Item ID Number	02747 ☐ **Not Scanned**
Author	
Corporate Author	National Cancer Institute, United States Department of
Report/Article Title	Bioassay of Hexachlorophene for Possible Carcinogenicity
Journal/Book Title	
Year	1978
Month/Day	
Color	☐
Number of Images	59
Description Notes	CAS No. 70-30-4; NCI-CG-TR-40; Dhew Publication No. (NIH) 78-840

Capt Young/EC/3668/yc/17 May 78/#540

EC

Carcinogenicity of Hexachlorophene

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National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 40
1978

BIOASSAY OF HEXACHLOROPHENE FOR POSSIBLE CARCINOGENICITY

CAS No. 70-30-4

NCI-CG-TR-40

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

BIOASSAY OF

HEXACHLOROPHENE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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CONTRIBUTORS: This report presents the results of the bioassay of hexachlorophene for possible carcinogenicity, conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. The bioassay was conducted by Stanford Research Institute, Menlo Park, California, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design and doses were determined by Drs. R. R. Bates[1,2], D. C. L. Jones[3], D. P. Sasmore[3], G. W. Newell[3], and R. M. Elashoff[4], and Mr. W. E. Davis[3]. The principal investigator was Dr. D. C. L. Jones; the technical supervisor of animal treatment, observation, and data handling was Mr. W. E. Davis; necropsy and tissue fixation were supervised by Dr. D. P. Sasmore.

Histopathologic examinations were performed by Dr. H. Elster[5], and the diagnoses included in this report represent his interpretation. Neoplasms and compound-related hyperplastic lesions were reviewed by Dr. W. M. Busey[5], who also prepared the interpretive pathology summary included in this report.

Animal pathology tables and animal survival tables were compiled at EG&G Mason Research Institute[7]. The statistical analyses were performed by Dr. J. R. Joiner[8], using methods selected for the bioassay program by Dr. J. J. Gart[9]. Chemicals used in this bioassay were analyzed at Stanford Research Institute, and the analytical results were reviewed by Dr. C. W. Jameson[8].

This report was prepared at Tracor Jitco[8] under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. Marshall Steinberg, Director of the Bioassay Program; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Ms. L. A. Waitz and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The statistical analysis was reviewed by one or more members of the Mathematical Statistics and Applied Mathematics Section of NCI[9]: Dr. John J. Gart, Mr. Jun-mo Nam, Dr. Hugh M. Pettigrew, and Dr. Robert E. Tarone.

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SUMMARY

A bioassay of hexachlorophene for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats.

Groups of 24 rats of each sex were administered hexachlorophene at one of three doses, either 17, 50, or 150 ppm, for 105-106 weeks. Higher doses of 200-600 ppm, used in 8-week subchronic studies, induced neuronal necrosis of the brain and clinical signs of toxicity. Matched-control groups consisted of 24 untreated rats of each sex. All surviving animals were killed at 105-106 weeks.

Mean body weights of the rats were unaffected by the hexachlorophene, and no clinical signs of toxicity were recorded. Survival also was unaffected, and adequate numbers of animals survived, permitting meaningful evaluation of the incidences of late-appearing tumors.

No tumors were present in a statistically significant incidence at any site in the treated rats.

It is concluded that under the conditions of this bioassay, hexachlorophene did not induce malignant or benign tumors in Fischer 344 rats.

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I. INTRODUCTION

Hexachlorophene (CAS 70-30-4; NCI C02653) is a chlorinated bisphenol which was widely used as an antiseptic prior to 1972. It is highly effective against gram-positive bacteria and many pathogenic fungi (Harvey, 1975). The chemical was used as a surgical scrubbing agent, in bathing newborns to prevent staphylococcal skin infection, and in many over-the-counter drugs such as mouthwashes, powders, cosmetics, soaps, and skin cleansing agents. In 1972, the Food and Drug Administration restricted the uses of hexachlorophene because of neurologic toxicity and deaths that occurred following its misuse on infants (FDA, 1972; FDA, 1976).

Agricultural chemicals containing hexachlorophene are currently registered for use on three vegetables and a few ornamental plants to control mildew and bacterial spot. Limited industrial and household applications are also permitted for disinfectant purposes (EPA, 1975).

This bioassay of hexachlorophene was conducted as a part of a larger study that was designed to assess the combined effects of a group of chemicals, including known or suspected carcinogens. Only the results of the study of the administration of hexachlorophene are reported herein.

II. MATERIALS AND METHODS

A. Chemical

Hexachlorophene is the generic name for 2,2′-methylenebis-(3,4,6-trichlorophenol). The chemical was obtained in two batches (both from Lot No. 91387), from the Givaudan Corporation, Clifton, New Jersey. The purity of these batches was determined to be 98-100% by analyses at Stanford Research Institute. The melting point was 161-162°C (literature: 161°C), and the elemental analyses (C, H, Cl) were correct for $C_{13}H_6Cl_6O_2$, the molecular formula of hexachlorophene. The identity of the chemical was confirmed by nuclear magnetic resonance, infrared, and ultraviolet spectra, which were in agreement with the structure and matched the spectra given in the literature. No attempt was made to identify or quantitate impurities.

The chemical was stored at room temperature in clear glass bottles.

B. Dietary Preparation

All diets were formulated every 2 weeks using Low Fat Lab Chow® (Ralston Purina Co., St. Louis, Mo.). A stock diet was prepared by first grinding the chemical to a fine powder and then mixing by hand a weighed amount with a small amount of feed. Corn oil

and more feed were then added to give a final concentration of 2,000 ppm hexachlorophene and 3% corn oil, and mixed in a Hobart blender for 30 minutes. Each stock diet was analyzed for content of hexachlorophene by a method involving extraction, Florisil® chromatography, and quantitation by gas-liquid chromatography. Concentrations of 2,000 ppm ± 200 ppm were considered acceptable for use in preparing test diets. Hexachlorophene at 2,000 ppm in the stock diet was found to be stable when held in rat feeders at room temperature for a 2-week period.

To obtain test diets having appropriate concentrations of hexachlorophene, the stock diet was diluted, as required, with control diet containing 3% corn oil and mixed in a Hobart blender for 7 minutes. The stock and test diets were stored at room temperature in covered plastic containers.

C. Animals

Male and female Fischer 344 rats, obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were used in these bioassays. The rats were obtained from Simonsen Laboratory, Gilroy, California. On arrival at the laboratory, all animals were quarantined for 2 weeks as an acclimation period. Following this period, all males gaining less than 25 grams, all females gaining less than 15 grams, and all unhealthy

animals were culled. The remaining animals were assigned to cages, one per cage, until each cage contained three animals. Cages were then numbered and assigned to control and treated groups using a computer-generated randomization table. Rats were ear-clipped for individual identification.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature was maintained at 22°C with a range from 21-24°C, and the relative humidity was maintained at approximately 45%. The room air was changed 10 times per hour and was maintained under positive pressure relative to the access halls. Fluorescent lighting provided illumination 12 hours per day. Food and water were available ad libitum. Drinking water was softened, filtered, sterilized with ultraviolet light, and supplied by means of an automatic watering system.

The rats were housed three per cage in polycarbonate cages equipped with disposable polyester woven filter tops. Autoclaved hardwood chips (Iso-Dri®, Becton, Dickinson, and Carworth, Warrensburg, N. Y.) were used as bedding. The cages were changed, washed, and provided with fresh bedding twice per week. Filter tops were replaced once per month.

Rats fed hexachlorophene were housed in the same room as rats treated with aflatoxin B_1 (CAS 1162-65-8), N-nitrosodipentylamine (CAS 13256-06-9), or Aroclor® 1254 (CAS 27323-18-8).

E. Subchronic Studies

Subchronic feeding studies were conducted with male and female Fischer 344 rats to estimate the maximum tolerated dose of hexachlorophene, on the basis of which low, mid, and high concentrations (hereinafter referred to as "low doses", "mid doses", and "high doses") were determined for administration in the chronic studies. In the subchronic studies, hexachlorophene was added to feed in concentrations of 50, 100, 200, 400, or 600 ppm. Treated and control groups each consisted of 15 male and 15 female rats. The chemical was provided in feed to the treated groups for 8 weeks.

Animals treated at 600 ppm developed hindquarter paralysis and exophthalmos, and had a generally wasted appearance; by the end of the study, 12/15 males and 11/15 females at this dose had died. Histologically, neuronal necrosis of the brain was found in groups treated at 600 ppm, 400 ppm, and, to a lesser degree, 200 ppm. Body weight gain in animals treated at 400 ppm was 76% of that of controls in males and 74% of that of controls in females. Weight gain was unaffected at lower doses, and no

deaths occurred at doses of 400 ppm or lower. The low, mid, and high doses for the chronic studies were set at 17, 50, and 150 ppm.

F. Design of Chronic Studies

The design of the chronic studies is shown in table 1.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity and palpated for masses at each weighing. Animals were weighed individually every other week for 12 weeks, and once every fourth week for the remainder of the study. Animals that were moribund at the time of clinical examination were killed and necropsied.

The pathologic evaluation consisted of gross examination of major organs and tissues from killed animals and from animals found dead. The following tissues were routinely examined microscopically from both control and treated animals: lungs and bronchi, spleen, liver, kidney, pituitary, testis, and brain. In addition, esophagus, stomach, urinary bladder, thyroid, uterus, and ovary were examined from a majority of the control animals; these tissues were examined from treated animals only if a lesion was found at necropsy. Occasionally, additional tissues were examined microscopically. Gross lesions from all animals were

Table 1. Design of Hexachlorophene Chronic Feeding Studies in Rats

Sex and Treatment Group	Initial No. of Animals[a]	Hexachlorophene in Diet[b] (ppm)	Time on Study	
			Treated[c] (weeks)	Untreated (weeks)
MALE				
Matched-Control	24	0		106
Low-Dose	24	17	105-106	
Mid-Dose	24	50	106	
High-Dose	24	150	106	
FEMALE				
Matched-Control	24	0		105-106
Low-Dose	24	17	105-106	
Mid-Dose	24	50	106	
High-Dose	24	150	106	

[a]All animals were approximately 52 ± 3 days of age when placed on study.

[b]All diets contained 3% corn oil.

[c]All animals were started on study within 2 days of each other.

also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few of the tissues selected by design from some animals were not examined. Also, some animals were judged to be in such an advanced state of autolysis as to preclude histopathologic evaluation. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques

described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals necropsied (denominator).

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control

animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of treated animals at each dose level. When results for a number of treated groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical

tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each treated group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The

relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result ($P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the

induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS

A. Body Weights and Clinical Signs

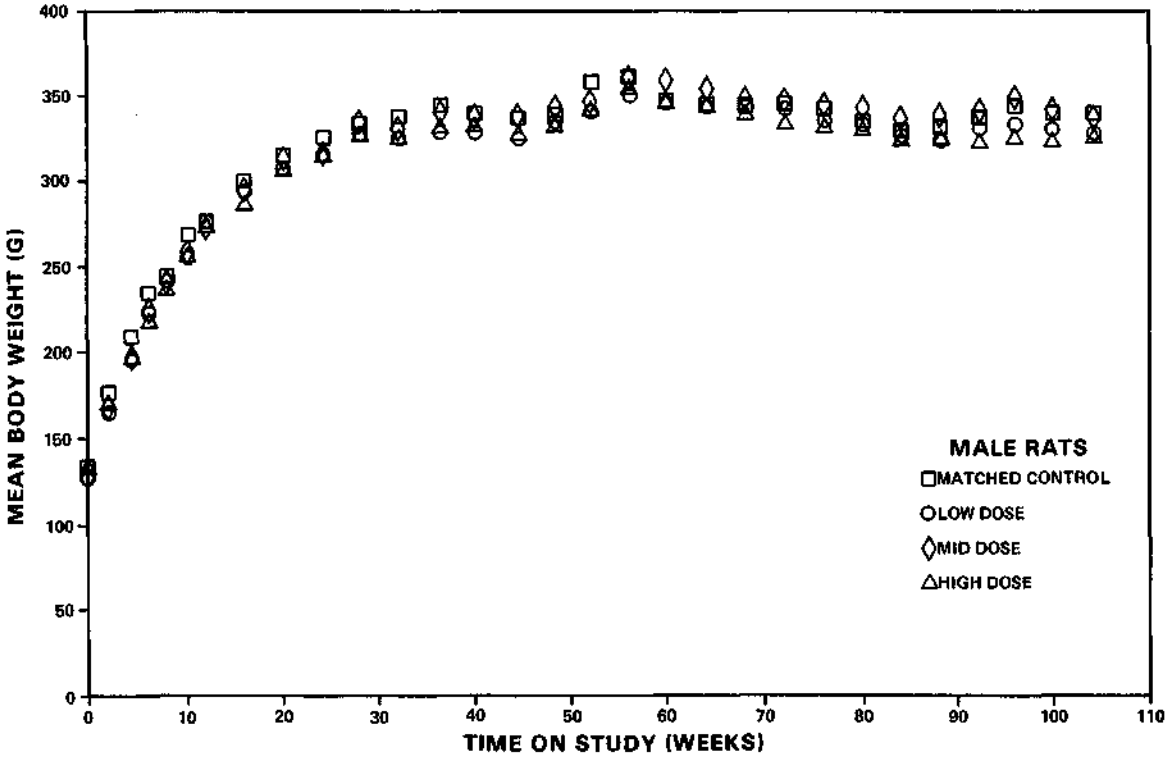
Hexachlorophene at the doses used in this bioassay had no effect on the mean body weights of the rats (figure 1). At week 24, an intercurrent respiratory infection occurred in the colony, but weights of animals in this bioassay were scarcely affected and recovery occurred within 4 weeks without treatment for infection.

No other clinical signs were recorded.

B. Survival

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats fed hexachlorophene in the diet at the doses of this study, together with those of the controls, are shown in figure 2.

In neither sex is the Tarone test result significant for positive dose-related trend in mortality. In male rats, 79% of the high-dose group, 88% of the mid-dose and matched-control groups, and 67% of the low-dose group lived to termination of the study. In females, 75% of the high-dose group, 79% of the mid-dose group, 50% of the low-dose group, and 63% of the matched-control group survived to termination of the study. Sufficient numbers of male



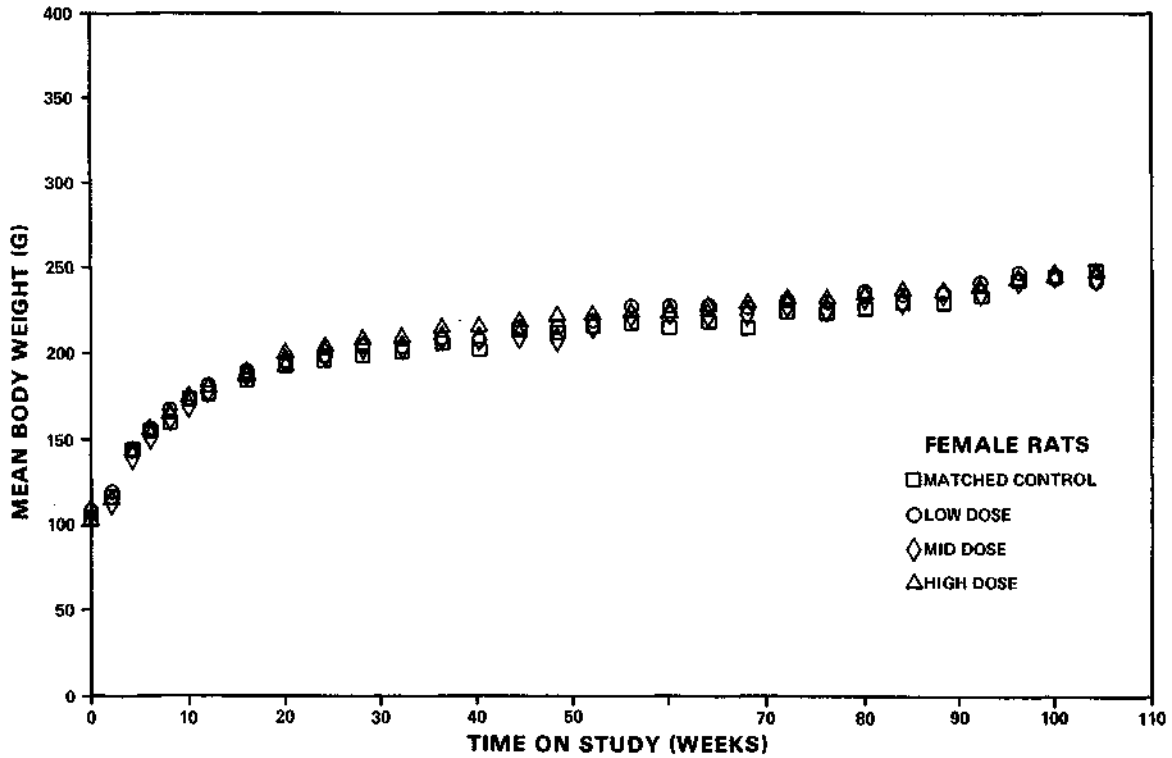


Figure 1. Growth Curves for Rats Fed Hexachlorophene in the Diet

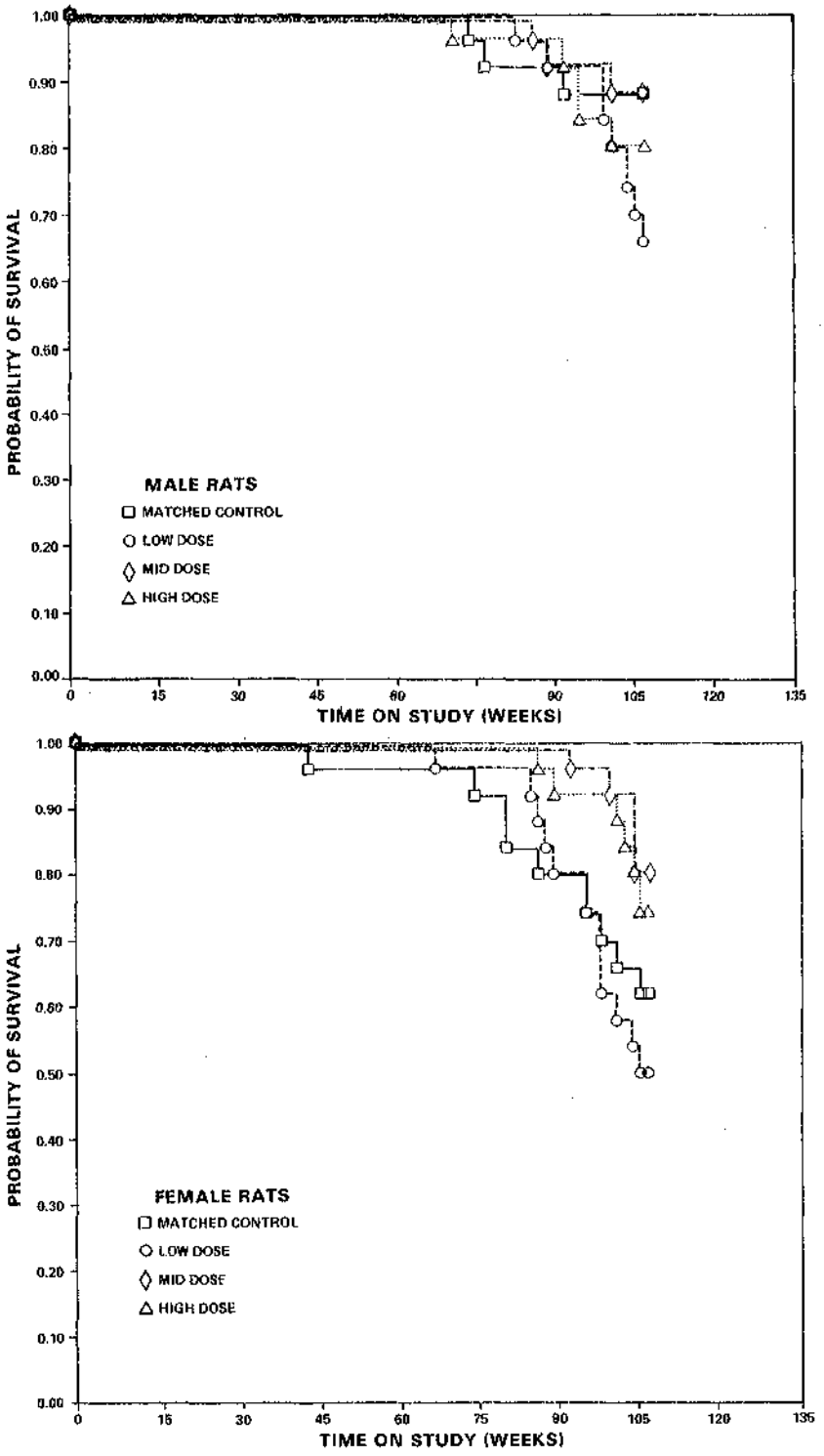


Figure 2. Survival Curves for Rats Fed Hexachlorophene in the Diet

and female rats were available for analyses of the incidences of late-appearing tumors.

C. Pathology

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix B, tables B1 and B2.

A variety of neoplastic processes were observed in both the control and treated rats. Interstitial-cell tumors of the testes were the most frequently observed neoplasm in the control and treated males. Leukemia, generally of the granulocytic type, was the next most frequently observed neoplastic process in both the male and female animals. The incidence of this neoplasm was comparable among the control and treated groups. The following neoplasms were randomly distributed throughout the control and treated rats: squamous-cell carcinomas of the skin, alveolar/bronchiolar adenomas of the lung, adenomas of the liver, transitional-cell carcinoma of the urinary bladder, adenomas of the pituitary, adenomas of the thyroid, adenomas and fibroadenomas of the mammary gland, and endometrial stromal polyps of the uterus.

The results of the microscopic examination indicate that the administration of hexachlorophene at the three doses used in this

study did not have a carcinogenic effect in the Fischer 344 rat. With the exception of interstitial-cell tumors of the testes and granulocytic leukemia, the incidence of neoplasia in both the control and treated rats was relatively low.

D. *Statistical Analyses of Results*

Tables C1 and C2 in Appendix C contain the statistical analyses of the incidences of those primary tumors that were observed in at least 5% of one or more of the treated groups.

In male rats, the results of the Cochran-Armitage test for positive dose-related trend in the proportions of fibrosarcoma of the subcutaneous tissue and of mesothelioma, NOS (not otherwise specified), of the tunica vaginalis are significant ($P < 0.050$), but none of the results of the Fisher exact test are significant in any treated group when compared with controls. There is no other incidence of tumors at any specific site which is statistically significant in either sex.

In each of the intervals of relative risk, shown in the tables, the value of one is included; this indicates the absence of positive significant results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by hexa-

chlorophene, which could not be detected under the conditions of this test.

IV. DISCUSSION

At the doses used in this bioassay, hexachlorophene had no effect on mean body weights of Fischer 344 rats of either sex, and no clinical signs of toxicity were recorded. Survival also was unaffected at the doses used. Adequate numbers of rats in treated and control groups were available for analyses of the incidences of late-appearing tumors.

In the subchronic study, neuronal necrosis of the brain was found in animals treated for 8 weeks at 200, 400, or 600 ppm, and the animals at 600 ppm also showed numerous clinical signs of toxicity. However, even at the highest dose used in the chronic study, i.e., 150 ppm, there were no effects on the nervous system, either clinically or histopathologically. Brains from all animals were routinely examined histologically; however, no other effort was made to demonstrate lesions of the nervous system. No tumors at any site were present in the treated rats in a statistically significant incidence.

No previous studies of the carcinogenicity of hexachlorophene have been reported. However, toxicity studies in rats (Kimbrough, 1976) have demonstrated neurotoxic signs (nervousness and hindquarter paralysis) and morphological changes (vacuolization of white matter) in the brain and spinal cord, following

either oral (500 ppm, 10-14 weeks) or dermal (24 mg/kg) administration of hexachlorophene. Reversibility of toxic signs after discontinuing administration of hexachlorophene has also been reported (Kimbrough, 1971).

It is concluded that under the conditions of this bioassay, hexachlorophene did not induce malignant or benign tumors in Fischer 344 rats.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED HEXACHLOROPHENE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED HEXACHLOROPHENE IN THE DIET

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	24
INTEGUMENTARY SYSTEM				
*SKIN	(24)	(24)	(24)	(24)
SQUAMOUS CELL CARCINOMA			1 (4%)	
*SUBCUT TISSUE	(24)	(24)	(24)	(24)
BASAL-CELL CARCINOMA	1 (4%)			
FIBROSARCOMA				3 (13%)
RESPIRATORY SYSTEM				
#LUNG	(24)	(24)	(24)	(24)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (8%)		2 (8%)	
ANGIOSARCOMA, METASTATIC	1 (4%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(24)	(24)	(24)	(24)
GRANULOCYTIC LEUKEMIA	5 (21%)	5 (21%)	3 (13%)	4 (17%)
#SPLEEN	(23)	(24)	(23)	(24)
HAMARTOMA				1 (4%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(1)	(1)		
ANGIOSARCOMA	1 (100%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#LIVER	(22)	(23)	(24)	(23)
ADENOMA, NOS	1 (5%)			1 (4%)
#COLON		(2)		(2)
ADENOMATOUS POLYP, NOS				1 (50%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(24)	(24)	(24)	(24)
FIBROMA			1 (4%)	
LIPOMA				1 (4%)
*TESTIS	(24)	(24)	(24)	(24)
INTERSTITIAL-CELL TUMOR	24 (100%)	24 (100%)	24 (100%)	24 (100%)
NERVOUS SYSTEM				
#BRAIN	(23)	(24)	(24)	(24)
GLIOMA, NOS	1 (4%)			
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(24)	(24)	(24)	(24)
MESOTHELIOMA, NOS	1 (4%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
*TUNICA VAGINALIS	(24)	(24)	(24)	(24)
MESOTHELIOMA, NOS				2 (8%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(24)	(24)	(24)	(24)
MESOTHELIOMA, MALIGNANT	1 (4%)			1 (4%)
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	24	24	24	24
NATURAL DEATH@		3	2	1
MORIBUND SACRIFICE	3	5	1	4
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	21	16	21	19
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	24	24	24	24
TOTAL PRIMARY TUMORS	37	29	31	38
TOTAL ANIMALS WITH BENIGN TUMORS	24	24	24	24
TOTAL BENIGN TUMORS	27	24	27	28
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	5	4	7
TOTAL MALIGNANT TUMORS	9	5	4	8
TOTAL ANIMALS WITH SECONDARY TUMORS#	1			
TOTAL SECONDARY TUMORS	1			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	1			2
TOTAL UNCERTAIN TUMORS	1			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED HEXACHLOROPHENE IN THE DIET

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	23
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(24)	(24)	(24)	(24)
SQUAMOUS CELL CARCINOMA				1 (4%)
ADENOCARCINOMA, NOS	1 (4%)			
CYSTADENOMA, NOS			1 (4%)	
FIBROMA	1 (4%)		1 (4%)	
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (4%)		
LIPOMA	1 (4%)			
RESPIRATORY SYSTEM				
#TRACHEA	(22)	(4)	(1)	
FIBROSARCOMA		1 (25%)		
#LUNG	(24)	(23)	(24)	(23)
ADENOCARCINOMA, NOS, METASTATIC				1 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (8%)	
PHEOCHROMOCYTOMA, METASTATIC	1 (4%)			
FIBROUS HISTIOCYTOMA, METASTATIC		1 (4%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(24)	(24)	(24)	(24)
GRANULOCYTIC LEUKEMIA	8 (33%)	6 (25%)	10 (42%)	3 (13%)
#LYMPH NODE	(3)	(5)	(4)	(9)
ADENOCARCINOMA, NOS, METASTATIC				1 (11%)
#LUNG	(24)	(23)	(24)	(23)
GRANULOCYTIC LEUKEMIA			1 (4%)	
CIRCULATORY SYSTEM				
NONE				

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
NONE				
URINARY SYSTEM				
#KIDNEY	(24)	(22)	(24)	(23)
ADENOMA, NOS	1 (4%)			
#URINARY BLADDER	(18)			
TRANSITIONAL-CELL PAPILLOMA	1 (6%)			
TRANSITIONAL-CELL CARCINOMA	1 (6%)			
ENDOCRINE SYSTEM				
#PITUITARY	(24)	(23)	(24)	(23)
ADENOMA, NOS	3 (13%)	2 (9%)	4 (17%)	4 (17%)
#ADRENAL	(2)		(1)	(1)
PHEOCHROMOCYTOMA			1 (100%)	
PHEOCHROMOCYTOMA, MALIGNANT	1 (50%)			
#THYROID	(20)	(2)	(1)	(1)
ADENOMA, NOS	2 (10%)		1 (100%)	
ADENOCARCINOMA, NOS				1 (100%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(24)	(24)	(24)	(24)
ADENOMA, NOS	2 (8%)			1 (4%)
ADENOCARCINOMA, NOS	1 (4%)			
CYSTADENOMA, NOS			1 (4%)	
FIBROMA		3 (13%)		
FIBROADENOMA		4 (17%)	1 (4%)	
*GENITAL SYSTEM	(24)	(24)	(24)	(24)
SQUAMOUS CELL CARCINOMA		1 (4%)		
#UTERUS	(22)	(12)	(11)	(10)
ENDOMETRIAL STROMAL POLYP	13 (59%)	9 (75%)	7 (64%)	8 (80%)
ENDOMETRIAL STROMAL SARCOMA	1 (5%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
*OVARY	(23)	(2)		
GRANULOSA-CELL CARCINOMA		1 (50%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(24)	(24)	(24)	(24)
SQUAMOUS CELL CARCINOMA			1 (4%)	
THORAX				
SQUAMOUS CELL CARCINOMA				1
OMENTUM				
LIPOSARCOMA	1			
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	24	24	24	24
NATURAL DEATH@	1	4	4	2
MORIBUND SACRIFICE	8	8	1	4
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	15	12	19	18
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	21	17	21	13
TOTAL PRIMARY TUMORS	38	28	31	19
TOTAL ANIMALS WITH BENIGN TUMORS	16	12	15	11
TOTAL BENIGN TUMORS	24	18	19	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	8	12	5
TOTAL MALIGNANT TUMORS	14	10	12	6
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1		1
TOTAL SECONDARY TUMORS	1	1		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED HEXACHLOROPHENE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED HEXACHLOROPHENE IN THE DIET

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	24
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(24)	(24)	(24)	(24)
NECROSIS, NOS			1 (4%)	
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(24)	(24)	(24)	(24)
BRONCHIECTASIS				1 (4%)
#LUNG	(24)	(24)	(24)	(24)
ATELECTASIS	2 (8%)	4 (17%)	1 (4%)	
CONGESTION, NOS	7 (29%)	12 (50%)	12 (50%)	11 (46%)
INFLAMMATION, NOS		2 (8%)	1 (4%)	1 (4%)
INFLAMMATION, FOCAL				1 (4%)
ABSCESS, NOS	1 (4%)	1 (4%)	1 (4%)	
HEMATOPOIETIC SYSTEM				
#SPLEEN	(23)	(24)	(23)	(24)
HEMATOPOIESIS				1 (4%)
#LYMPH NODE	(1)	(1)	(1)	(6)
LYMPHANGIECTASIS			1 (100%)	5 (83%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(1)			
FIBROSIS	1 (100%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(1)	(1)		
INFLAMMATION, NOS		1 (100%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, NOS	1 (50%)			
*SEMINAL VESICLE	(24)	(24)	(24)	(24)
DILATATION, NOS		1 (4%)	1 (4%)	1 (4%)
HYPERPLASIA, NOS		1 (4%)		
*TESTIS	(24)	(24)	(24)	(24)
ATROPHY, NOS	2 (8%)			
*EPIDIDYMIS	(24)	(24)	(24)	(24)
INFLAMMATION, NOS		1 (4%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*MUSCLE OF BACK	(24)	(24)	(24)	(24)
INFLAMMATION, NOS		1 (4%)		
BODY CAVITIES				
*INGUINAL REGION	(24)	(24)	(24)	(24)
NECROSIS, FAT	4 (17%)	5 (21%)	8 (33%)	6 (25%)
*MESENTERY	(24)	(24)	(24)	(24)
NECROSIS, HEMORRHAGIC		1 (4%)		
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#LIVER	(22)	(23)	(24)	(23)
CONGESTION, NOS		7 (30%)	1 (4%)	2 (9%)
INFLAMMATION, NOS			1 (4%)	
INFLAMMATION, FOCAL		1 (4%)		
ABSCESS, NOS			1 (4%)	
HEPATITIS, TOXIC		1 (4%)		
NECROSIS, NOS		2 (9%)		
NECROSIS, FOCAL		1 (4%)		
HYPERPLASIA, NODULAR	1 (5%)		1 (4%)	1 (4%)
ANGIECTASIS	1 (5%)	1 (4%)		1 (4%)
HEMATOPOIESIS				1 (4%)
#STOMACH	(23)	(8)	(1)	(3)
DIVERTICULUM	1 (4%)			
EDEMA, NOS		1 (13%)		
#GASTRIC MUCOSA	(23)	(8)	(1)	(3)
HYPERPLASIA, NOS			1 (100%)	
#COLON		(2)		(2)
ATYPIA, NOS				1 (50%)
#CECUM		(2)		(2)
EDEMA, NOS		1 (50%)		
INFLAMMATION, NOS				1 (50%)
URINARY SYSTEM				
#KIDNEY	(22)	(24)	(24)	(24)
HYDRONEPHROSIS				1 (4%)
CYST, NOS	1 (5%)			
#KIDNEY/PELVIS	(22)	(24)	(24)	(24)
HEMORRHAGE		1 (4%)		
ENDOCRINE SYSTEM				
#PITUITARY	(24)	(24)	(24)	(23)
CONGESTION, NOS			1 (4%)	
REPRODUCTIVE SYSTEM				
#PROSTATE	(2)			(3)
DILATATION, NOS				1 (33%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED HEXACHLOROPHENE IN THE DIET

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	23
INTEGUMENTARY SYSTEM				
*SKIN	(24)	(24)	(24)	(24)
EPIDERMAL INCLUSION CYST			1 (4%)	
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(24)	(23)	(24)	(23)
BRONCHIECTASIS			1 (4%)	
INFLAMMATION, NOS	1 (4%)			
#LUNG	(24)	(23)	(24)	(23)
ATELECTASIS	2 (8%)	2 (9%)		3 (13%)
CONGESTION, NOS	7 (29%)	8 (35%)	4 (17%)	12 (52%)
INFLAMMATION, NOS			1 (4%)	
ABSCESS, NOS			1 (4%)	
HEMATOPOIETIC SYSTEM				
#SPLEEN	(24)	(22)	(21)	(23)
CONGESTION, NOS				1 (4%)
INFLAMMATION, GRANULOMATOUS	1 (4%)			
FIBROSIS				1 (4%)
HEMATOPOIESIS	2 (8%)			
#LYMPH NODE	(3)	(5)	(4)	(9)
LYMPHANGIECTASIS	1 (33%)	1 (20%)	1 (25%)	6 (67%)
INFLAMMATION, GRANULOMATOUS	1 (33%)			
CIRCULATORY SYSTEM				
NONE				

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(24)	(23)	(23)	(20)
CONGESTION, NOS	1 (4%)	1 (4%)		3 (15%)
INFLAMMATION, NOS		1 (4%)	2 (9%)	1 (5%)
ABSCESS, NOS		3 (13%)	2 (9%)	
INFLAMMATION, GRANULOMATOUS	3 (13%)	1 (4%)	3 (13%)	
HYPERPLASIA, NODULAR	1 (4%)		2 (9%)	
ANGIECTASIS				1 (5%)
#COLONIC SEROSA	(1)			(3)
INFLAMMATION, NOS				1 (33%)
ADHESION, NOS				1 (33%)
#CECUM	(1)			(3)
INFLAMMATION, NOS				3 (100%)
ADHESION, NOS				1 (33%)
HYPERPLASIA, LYMPHOID				1 (33%)
URINARY SYSTEM				
#KIDNEY	(24)	(22)	(24)	(23)
PYELONEPHRITIS, NOS			1 (4%)	
#URINARY BLADDER	(18)			
POLYP, INFLAMMATORY	1 (6%)			
ENDOCRINE SYSTEM				
#PITUITARY	(24)	(23)	(24)	(23)
CYST, NOS		1 (4%)	1 (4%)	3 (13%)
CONGESTION, NOS	2 (8%)	2 (9%)	1 (4%)	2 (9%)
HEMORRHAGE	1 (4%)	3 (13%)	1 (4%)	1 (4%)
#THYROID	(20)	(2)	(1)	(1)
INFLAMMATION, NOS	2 (10%)			
REPRODUCTIVE SYSTEM				
#UTERUS	(22)	(12)	(11)	(10)
HYDROMETRA	2 (9%)	1 (8%)	1 (9%)	1 (10%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
PYOMETRA	4 (18%)		1 (9%)	2 (20%)
ABSCESS, NOS				1 (10%)
INFARCT, NOS			1 (9%)	
#CERVIX UTERI	(22)	(12)	(11)	(10)
CYST, NOS			1 (9%)	
#UTERUS/ENDOMETRIUM	(22)	(12)	(11)	(10)
HYPERPLASIA, CYSTIC	2 (9%)	1 (8%)		
#UTERUS/MYOMETRIUM	(22)	(12)	(11)	(10)
INFLAMMATION, NOS		1 (8%)		
#OVARY	(23)	(2)		
CONGESTION, NOS		1 (50%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(24)	(24)	(24)	(24)
INFARCT, NOS		1 (4%)		
ADIPOSE TISSUE				
INFLAMMATION, NOS				1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1		1	1
AUTO/NECROPSY/NO HISTO				1

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX C

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED HEXACHLOROPHENE IN THE DIET

Table C1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Hexachlorophene in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Subcutaneous Tissue: Fibrosarcoma[b]	0/24 (0)	0/24 (0)	0/24 (0)	3/24 (13)
P Values[c,d]	P = 0.009	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	--	Infinite
Lower Limit		--	--	0.624
Upper Limit		--	--	Infinite
Weeks to First Observed Tumor	--	--	--	71
Lung: Alveolar/Bronchiolar Adenoma[b]	2/24 (8)	0/24 (0)	2/24 (8)	0/24 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.000	1.000	0.000
Lower Limit		0.000	0.078	0.000
Upper Limit		3.283	12.790	3.283
Weeks to First Observed Tumor	73	--	106	--

Table C1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Hexachlorophene in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Hematopoietic System:				
Leukemia[b]	5/24 (21)	5/24 (21)	3/24 (13)	4/24 (17)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.000	0.600	0.800
Lower Limit		0.263	0.104	0.181
Upper Limit		3.777	2.720	3.255
Weeks to First Observed Tumor	92	83	86	92
Testis: Interstitial-cell Tumor[b]	24/24 (100)	24/24 (100)	24/24 (100)	24/24 (100)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	--	--
Lower Limit		--	--	--
Upper Limit		--	--	--
Weeks to First Observed Tumor	73	83	86	71

Table C1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Hexachlorophene in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Tunica Vaginalis:				
Mesothelioma, NOS[b]	0/24 (0)	0/24 (0)	0/24 (0)	2/24 (8)
P Values[c,d]	P = 0.042	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	--	Infinite
Lower Limit		--	--	0.305
Upper Limit		--	--	Infinite
Weeks to First Observed Tumor	--	--	--	106

[a]Treated groups received doses of 17, 50, or 150 ppm in feed.

[b]Number of tumor-bearing animals/number of animals necropsied (percent).

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in the control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the matched-control group.

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Hexachlorophene in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	0/24 (0)	0/24 (0)	2/24 (8)	0/24 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	Infinite	--
Lower Limit		--	0.305	--
Upper Limit		--	Infinite	--
Weeks to First Observed Tumor	--	--	106	--
Hematopoietic System: Leukemia[b]	8/24 (33)	6/24 (25)	11/24 (46)	3/24 (13)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.750	1.375	0.375
Lower Limit		0.254	0.619	0.073
Upper Limit		2.075	3.160	1.350
Weeks to First Observed Tumor	74	84	92	88

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Hexachlorophene in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Pituitary: Adenoma, NOS[b]	3/24 (13)	2/24 (8)	4/24 (17)	4/24 (17)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.667	1.333	1.333
Lower Limit		0.060	0.254	0.254
Upper Limit		5.292	8.185	8.185
Weeks to First Observed Tumor	101	88	106	86
Mammary Gland: Fibroma[b]	0/24 (0)	3/24 (13)	0/24 (0)	0/24 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.018			
Relative Risk (Matched Control)[f]		Infinite	--	--
Lower Limit		0.624	--	--
Upper Limit		Infinite	--	--
Weeks to First Observed Tumor	--	98	--	--

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Hexachlorophene in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Mammary Gland: Fibroadenoma[b]	0/24 (0)	4/24 (17)	1/24 (4)	0/24 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.022			
Relative Risk (Matched Control)[f]		Infinite	Infinite	--
Lower Limit		0.961	0.055	--
Upper Limit		Infinite	Infinite	--
Weeks to First Observed Tumor	--	66	103	--
Mammary Gland: Adenoma, NOS, Cystadenoma, NOS, or Fibroadenoma[b]	2/24 (8)	4/24 (17)	2/24 (8)	1/24 (4)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.000	1.000	0.500
Lower Limit		0.319	0.078	0.009
Upper Limit		20.335	12.790	8.943
Weeks to First Observed Tumor	105	66	103	106

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Hexachlorophene in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Uterus: Endometrial Stromal Polyp[b]	13/24 (54)	9/24 (38)	7/24 (29)	8/24 (33)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.692	0.539	0.615
Lower Limit		0.334	0.231	0.281
Upper Limit		1.398	1.179	1.290
Weeks to First Observed Tumor	42	88	106	88

[a]Treated groups received doses of 17, 50, or 150 ppm in feed.

[b]Number of tumor-bearing animals/number of animals necropsied (percent).

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in the control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the matched-control group.

Review of the Bioassay of Hexachlorophene* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

November 28, 1977

The Clearinghouse on Environmental Carcinogens was established in May, 1976 under the authority of the National Cancer Act of 1971 (P.L. 92-218). The purpose of the Clearinghouse is to advise on the National Cancer Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in organic chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of NCI bioassay reports on chemicals studied for carcinogenicity. In this context, below is the edited excerpt from the minutes of the Subgroup's meeting at which Hexachlorophene was reviewed.

Hexachlorophene had been used as a local antibiotic until it was shown to cause neurologic toxicity and deaths in babies. Hexachlorophene was tested in rats as part of another study designed to investigate the combined effects of chemicals. None of the treated groups showed an increased tumor incidence compared to the controls.

As a negative study, one member said that it may be deficient since only one species was used instead of the usual two. He added that greater emphasis should have been given to the histopathology of the central nervous system. He also opined that it would have been more appropriate to have tested Hexachlorophene by topical application than by the oral route. Despite the shortcomings, the reviewer agreed with the staff's conclusion that Hexachlorophene was not carcinogenic under the conditions of test.

A staff member pointed out that when no lesions are found at an organ site, the tissue count is not given in the report. He suggested that this may have been the case for the treated female rats. The Subgroup recommended that the table showing the neoplasms be changed to include tissue counts in the absence of tumors.

One Subgroup member questioned the validity of including animals who die before terminal sacrifice in the total animal count. A staff member said that animals are included

in the denominator only when they live long enough to have been at risk (usually 75 weeks) or until the time that the first tumor was detected, whichever is earlier.

It was moved that the bioassay report on Hexachlorophene be accepted. The motion was seconded and approved by all present except Mr. Garfinkel, who opposed it.

Members present were:

Gerald N. Wogan (Chairman), Massachusetts Institute of Technology
Lawrence Garfinkel, American Cancer Society
Henry C. Pitot, University of Wisconsin Medical Center
George Roush, Jr., Monsanto Company
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center
John H. Weisburger, American Health Foundation

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

*U.S. GOVERNMENT PRINTING OFFICE: 1978 260-899/3020 1-3