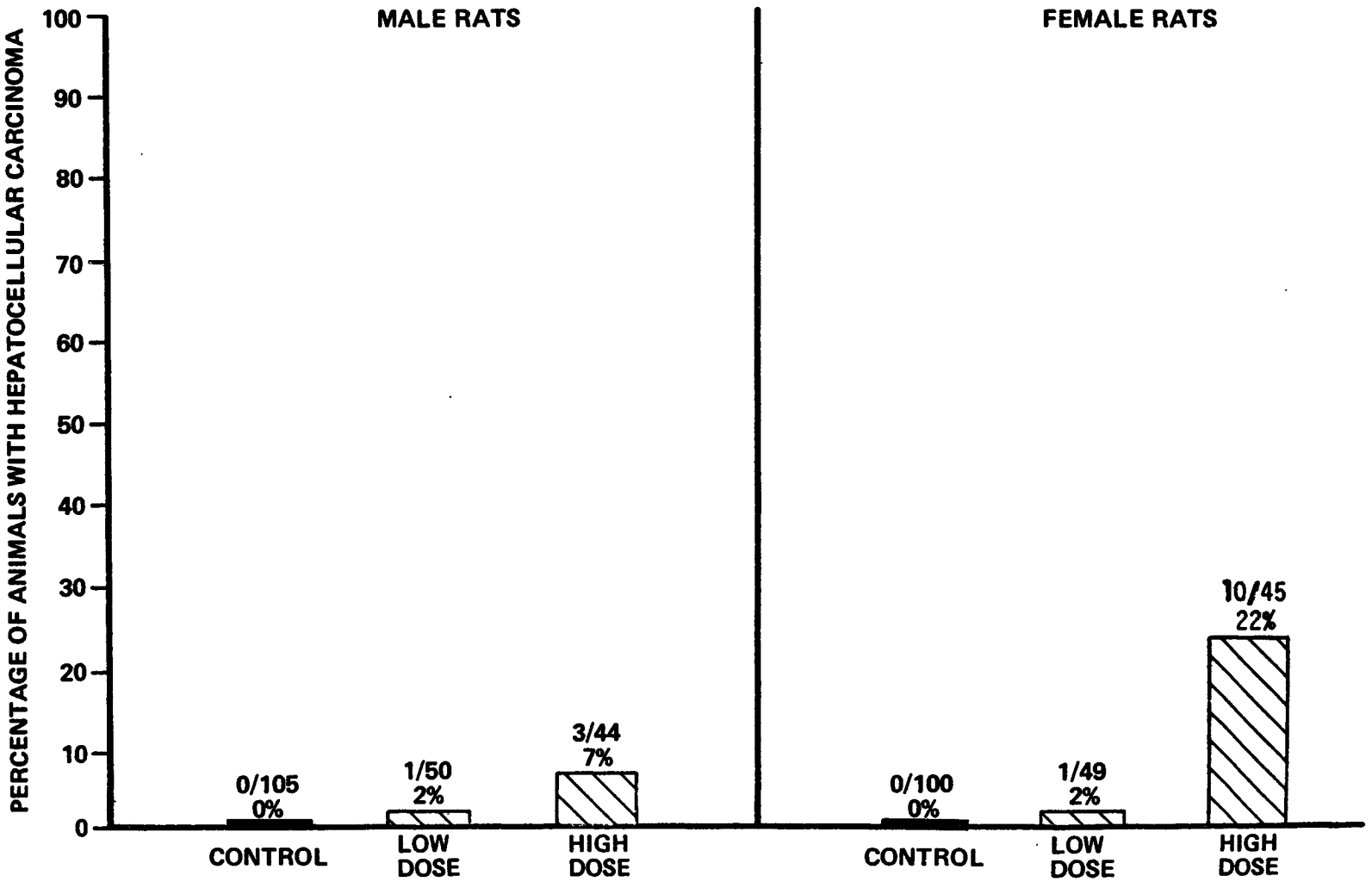

Figure 1. Comparison of Incidence of Hepatocellular Carcinoma (Chlordecone)

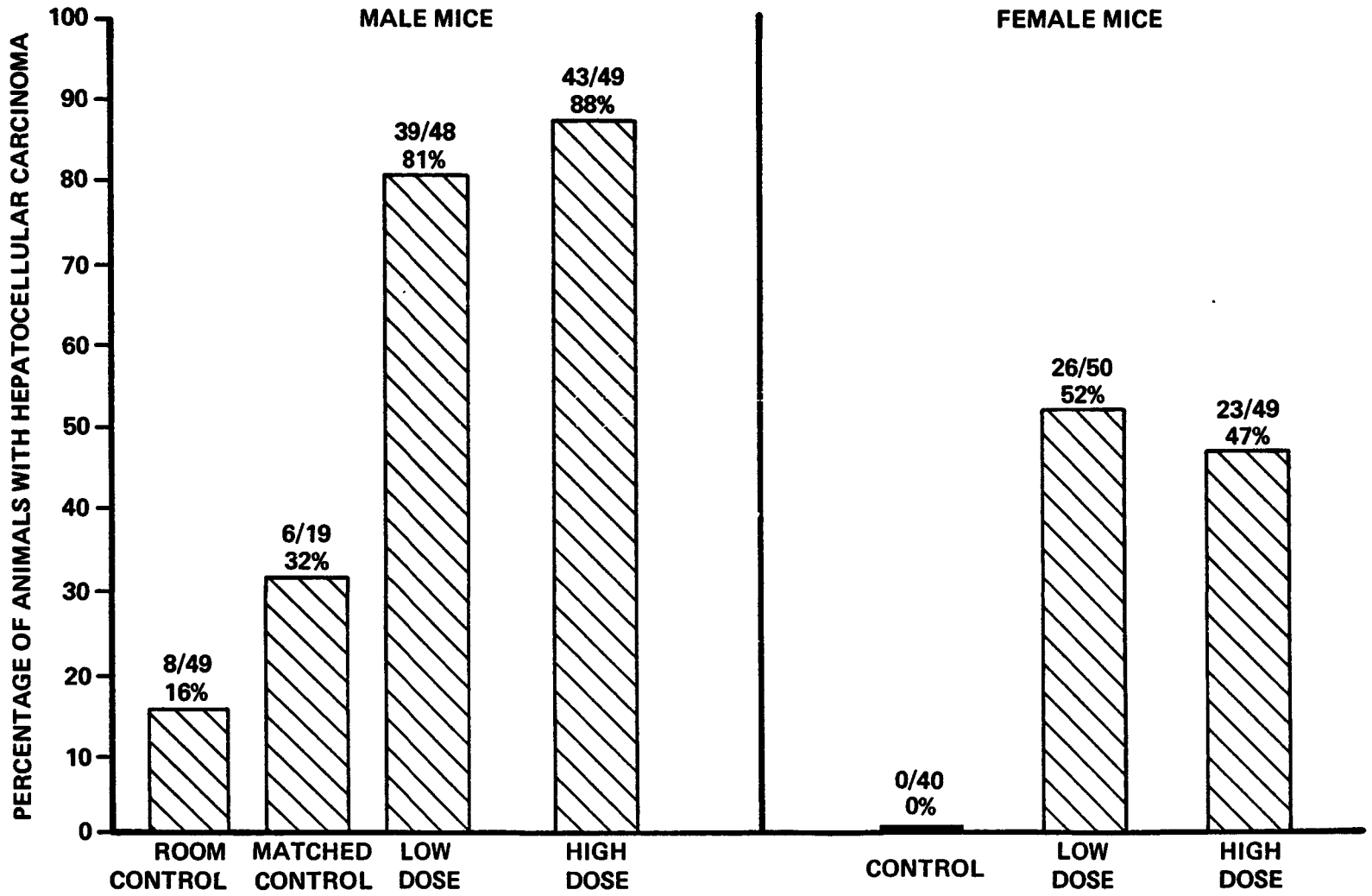

Figure 2. Comparison of Incidence of Hepatocellular Carcinoma (Chlordecone)

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