

**NATIONAL TOXICOLOGY PROGRAM**  
**Technical Report Series**  
**No. 437**



**TOXICOLOGY AND CARCINOGENESIS**  
**STUDIES OF HEXACHLOROCYCLOPENTADIENE**

**(CAS NO. 77-47-4)**

**IN F344/N RATS AND B6C3F<sub>1</sub> MICE**

**(INHALATION STUDIES)**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**Public Health Service**  
**National Institutes of Health**

## FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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**NTP TECHNICAL REPORT**  
**ON THE**  
**TOXICOLOGY AND CARCINOGENESIS**  
**STUDIES OF HEXACHLOROCYCLOPENTADIENE**  
**(CAS NO. 77-47-4)**  
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**Public Health Service**  
**National Institutes of Health**

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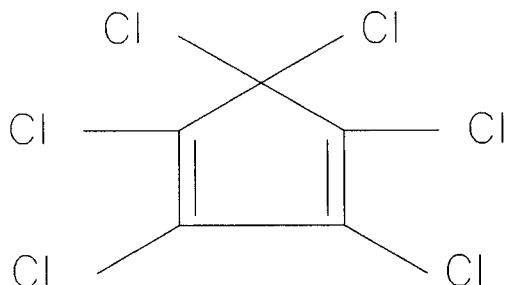
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## ABSTRACT



### HEXACHLOROCYCLOPENTADIENE

CAS No. 77-47-4

Chemical Formula:  $C_5Cl_6$       Molecular Weight: 272.8

**Synonyms:** Perchlorocyclopentadiene, hexachloro-1,3-cyclopentadiene, HEX, HCPD, HCCP, HCCPD

**Trade Name:** C-56-Graphlox

Hexachlorocyclopentadiene is an intermediate used in the manufacture of flame retardants, resins, and chlorinated cyclo diene pesticides. Toxicology and carcinogenesis studies were conducted by exposing male and female F344/N rats and B6C3F<sub>1</sub> mice to atmospheres containing hexachlorocyclopentadiene (approximately 98% pure) for 6 hours per day, 5 days per week, for 13 weeks or 2 years. A stop-exposure evaluation was conducted in male B6C3F<sub>1</sub> mice to determine the influence of exposure level and exposure duration on the development of nonneoplastic lesions of the respiratory tract and on their regression or progression after exposure was stopped. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, *Drosophila melanogaster*, and mouse peripheral blood samples were analyzed for frequency of micronucleated normochromatic erythrocytes.

#### 13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were exposed to atmospheres containing 0, 0.04, 0.15, 0.4, 1, or 2 ppm (equivalent to 0, 0.45, 1.67, 4.46, 11.14, and 22.28 mg/m<sup>3</sup>) hexachlorocyclopentadiene. Additional rats were exposed to 0, 0.04, 0.4, or 2 ppm hexa-

chlorocyclopentadiene and evaluated for differences in clinical pathology parameters. All rats in the 1 and 2 ppm groups died during the first 4 weeks of the study. The final mean body weight and mean body weight gain of males exposed to 0.4 ppm were significantly lower than those of the controls. Listlessness was observed in 2 ppm rats from week 1, in 1 ppm rats from week 2, and in 0.4 ppm rats during week 3. Rats exposed to 1 or 2 ppm also experienced respiratory distress. No chemical-related differences in hematology, clinical chemistry, or urinalysis parameters were observed in male or female rats. Absolute and relative lung weights of 0.4 ppm males were significantly greater than those of the controls. Inflammation (necrotizing, chronic, or suppurative) of the nose, larynx, trachea, and lung was observed in 0.4, 1, and 2 ppm males and females. Squamous metaplasia of the epithelial lining of the nose of 0.4 ppm males and 1 and 2 ppm males and females was also observed.

#### 13-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice were exposed to atmospheres containing 0, 0.04, 0.15, 0.4, 1, or 2 ppm (equivalent to 0, 0.45, 1.67, 4.46, 11.14, and

22.28 mg/m<sup>3</sup>) hexachlorocyclopentadiene. Additional mice were exposed to 0, 0.04, 0.4, or 2 ppm and evaluated for differences in clinical pathology parameters. All 2 ppm mice died during the first week of exposure. All 1 ppm mice died during the first 5 weeks of exposure. Five males and two females in the 0.4 ppm group died during the first 2 weeks of exposure. Deaths in the other groups were not related to hexachlorocyclopentadiene exposure. Final mean body weights of males exposed to 0.15 and 0.4 ppm and the body weight gain of 0.4 ppm males were significantly lower than those of the controls. Treatment-related clinical findings included listlessness in 0.4 and 1 ppm males and females. No chemical-related differences in hematology, clinical chemistry, or urinalysis parameters were observed in male or female mice. Necrosis or inflammation of the nose, larynx, trachea, or lung occurred in mice exposed to 0.4, 1, and 2 ppm hexachlorocyclopentadiene. Squamous metaplasia of the larynx or trachea was observed in 0.15, 0.4, and 1 ppm males and in 0.4 and 1 ppm females.

## 2-YEAR STUDY IN RATS

### *Survival, Body Weights, Clinical Findings, and Urinalysis*

Groups of 60 male and 60 female rats were exposed to atmospheres containing 0, 0.01, 0.05, or 0.2 ppm (equivalent to 0, 0.11, 0.56, and 2.28 mg/m<sup>3</sup>) hexachlorocyclopentadiene. Survival rates and mean body weights of exposed rats were similar to those of the controls. No chemical-related clinical findings were observed in male or female rats during the 2-year study. No differences in urinalysis parameters at the 15-month interim evaluation could be attributed to exposure to hexachlorocyclopentadiene.

### *Pathology Findings*

No increases in neoplasm incidences could be attributed to hexachlorocyclopentadiene. Toxicity was limited to the respiratory tract and included an increase in the incidence of pigmentation of the respiratory epithelium of the nose, trachea, and the bronchi and bronchioles of the lung in both males and females. Exposure to hexachlorocyclopentadiene also caused an increase in the incidence of squamous metaplasia of the laryngeal epithelium of exposed females; the incidences in 0.01 and 0.2 ppm females were significantly greater than that of the controls. The severity of squamous metaplasia was minimal in all exposed and control females.

## 2-YEAR STUDY IN MICE

### *Survival, Body Weights, Clinical Findings, and Urinalysis*

Groups of 60 male and 60 female mice were exposed to atmospheres containing 0, 0.01, 0.05, or 0.2 ppm (equivalent to 0, 0.11, 0.56, and 2.28 mg/m<sup>3</sup>) hexachlorocyclopentadiene. The 2-year survival rate of female mice in the 0.2 ppm group was marginally lower than that of the controls due to a higher incidence of ovarian inflammation in 0.2 ppm females. Mean body weights of 0.2 ppm males (weeks 62 to 103) and females (throughout the study) were lower than those of the controls. No clinical findings in male or female mice were attributed to chemical exposure during the 2-year study. There were no chemical-related differences in urinalysis parameters at the 15-month interim evaluation.

### *Pathology Findings*

The site of toxicity of hexachlorocyclopentadiene exposure in mice in the 2-year study was the respiratory tract. Chemical-related pigmentation of the respiratory epithelium of the nose, trachea, and lung and suppurative inflammation of the nose were observed. No increased neoplasm incidences in males or females could be attributed to hexachlorocyclopentadiene exposure.

## STOP-EXPOSURE EVALUATION

### *Survival, Body Weights, and Clinical Findings*

Groups of male mice were exposed to atmospheres containing 0.2 ppm hexachlorocyclopentadiene for 33 or 66 weeks or 0.5 ppm for 26 or 42 weeks followed by exposure to air until the end of the study. Fifty male mice from each stop-exposure group were evaluated at 2 years. Two-year survival rates of stop-exposure groups were similar to that of the controls. Final mean body weights of stop-exposure groups were similar to that of the controls. No chemical-related clinical findings were observed.

### *Pathology Findings*

Nonneoplastic respiratory tract lesions similar to those observed in the core study were observed in males in the stop-exposure groups. Chemical-related pigmentation and inflammation of the respiratory epithelium were persistent as indicated by their presence in many male mice after recovery periods of 62 to 78 weeks, and the incidence and severity of the lesions were related to exposure concentration and duration.

## GENETIC TOXICOLOGY

Hexachlorocyclopentadiene was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested with and without S9. Hexachlorocyclopentadiene did induce sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, with and without S9. No induction of sex-linked recessive lethal mutations was observed in male *Drosophila melanogaster* treated with hexachlorocyclopentadiene by feeding or injection, and no increase in the frequency of micronucleated erythrocytes was seen in male or female B6C3F<sub>1</sub> mice exposed to hexachlorocyclopentadiene by inhalation for 13 weeks.

## CONCLUSIONS

Under the conditions of these 2-year studies, there was *no evidence of carcinogenic activity\** of hexachlorocyclopentadiene in male or female F344/N rats or B6C3F<sub>1</sub> mice exposed to 0.01, 0.05, or 0.2 ppm.

Exposure of rats to hexachlorocyclopentadiene produced pigmentation of the respiratory epithelium of the nose, trachea (males), and bronchi and bronchioles of the lung. Squamous metaplasia of the laryngeal epithelium occurred in female rats exposed to hexachlorocyclopentadiene. Suppurative inflammation of the nose as well as pigmentation of the respiratory mucosal epithelium occurred in mice exposed to hexachlorocyclopentadiene.

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\* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

**Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Hexachlorocyclopentadiene**

Variable	Male F344/N Rats	Female F344/N Rats	Male B6C3F <sub>1</sub> Mice	Female B6C3F <sub>1</sub> Mice
<b>Doses</b>	0, 0.01, 0.05, or 0.2 ppm by inhalation (equivalent to 0, 0.11, 0.56, or 2.28 mg/m <sup>3</sup> )	0, 0.01, 0.05, or 0.2 ppm by inhalation (equivalent to 0, 0.11, 0.56, or 2.28 mg/m <sup>3</sup> )	0, 0.01, 0.05, or 0.2 ppm by inhalation (equivalent to 0, 0.11, 0.56, or 2.28 mg/m <sup>3</sup> )	0, 0.01, 0.05, or 0.2 ppm by inhalation (equivalent to 0, 0.11, 0.56, or 2.28 mg/m <sup>3</sup> )
<b>Body weights</b>	Exposed groups similar to controls	Exposed groups similar to controls	High dose lower than controls	High dose lower than controls
<b>2-Year survival rates</b>	36/50, 33/50, 45/50, 32/50	28/50, 33/50, 30/49, 30/50	35/50, 33/50, 42/50, 34/50	31/50, 32/50, 30/50, 21/50
<b>Nonneoplastic effects</b>	Lung: bronchiole pigmentation (0/50, 0/50, 0/50, 49/50); peribronchiolar pigmentation (0/50, 0/50, 2/50, 16/50) Nose: pigmentation (1/48, 46/50, 48/49, 48/50) Trachea: pigmentation (0/48, 0/50, 0/48, 5/50)	Larynx: squamous metaplasia (9/50, 20/50, 15/48, 24/50) Lung: bronchiole pigmentation (0/50, 25/50, 42/49, 50/50); peribronchiolar pigmentation (3/50, 1/50, 4/49, 27/50) Nose: pigmentation (0/50, 34/50, 47/49, 48/50)	Lung: mucosal pigmentation (0/49, 2/50, 42/50, 45/50) Nose: suppurative inflammation (0/50, 0/50, 1/50, 36/50); mucosal pigmentation (0/50, 45/50, 50/50, 44/50) Trachea: mucosal pigmentation (0/50, 29/50, 48/50, 48/50)	Lung: mucosal pigmentation (0/48, 0/50, 27/50, 44/49) Nose: suppurative inflammation (4/49, 0/50, 3/50, 40/48); mucosal pigmentation (0/49, 40/50, 48/50, 41/48) Trachea: mucosal pigmentation (0/49, 6/50, 43/48, 42/47)
<b>Neoplastic effects</b>	None	None	None	None
<b>Level of evidence of carcinogenic activity</b>	No evidence	No evidence	No evidence	No evidence
<b>Genetic toxicology</b>				
<i>Salmonella typhimurium</i> gene mutation: Sister chromatid exchanges		Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537		
Chinese hamster ovary cells <i>in vitro</i> : Chromosomal aberrations		Positive with and without S9		
Chinese hamster ovary cells <i>in vitro</i> : Sex-linked recessive lethal mutation in <i>Drosophila melanogaster</i> :		Positive with and without S9		
Mouse peripheral blood erythrocytes <i>in vivo</i> :		Negative administered in feed or by injection Negative at 13 weeks		

## EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such neoplasms to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant neoplasm incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in neoplasm induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed neoplasm increase;
- concurrent control neoplasm incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

**NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS  
TECHNICAL REPORTS REVIEW SUBCOMMITTEE**

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on hexachlorocyclopentadiene on 22 June 1993 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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## SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 22 June 1993 the draft Technical Report on the toxicology and carcinogenesis studies of hexachlorocyclopentadiene received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of hexachlorocyclopentadiene by discussing the uses of the chemical, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in rats and mice. He said a stop-exposure evaluation in male mice was done to determine whether there was regression or progression of metaplastic lesions in the respiratory tract. The proposed conclusions were *no evidence of carcinogenic activity* in male or female F344/N rats or male or female B6C3F<sub>1</sub> mice.

Dr. Zeise, a principal reviewer, agreed in principle with the proposed conclusions. She thought that rats may have been able to tolerate higher doses, as indicated by the survival, mean body weights, and clinical findings in the 2-year study, and that this should be noted in the abstract and elsewhere. Dr. Zeise said that there needed to be more discussion of the significance of the alveolar epithelial hyperplasia seen in male mice in the stop-exposure evaluation. Dr. Abdo agreed.

Dr. Ward, the second principal reviewer, also agreed in principle with the proposed conclusions and stated that rats might have been able to tolerate a higher top dose because no effects on body weight gain or survival were observed and because toxic lesions were limited to pigmentation of the respiratory tract epithelium and mild squamous metaplasia in the larynx of females. Dr. Abdo responded that the sharp increase in mortality between rats exposed to 0.4 and 1.0 ppm along with the decreased body weight gain of 0.4 ppm males in the 13-week study justified the top dose chosen for the 2-year study.

Dr. Ward criticized the use of less than 50 animals for complete histopathology in the 0.01 and 0.05 ppm groups, and wondered if the reduced statistical power might have affected interpretation in organs where there were equivocal effects. Dr. S.L. Eustis, NIEHS, noted that the NTP has used the reduced protocol for many years, and that the only case in this study where use of a full protocol might have resolved uncertainty was pituitary gland neoplasms in male rats.

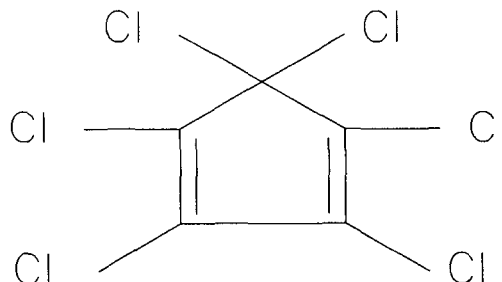
Dr. Davidson, the third principal reviewer, agreed with the proposed conclusions. She said information should be added to the abstract to describe the severity of the respiratory lesions and to explain how the exposure concentrations and durations were selected for the stop-exposure evaluation.

Mr. Beliczky asked that the report include comment on eye examinations and effects. Dr. G.N. Rao, NIEHS, responded that rodents close their eyes when exposed to an irritant chemical and that this might explain why no ocular lesions were observed. Dr. van Zwieten observed that there were significantly increased incidences of squamous metaplasia of the larynx in 0.01 and 0.2 ppm females yet the relevance of this finding was considered uncertain. Dr. Eustis said that uncertainty in interpretation is introduced because there is a transition point in the larynx from squamous to respiratory-type epithelium and it is difficult to get sections from precisely the same spot.

Dr. Davidson moved that the Technical Report of hexachlorocyclopentadiene be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Bailey seconded the motion. Dr. Zeise offered an amendment that a sentence be added to the conclusions stating that rats might have been able to tolerate higher doses. Dr. Ward seconded the amendment, which was then defeated by two yes votes (Drs. Ward and Zeise) to eight no votes. The original motion by Dr. Davidson was then accepted unanimously with ten votes.



## INTRODUCTION



### HEXACHLOROCYCLOPENTADIENE

CAS No. 77-47-4

Chemical Formula:  $C_5Cl_6$

Molecular Weight: 272.8

**Synonyms:** Perchlorocyclopentadiene, hexachloro-1,3-cyclopentadiene, HEX, HCPD, HCCP, HCCPD

**Trade Name:** C-56-Graphlox

### CHEMICAL AND PHYSICAL PROPERTIES

Hexachlorocyclopentadiene is a pale yellow liquid with a pungent musty odor. It has a melting point of  $-9.6^\circ\text{C}$ , a boiling point of  $239^\circ\text{C}$ , a density of 1.717 at  $15^\circ\text{C}$  (Hawley, 1977), a vapor pressure of 0.08 mm Hg at  $25^\circ\text{C}$  (Wolfe *et al.*, 1982), and a vapor density of 9.42 relative to air (Verschueren, 1977). It is practically insoluble in water (1.03 to 1.25 mg/L) (Chou and Griffin, 1983) and miscible in hexane (Bell *et al.*, 1979). Although the vapor pressure of hexachlorocyclopentadiene is low, it volatilizes rapidly from water (Atallah *et al.*, 1981). Hexachlorocyclopentadiene is a highly reactive compound, and it reacts with monoolefinic compounds to give Diels-Alder adducts (Ungnade and McBee, 1958).

### PRODUCTION AND USE

Hexachlorocyclopentadiene is prepared commercially either by chlorination of cyclopentadiene with alkaline hypochlorite at  $40^\circ\text{C}$  followed by fractional distillation or by thermal dechlorination of octachlorocyclopentene at  $470^\circ$  to  $480^\circ\text{C}$  (Kirk-Othmer,

1979). The first method gives a highly impure product (75% pure), and the second method gives a product with 90% purity. Major impurities found in commercial products include octachlorocyclopentene (0.68% to 1.5%), hexachloro-1,3-butadiene (0.2% to 1.11%), tetrachloroethane (0.09%), hexachlorobenzene (0.04%), and pentachlorobenzene (0.02%) (BUA, 1988).

Worldwide production of hexachlorocyclopentadiene was estimated to be 15,000 metric tons in 1988 (BUA, 1988). Annual United States production was 22,700 metric tons during the early 1970's (Lu *et al.*, 1975), after which production ranged from 3,600 to 6,800 metric tons (USEPA, 1977) due to restrictions placed on the use of cyclodiene pesticides.

Hexachlorocyclopentadiene is used as an intermediate in the synthesis of cyclodiene insecticides such as heptachlor, chlordane, aldrin, dieldrin, endrin, and mirex (Bell *et al.*, 1979). It is also used in the synthesis of flame retardants (chlorendic acid and other derivatives) and in the manufacture of plastics, nylon, polyurethanes, and other polymers (Sanders, 1978).

receiving 38 mg/kg, female rats receiving 75 mg/kg, and male and female mice receiving 150 and 300 mg/kg were lower than those of controls. Liver weight and brain weight ratios were significantly greater in female rats receiving 75 and 150 mg/kg and in all groups of dosed mice. Hexachlorocyclopentadiene caused inflammation and epithelial hyperplasia of the forestomach in male rats and male and female mice receiving 38 mg/kg and in female rats receiving 19 mg/kg. Toxic nephrosis characterized by proximal tubule dilatation, cytoplasmic vacuolization, cytomegaly, karyomegaly, and anisokaryosis occurred in male and female rats and female mice receiving 38 mg/kg.

Rand *et al.* (1982a) reported the results of 2-week and 14-week hexachlorocyclopentadiene inhalation toxicity studies. In the 2-week inhalation study, groups of 10 male and 10 female Sprague-Dawley rats were exposed to atmospheres containing 0, 0.022, 0.11, or 0.5 ppm hexachlorocyclopentadiene 6 hours per day, 5 days per week. Deaths occurred in males and females exposed to 0.5 ppm. Rats exposed to 0.5 ppm also had red eyes and exhibited signs of labored breathing. Males exposed to 0.11 and 0.5 ppm lost weight and had reduced liver weights. Rats exposed to 0.5 ppm had an increase in lung weight, histopathologic changes in the olfactory and bronchiole epithelia, and inflammatory exudate in the lumen of the lung. In the 14-week study, groups of 40 male and 40 female Sprague-Dawley rats were exposed to atmospheres containing 0, 0.01, 0.05, or 0.2 ppm hexachlorocyclopentadiene 6 hours per day, 5 days per week. No chemical-related effects on survival or body weight were observed. Males exposed to 0.05 or 0.2 ppm had reddened eyes at week 12; this effect did not persist. Rats exposed to 0.2 ppm had increased hemoglobin concentration and minor increases in serum cation levels. Rand *et al.* (1982b) also reported a dose-related increased incidence of electron lucent inclusions in bronchiolar Clara cells. In the same article, these authors reported the presence of similar inclusions in the bronchiolar Clara cells of *Cynomolgus* monkeys similarly exposed to hexachlorocyclopentadiene. No other effects were observed in these animals.

Exposure to atmospheres containing 0.5 ppm hexachlorocyclopentadiene 6 hours per day, 5 days per week for 30 weeks caused death and body weight depression in male and female Wistar rats. Histopathologic changes occurred in the lung and included

edema, epithelial necrosis and ulceration, and hyperplasia. These changes were more severe in males than in females. Other histopathologic changes observed in both males and females included bile duct hyperplasia, inflammatory cell infiltration of the liver, and protein casts and pigmentation of the renal tubules (Clark *et al.*, 1982).

### **Humans**

Members of a research group working with hexachlorocyclopentadiene developed headaches after accidental exposure to an unknown concentration in the air (Treon *et al.*, 1955). Stomachaches, headaches, and burning or watery eyes were reported by some residents of a 48-block area surrounding a hexachlorocyclopentadiene-contaminated sewer line in Kentucky (Kominsky and Wisseman, 1978). A wastewater treatment plant in Louisville, KY, was contaminated by the illegal dumping of 6 tons of hexachlorocyclopentadiene and octachlorocyclopentadiene. The concentration of hexachlorocyclopentadiene in the sewage at the plant was as high as 1,000 mg/L. The concentration in air samples taken from the sewer line was as high as 400 ppb. Out of 145 workers, 85 had eye irritation, 65 had headaches, and 39 had throat irritation (Morse *et al.*, 1978, 1979). These symptoms persisted in some employees for up to 6 weeks after exposure. Clinical chemistry analyses showed a marginal increase in serum lactic acid dehydrogenase activity, and urinalysis revealed proteinuria in these workers. Similar symptoms of intoxication were observed in wastewater treatment plant workers in Memphis, TN, processing hexachlorocyclopentadiene-contaminated waste from a pesticide manufacturer. No abnormalities were reported in liver function tests of these workers (Elia *et al.*, 1983).

## **REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

### **Experimental Animals**

Hexachlorocyclopentadiene administered orally at doses of up to 75 mg/kg per day on days 6 through 15 of gestation to CF-1 mice did not cause maternal toxicity, fetal toxicity, or teratogenic effects. In New Zealand rabbits receiving a daily oral dose of 75 mg/kg during days 6 to 8 of gestation there was a similar lack of effect except for an increase in the proportion of fetuses with 13 ribs (Murray *et al.*, 1980).

A study of Swiss (CD-1®) mice receiving daily oral doses of 45 mg hexachlorocyclopentadiene per kg body weight on days 8 through 12 of gestation showed no chemical-related effects on maternal weight or on the number or weight of live offspring (Chernoff and Kavlock, 1982).

### **Humans**

No information on the reproductive or developmental toxicity of hexachlorocyclopentadiene in humans was found in the literature.

## **CARCINOGENICITY**

### **Experimental Animals**

No information on the carcinogenic potential of hexachlorocyclopentadiene in experimental animals was found in the literature.

### **Humans**

Epidemiology studies of workers involved in the production or use of hexachlorocyclopentadiene showed no higher death rates due to cancer than for the general population (Wang and MacMahon, 1979; Buncher *et al.*, 1980; Shindell and Associates, 1981). The Wang and MacMahon (1979) study involved 1,403 males who were employed for at least 3 months in a chlordane and heptachlor plant between 1946 and 1976. The Buncher *et al.* (1980) study involved a total of 341 workers, 54 of whom were females, who were employed for at least 3 months in a hexachlorocyclopentadiene production plant between 1953 and 1974. The Shindell and Associates (1981) study involved 1,115 workers who were employed for at least 3 months at a heptachlor plant between 1952 and 1979.

## **GENETIC TOXICITY**

The published mutagenicity test data for hexachlorocyclopentadiene, although limited in type and amount, are uniformly negative. No induction of

mutations was observed in *Escherichia coli* (Goggelman *et al.*, 1978; Brooks *et al.*, 1983), *Salmonella typhimurium* (Brooks *et al.*, 1983; Haworth *et al.*, 1983), *Saccharomyces cerevisiae* (Brooks *et al.*, 1983), or mouse lymphoma L5178Y cells (Litton Bionetics, 1978a), with or without S9 metabolic activation enzymes. Studies with cultured rat hepatocytes showed no induction of chromosomal aberrations (Brooks *et al.*, 1983) or unscheduled DNA synthesis following treatment with hexachlorocyclopentadiene. *In vivo*, no significant increase in sex-linked recessive lethal mutations was noted in germ cells of male *Drosophila melanogaster* exposed to hexachlorocyclopentadiene through feeding or injection (Zimmering *et al.*, 1985; Mason *et al.*, 1992), and no increase in dominant lethal mutations was observed in Swiss (CD-1®) male mice administered up to 1 mg hexachlorocyclopentadiene per kg body weight by gavage (Litton Bionetics, 1978b).

## **STUDY RATIONALE**

The National Cancer Institute nominated hexachlorocyclopentadiene for study because it has a large production volume, which suggests the potential for significant human exposure; because it has a structural relationship to compounds identified as hepatocarcinogens such as heptachlor, aldrin, and dieldrin (NCI, 1977a, 1978); and because information on its chronic toxicity was lacking.

Because hexachlorocyclopentadiene has no end use of its own, occupational exposure appears to be the most serious human health hazard. Workplace exposure occurs primarily via inhalation; therefore, this exposure route was selected for the NTP studies. The 2-year mouse study included a stop-exposure evaluation of male mice to determine the importance of exposure concentration versus exposure duration on the development of nonneoplastic lesions and the regression or progression of the lesions during a postexposure recovery period.

## MATERIALS AND METHODS

### PROCUREMENT AND CHARACTERIZATION OF HEXACHLOROCYCLOPENTADIENE

Hexachlorocyclopentadiene was obtained from Velsicol Chemical Corporation (Chicago, IL) in one lot (2291-1) which was used throughout the 13-week and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and were confirmed by the study laboratory. Reports on the analyses performed in support of the hexachlorocyclopentadiene studies are on file at the National Institute of Environmental Health Sciences (NIEHS). The methods and results of these studies are detailed in Appendix I.

The chemical, a viscous, pale yellow liquid, was identified as hexachlorocyclopentadiene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity was determined by elemental analysis, free acid titration, thin-layer chromatography, and gas chromatography. Elemental analyses of carbon and chlorine agreed with the theoretical values for hexachlorocyclopentadiene. Free acid titration indicated  $224 \pm 16$ (s) ppm hydrochloric acid. In one system, thin-layer chromatography indicated one trace impurity; in the second system, one trace and two slight trace impurities were observed. Two gas chromatography systems gave two impurity peaks with areas greater than 0.1% relative to the major peak. Results of these analyses indicated an overall purity of approximately 98% for the bulk chemical.

Capillary gas chromatography-mass spectrometry was used by the analytical chemistry laboratory to identify one of the impurity peaks observed by the initial gas chromatographic analysis. The impurity was identified as hexachloro-1,3-butadiene. Using a reference standard, its concentration in the bulk chemical was determined to be 0.4%. The study laboratory used a gas chromatography-electron capture method along with a reference standard to quantitate the known impurity, hexachloro-3-cyclopentadiene-1-one (hex-ketone), in the bulk chemical. The concentration of the hex-ketone was approximately 1.5%.

Bulk chemical stability studies were conducted using gas chromatography. Hexachlorocyclopentadiene was determined to be stable as a bulk chemical when stored in sealed containers with a nitrogen headspace and protected from light for as long as 2 weeks at temperatures up to 60° C. The study laboratory stored the bulk chemical at room temperature in the original shipping containers.

The study laboratory monitored the stability of the bulk chemical using gas chromatography and free acid titration. No degradation of the bulk chemical occurred during the 13-week or 2-year studies.

### GENERATION AND MONITORING OF CHAMBER CONCENTRATIONS

Detailed descriptions of the inhalation chambers (Hazleton 2000, Lab Products, Inc., Aberdeen, MD) and the vapor generation system are contained in Appendix I. A single on-line gas chromatograph equipped with an electron capture detector was used to monitor vapor concentrations of hexachlorocyclopentadiene. The monitor was coupled with the inhalation chambers using an automated, multiplexed, 8-port (13-week studies) or 12-port sampling valve. Calibration was maintained by periodic analysis of grab samples from the chambers, which were obtained using bubblers filled with isooctane. Bubbler contents were analyzed using an off-line gas chromatograph, which was calibrated using gravimetrically prepared standards of hexachlorocyclopentadiene. The uniformity of the chamber atmosphere was maintained throughout the 13-week and 2-year studies. Mean exposure concentrations for each chamber during the 2-year studies are presented in Figures I6 through I12.

Buildup and decay rates for chamber concentrations were determined with and without animals present in the chambers. The time to achieve 90% of target concentration after the start of vapor generation ( $T_{90}$ ) without animals ranged from 15 to 25 minutes for the 13-week and 2-year studies. The time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated

( $T_{10}$ ) ranged from 11 to 19 minutes. Additional tests with animals present were conducted during the first 2 weeks of the 2-year study, and a  $T_{90}$  of 20 minutes was adopted.

Studies of hexachlorocyclopentadiene degradation in the chambers were conducted during the 13-week and 2-year studies by comparing samples collected with the isooctane bubblers to a reference sample of bulk hexachlorocyclopentadiene. No significant degradation of the bulk chemical was observed during the 13-week or 2-year studies.

### 13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to hexachlorocyclopentadiene and to determine the appropriate concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F<sub>1</sub> mice were obtained from Frederick Cancer Research Facility (Frederick, MD). At receipt, the animals were 6 weeks old. The rats were quarantined for 14 days before exposure began; the mice were quarantined for 11 days. Before the beginning of the studies, 5 male and 5 female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on 5 male and 5 female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female rats and mice were exposed to hexachlorocyclopentadiene at concentrations of 0, 0.04, 0.15, 0.4, 1, or 2 ppm (equivalent to 0, 0.45, 1.67, 4.46, 11.14, or 22.28 mg/m<sup>3</sup>) for 6 hours per day, 5 days per week, for 13 weeks (Table 1). At the end of the studies, blood was collected from the lumbar aorta (rats) or supraorbital sinus (mice) for hematology and clinical chemistry analyses. The clinical pathology parameters measured are listed in Table 1. The adrenal gland, brain, heart, right kidney, liver, lungs, right testis, and thymus of all surviving animals were weighed.

A special study was conducted to examine differences in hematology, clinical chemistry, or urinalysis parameters that could be associated with kidney and respiratory tract lesions previously observed in rats and mice exposed to hexachlorocyclopentadiene.

Groups of 20 male and 20 female rats and mice were exposed to 0, 0.04, 0.4, or 2 ppm hexachlorocyclopentadiene for 6 hours per day, 5 days per week, for 13 weeks. Five male and five female rats and mice from each exposure group were placed in metabolism chambers for 16 hours on days 3, 15, 45, and 92 for urinalysis evaluations. During this time period, body weights were also recorded. On days 4, 16, 46, and 93, the animals were anesthetized and blood samples were collected from the lumbar aorta (rats) or supraorbital sinus (mice) for hematology and clinical chemistry analyses. The clinical pathology parameters measured are listed in Table 1.

Animals were housed individually; water and feed were available *ad libitum*. Clinical observations were recorded weekly. Animals were weighed initially, weekly, and at the end of the studies.

A necropsy was performed on all animals. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 6  $\mu$ m, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all controls, all animals dying before the end of the studies, and all 0.4 ppm animals surviving to the end of the studies. If a lesion was observed, that organ was examined at the next lower dose level until a dose level was found without the lesion. Table 1 lists the tissues and organs routinely examined.

### 2-YEAR STUDIES

#### Study Design

Groups of 60 male and 60 female rats and mice were exposed to hexachlorocyclopentadiene at concentrations of 0, 0.01, 0.05, or 0.2 ppm (equivalent to 0, 0.11, 0.56, or 2.28 mg/m<sup>3</sup>) for 6 hours per day, 5 days per week, for 103 to 104 weeks. Ten male and 10 female rats and mice from each exposure group were evaluated at 15 months.

A stop-exposure evaluation was conducted in male mice. The purpose of the stop-exposure evaluation was to determine the influence of exposure concentration and exposure duration on the development of nonneoplastic lesions and their regression or progression after stopping the exposure. Thirty males served as controls for the stop-exposure groups; 10 were evaluated at 27, 34, and 43 weeks. Eighty males were

exposed to 0.2 ppm hexachlorocyclopentadiene for 33 weeks; 10 were evaluated at 34, 43, and 66 weeks. The remaining 50 males from the 33-week stop-exposure group were evaluated at 105 weeks. Another group of 50 males was exposed to 0.2 ppm hexachlorocyclopentadiene for 66 weeks and was evaluated at 105 weeks. Ninety males were exposed to 0.5 ppm hexachlorocyclopentadiene for 26 weeks; 10 males were evaluated at 27, 34, 43, and 66 weeks. The remaining 50 males from the 26-week stop-exposure group were evaluated at 105 weeks. Another group of 70 males was exposed to 0.5 ppm hexachlorocyclopentadiene for 42 weeks; 10 males were evaluated at 43 and 66 weeks. The remaining 50 males from the 42-week stop-exposure group were evaluated at 105 weeks.

### Source and Specification of Animals

Male and female F344/N rats and B6C3F<sub>1</sub> mice were obtained from Frederick Cancer Research Facility (Frederick, MD) for use in the 2-year studies. Rats were quarantined 19 days, and mice were quarantined 18 days. Ten male and 10 female rats and mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice were approximately 6 to 7 weeks old at the beginning of the 2-year studies. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

### Animal Maintenance

All animals were housed individually. Feed and water were available *ad libitum* except during daily exposure periods. Cages and racks within exposure chambers were washed as a unit and rotated every week during the studies. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix J.

### Clinical Examinations and Pathology

All animals were observed twice daily for moribundity and mortality. Clinical observations were recorded every 4 weeks. Animals were weighed at study initiation, weekly for 13 weeks, and monthly thereafter.

Groups of 10 core male and 10 core female rats and mice and 10 stop-exposure male mice were designated for 15-month interim evaluations. The volume and specific gravity of urine from core rats and mice were

measured at the 15-month interim evaluations. Animals were anesthetized using 70% carbon dioxide followed by exsanguination. The brain, right kidney, liver, and lungs were weighed at the interim evaluations.

A necropsy was performed on all animals. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. A complete histopathologic examination was performed on all controls, all female mice, all animals dying early, and all rats and male mice exposed to 0.2 ppm in the 2-year core studies. In addition, the larynx (rats only), lung, nose, and trachea of rats and male mice exposed to 0.01 and 0.05 ppm in the 2-year core studies were examined. The larynx, lung, nose, and trachea were examined from all stop-exposure male mice. Tissues examined are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscope slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet-tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent pathology quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated by the quality assessment laboratory. The quality assessment pathologist microscopically reviewed the nose, larynx, and lungs of rats and mice for neoplasms and non-neoplastic lesions. Selected neoplasms at other sites were also examined by the quality assessment pathologist.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologist existed. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnosis between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair to the

PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

## Statistical Methods

### *Survival Analyses*

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Missexed animals and animals found dead of other than natural causes were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

### *Calculation of Incidence*

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B4, C1, C5, D1, D5, E1, and E3 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, D3, and E2) and of all nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed.

### *Analysis of Neoplasm Incidences*

The majority of neoplasms in these studies were considered to be incidental to the cause of death or

not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if the fit of the model was not significantly enhanced. The neoplasm incidences of exposed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of lesion-bearing animals.

Tests of significance included pairwise comparisons of each exposure group with controls, and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, see Haseman (1984).

### *Analysis of Nonneoplastic Lesion Incidences*

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

### *Analysis of Continuous Variables*

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, and urinalysis data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Dunn (1964) and Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

### *Historical Control Data*

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of lesion incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

### *Quality Assurance Methods*

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and board draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

## GENETIC TOXICOLOGY

The genetic toxicology of hexachlorocyclopentadiene was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster*, and the frequency of micronucleated erythrocytes in peripheral blood. The protocols for these studies and the results are given in Appendix F.

The genetic toxicity studies of hexachlorocyclopentadiene are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.



**TABLE 1**  
**Experimental Design and Materials and Methods in the Inhalation Studies of Hexachlorocyclopentadiene**

13-Week Studies	2-Year Studies (including Stop-Exposure Evaluation)
<b>Study Laboratory</b> Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
<b>Strain and Species</b> Rats: F344/N Mice: B6C3F <sub>1</sub>	Rats: F344/N Mice: B6C3F <sub>1</sub>
<b>Animal Source</b> Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)
<b>Size of Study Groups</b> Core studies: 10 males and 10 females Special studies: 20 males and 20 females	Core study: 60 males and 60 females Stop-exposure evaluation: (male mice only) 30 (0 ppm), 80 (0.2 ppm for 33 weeks), 50 (0.2 ppm for 66 weeks), 90 (0.5 ppm for 26 weeks), 70 (0.5 ppm for 42 weeks)
<b>Time Held Before Studies</b> Rats: 14 days Mice: 11 days	Rats: 19 days Mice: 18 days
<b>Average Age When Studies Began</b> 6 weeks	6-7 weeks
<b>Date of First Exposure</b> Rats: 25 October 1983 Mice: 1 November 1983	Rats: 2 December 1985 Mice: 18 November 1985
<b>Duration of Exposure</b> 6 hours per day, 5 days per week, for 13 weeks	Core study: 6 hours per day, 5 days per week, for 15 months or 2 years Stop-exposure evaluation: 6 hours per day, 5 days per week, for 26, 33, 42, or 66 weeks
<b>Date of Last Exposure</b> Rats: 24-26 January 1984 Mice: 1-3 February 1984	Core study - Rats: 20 November 1987 Mice: 13 November 1987 Stop-exposure evaluation - 26-week exposure: 16 May 1986 33-week exposure: 4 July 1986 42-week exposure: 5 September 1986 66-week exposure: 17 February 1987
<b>Method of Sacrifice</b> Pentobarbital sodium	70% CO <sub>2</sub> and exsanguination

**TABLE 1**  
**Experimental Design and Materials and Methods in the Inhalation Studies of Hexachlorocyclopentadiene**  
 (continued)

13-Week Studies	2-Year Studies (including Stop-Exposure Evaluation)
<p><b>Necropsy Dates</b>            Rats: 25-27 January 1984            Mice: 1-3 February 1984</p>	<p>Core study - Rats: 1-4 December 1987            Mice: 16-24 November 1987            Stop-exposure evaluation -            27-week interim evaluation: 19 May 1986            34-week interim evaluation: 7 July 1986            43-week interim evaluation: 8 September 1986            66-week interim evaluation: 18-19 February 1987</p>
<p><b>Average Age at Necropsy</b>            19 weeks</p>	<p>15-month interim evaluation: 72-73 weeks            2-year study: 111-112 weeks</p>
<p><b>Method of Animal Distribution</b>            Animals were randomized by weight with a computer randomization program.</p>	<p>Animals were randomized by weight with the XYBION PATH/TOX System.</p>
<p><b>Animals per Cage</b>            1</p>	<p>1</p>
<p><b>Method of Animal Identification</b>            Ear tag</p>	<p>Toe clip</p>
<p><b>Diet</b>            NIH-07 pelleted rodent diet (Zeigler Brothers, Inc., Gardners, PA), available <i>ad libitum</i> except during exposure period; changed weekly or as necessary;            NIH-07 mash (Zeigler Brothers, Inc., Gardners, PA) (special study)</p>	<p>NIH-07 pelleted rodent diet (Zeigler Brothers, Inc., Gardners PA), available <i>ad libitum</i> except during exposure period; changed weekly or as necessary</p>
<p><b>Water</b>            Tap water (City of Richland) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available <i>ad libitum</i>; changed weekly</p>	<p>Same as 13-week studies</p>
<p><b>Chambers</b>            Stainless steel multitiered whole-body exposure chambers (Hazleton Systems, Aberdeen, MD); washed weekly</p>	<p>Same as 13-week studies</p>
<p><b>Cages</b>            Stainless steel (Hazleton Systems, Inc., Aberdeen, MD); changed weekly</p>	<p>Same as 13-week studies</p>
<p><b>Bedding</b>            Catch pans during exposure days and catch pans lined with untreated paper over weekends</p>	<p>Untreated paper cageboard (Techboard® until 12 March 1986, then Techsorb®, Shepherd Specialty Papers, Inc., Kalamazoo, MI); changed daily</p>

**TABLE 1**  
**Experimental Design and Materials and Methods in the Inhalation Studies of Hexachlorocyclopentadiene**  
 (continued)

13-Week Studies	2-Year Studies (including Stop-Exposure Evaluation)
<p><b>Cage Filters</b>            Room High Efficiency Particle Air (HEPA) filter (prefilter and intake) (American Air Filter, Louisville, KY)</p>	<p>Room High Efficiency Particle Air (HEPA) filter (prefilter and intake) (American Air Filter, Louisville, KY); chamber HEPA filter (Flanders Filters, Inc., San Rafael, CA); and charcoal filters (RSE, Inc., New Baltimore, MD)</p>
<p><b>Animal Room Environment</b>            Temperature: 20°-21° C            Relative humidity: 35%-65%            Fluorescent light: 12 hours/day            Room air changes: 20 changes/hour</p>	<p>Temperature: 20°-29° C            Relative humidity: 21%-88%            Fluorescent light: 12 hours/day            Room air changes: 9-20 changes/hour</p>
<p><b>Exposure Concentrations</b>            0, 0.04, 0.15, 0.4, 1, or 2 ppm hexachlorocyclopentadiene by inhalation</p>	<p>Core study: 0, 0.01, 0.05, or 0.2 ppm hexachlorocyclopentadiene by inhalation            Stop-exposure evaluation:            0, 0.2, or 0.5 ppm hexachlorocyclopentadiene by inhalation</p>
<p><b>Type and Frequency of Observation</b>            Animals were observed twice daily, and clinical observations were recorded weekly; animals were weighed initially, weekly, and at the end of the studies.</p>	<p>Animals were observed twice daily, and clinical observations were recorded every 4 weeks; animals were weighed initially, weekly during first 13 weeks, and monthly thereafter.</p>
<p><b>Necropsy</b>            Necropsy was performed on all animals. Organs weighed (core animals only) were adrenal gland, brain, heart, right kidney, liver, lungs, right testis, and thymus.</p>	<p>Necropsy was performed on all animals. Organs weighed at 27, 34, and 43 weeks for stop-exposure male mice and at 15 months for core and stop-exposure animals were brain, right kidney, liver, and lungs.</p>
<p><b>Clinical Pathology</b>            During the special studies, 5 male and 5 female rats and mice from each group were removed from exposure chambers on days 3, 15, 45, and 92 and placed in individual metabolism cages for 16-hour urine collection.            Blood samples were collected from the lumbar aorta of rats and the supraorbital sinus of mice on days 4, 16, 46, and 93 of the special studies and all animals from the core studies on day 93.  <i>Hematology:</i> packed cell volume, hemoglobin, erythrocytes, reticulocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, leukocyte count and differential  <i>Clinical Chemistry:</i> urea nitrogen, creatinine, glucose, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase (except core mice)  <i>Urinalysis:</i> osmolality, creatinine, glucose, protein, volume</p>	<p>Urine was collected over a 16-hour period from all animals (except stop-exposure animals) at the 15-month interim evaluations using metabolism cages.  <i>Urinalysis:</i> volume and specific gravity</p>

**TABLE 1**  
**Experimental Design and Materials and Methods in the Inhalation Studies of Hexachlorocyclopentadiene**  
 (continued)

13-Week Studies	2-Year Studies (including Stop-Exposure Evaluation)
<p><b>Histopathology</b>            Complete histopathology was performed on all controls, all animals dying before the end of the studies, and all 0.4 ppm animals surviving to the end of the studies. In addition to gross lesions, the tissues examined included: adrenal gland, bone and marrow, brain, epididymis, esophagus, heart, kidney, large intestine (cecum, colon, rectum), larynx, liver, lung, lymph nodes (mandibular, mesenteric [rats only], and tracheobronchial), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. If any lesion was found, that organ was examined at the next lower dose level until a dose level was found without the lesion.</p>	<p>Core study: Complete histopathology was performed on all controls, all female mice, all animals dying before the end of the studies, and all rats and male mice exposed to 0.2 ppm. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, brain, epididymis, esophagus, gallbladder (mice only), heart, kidney, large intestine (cecum, colon, rectum), larynx (rats only), liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, seminal vesicle, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The larynx (rats only), lung, nose, and trachea were also examined in the 0.01 and 0.05 ppm rats and male mice.</p> <p>Stop-exposure evaluation: In addition to gross lesions and tissue masses, the tissues microscopically examined from all stop-exposure male mice included: larynx, lung, nose, and trachea.</p>

## RESULTS

### RATS

#### 13-WEEK STUDY

All male and female rats exposed to 2 ppm hexachlorocyclopentadiene died during the first 3 weeks of the study and all those exposed to 1 ppm died during the first 4 weeks (Table 2). Rats in the 0, 0.04, 0.15, and 0.4 ppm groups survived until the end of the 13-week study. The final mean body weight and mean body weight gain of 0.4 ppm males were

significantly less than those of the controls. The final mean body weights of 0.04 and 0.15 ppm males and all female exposure groups with survivors were similar to those of the controls. Listlessness was observed in 2 ppm rats from week 1, in 1 ppm rats from week 2, and in 0.4 ppm rats during week 3. Rats exposed to 1 or 2 ppm also experienced respiratory distress (mouth breathing and increased respiration rate). No other treatment-related clinical findings of toxicity were noted.

TABLE 2  
Survival and Body Weights of Rats in the 13-Week Inhalation Study of Hexachlorocyclopentadiene

Dose (ppm)	Survival <sup>a</sup>	Mean Body Weight <sup>b</sup> (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
<b>Male</b>					
0	10/10	118 ± 6	352 ± 5	234 ± 6	
0.04	10/10	126 ± 4	335 ± 9	209 ± 7*	95
0.15	10/10	120 ± 3 <sup>c</sup>	332 ± 9	213 ± 8*	94
0.4	10/10	124 ± 4	326 ± 7*	202 ± 5**	93
1	0/10 <sup>d</sup>	127 ± 3	—	—	—
2	0/10 <sup>e</sup>	123 ± 3	—	—	—
<b>Female</b>					
0	10/10	102 ± 2	200 ± 5	98 ± 5	
0.04	10/10	103 ± 2	199 ± 5	96 ± 4	99
0.15	10/10	108 ± 2	202 ± 4	94 ± 2	101
0.4	10/10	103 ± 2	197 ± 4	94 ± 3	98
1	0/10 <sup>f</sup>	103 ± 2	—	—	—
2	0/10 <sup>g</sup>	101 ± 2	—	—	—

\* Significantly different ( $P \leq 0.05$ ) from the control group by Williams' test

\*\*  $P \leq 0.01$

<sup>a</sup> Number of animals surviving/number initially in group

<sup>b</sup> Weights and weight changes are given as mean ± standard error. Final mean body weights were not calculated for groups with 100% mortality.

<sup>c</sup> Nine animals weighed

<sup>d</sup> Week of death: 2, 2, 2, 3, 3, 3, 3, 3, 3

<sup>e</sup> Week of death: 1, 1, 1, 1, 1, 2, 2, 2, 3, 3

<sup>f</sup> Week of death: 2, 2, 2, 2, 2, 2, 3, 3, 3, 4

<sup>g</sup> Week of death: 1, 1, 1, 1, 1, 1, 2, 2, 2, 3

Statistically significant differences in hematology, clinical chemistry (except core females), and urinalysis (special study) parameters were noted in exposed male and female rats in the core and special studies (Tables H1 and H2). However, these differences were not attributed to hexachlorocyclopentadiene exposure because the differences were not persistent, were not dose related, or were inconsistent between identical exposure groups and between sexes.

Absolute and relative lung weights of male rats exposed to 0.4 ppm were significantly greater than those of the controls; differences in relative weights of other organs were likely affected by the lower body weights of exposed rats (Table G1). Absolute and relative thymus weights of 0.04 ppm females and relative thymus weight of 0.15 ppm females were marginally lower than those of the controls, but these differences were not related to exposure.

The primary lesion in rats exposed to 1 or 2 ppm hexachlorocyclopentadiene was extensive coagulation necrosis (inflammation, necrotizing) of the respiratory epithelium of the nose, larynx, trachea, and bronchi and bronchioles of the lung (Table 3). The necrosis was accompanied by varying degrees of acute to subacute inflammation consisting of vascular congestion, edema, accumulation of fibrin, and infiltrates of neutrophils and mononuclear cells. In

some animals, portions of the necrotic epithelium were sloughed and replaced by a fibrinosuppurative exudate. Suppurative alveolar inflammation was also observed in the centriacinar regions of the lung (terminal bronchioles and adjacent alveoli) possibly due to inhalation of necrotic debris from the upper airways. Particularly in animals which survived longer, there were areas of epithelial regeneration characterized by a single layer of flattened polygonal cells or low cuboidal cells.

In rats exposed to 0.4 ppm hexachlorocyclopentadiene, necrosis of the respiratory epithelium did not occur or was much less extensive in the few affected animals (Table 3). Focal or multifocal suppurative inflammation of the nose or lung was observed, particularly in male rats. Focal squamous metaplasia was observed in the nose of some 0.4 ppm males and some 1 and 2 ppm males and females. The lesion was usually observed on the tips of the turbinates and was characterized by stratification of the epithelium to form three to four poorly defined layers of flattened, nonkeratinized polygonal cells.

*Dose Selection Rationale:* Based on mortality, lower mean body weights, and chemical-related respiratory tract lesions, hexachlorocyclopentadiene exposure levels selected for the 2-year inhalation study in rats were 0.01, 0.05, and 0.2 ppm.

**TABLE 3**  
**Incidences of Selected Nonneoplastic Lesions of the Respiratory Tract in Rats**  
**in the 13-Week Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

Dose (ppm)	0	0.15	0.4	1	2
<b>Male</b>					
Nose <sup>b</sup>	10	10	10	10	10
Inflammation, Necrotizing <sup>c</sup>	0	0	2 (2.0) <sup>d</sup>	10** (2.8)	10** (3.8)
Inflammation, Suppurative	0	1 (1.0)	7** (1.4)	0	0
Metaplasia, Squamous	0	0	4* (1.8)	5* (1.8)	3 (2.3)
Larynx	10	10	10	10	10
Inflammation, Necrotizing	0	0	0	6** (2.2)	10** (3.3)
Trachea	10	10	10	10	10
Inflammation, Necrotizing	0	0	1 (1.0)	10** (2.2)	10** (3.9)
Lung	10	10	10	10	10
Inflammation, Necrotizing					
Bronchus/bronchiole	0	0	5* (1.2)	10** (3.4)	10** (4.0)
Inflammation, Suppurative					
Bronchus/bronchiole	0	0	5* (1.2)	0	1 (3.0)
Hemorrhage, Alveolus	0	0	0	9** (2.3)	10** (2.7)
Inflammation, Suppurative, Alveolus	0	0	1 (1.0)	7** (2.6)	1 (3.0)
<b>Female</b>					
Nose	10	10	10	10	10
Inflammation, Necrotizing	0	0	0	10** (2.9)	10** (3.7)
Inflammation, Suppurative	1 (3.0)	0	2 (1.0)	0	0
Metaplasia, Squamous	1 (3.0)	0	0	1 (3.0)	4 (2.5)
Larynx	10	10	10	10	10
Inflammation, Necrotizing	0	0	1 (1.0)	9** (1.6)	9** (2.8)
Trachea	10	10	10	10	10
Inflammation, Necrotizing	0	0	1 (1.0)	10** (2.1)	10** (3.6)
Lung	10	10	10	10	10
Inflammation, Necrotizing					
Bronchus/bronchiole	0	0	3 (1.3)	10** (3.3)	10** (3.9)
Inflammation, Suppurative					
Bronchus/bronchiole	0	0	2 (1.0)	0	1 (3.0)
Hemorrhage, Alveolus	0	0	0	5* (2.4)	7** (3.1)
Inflammation, Suppurative, Alveolus	0	1 (1.0)	1 (1.0)	9** (2.7)	2 (3.0)

\* Significantly different ( $P \leq 0.05$ ) from the control group by Fisher's exact test

\*\*  $P \leq 0.01$

<sup>a</sup> Animals in the 0.04 ppm group were not examined

<sup>b</sup> Number of animals with organ examined microscopically

<sup>c</sup> Number of animals with lesion

<sup>d</sup> Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe

## 2-YEAR STUDY

### Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 4 and the Kaplan-Meier survival curves (Figure 1). Survival of exposed male and female rats was similar to that of controls.

### Body Weights and Clinical Findings

Mean body weights of exposed male and female rats were similar to those of the controls throughout the study (Tables 5 and 6 and Figure 2). No chemical-related clinical findings were observed in male or female rats during the 2-year study.

### Urinalysis

At the 15-month interim evaluation, specific gravity measurements of urine from males exposed to 0.01, 0.05, and 0.2 ppm and from females exposed to 0.05 and 0.2 ppm hexachlorocyclopentadiene were significantly greater than those from the controls (Table H3). Urine volume of females in the 0.2 ppm group was significantly lower than that of the controls. These differences suggest a chemical-related renal disorder, but the lack of chemical-related kidney lesions does not support such a conclusion.

TABLE 4  
Survival of Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene

Dose (ppm)	0	0.01	0.05	0.2
<b>Male</b>				
Animals initially in study	60	60	60	60
15-Month interim evaluation <sup>a</sup>	10	10	10	10
Moribund	27	30	23	31
Natural deaths	5	4	5	3
Animals surviving to study termination	18	16	22	16
Percent probability of survival at end of study <sup>b</sup>	36	33	45	32
Mean survival (days) <sup>c</sup>	627	616	624	609
Survival analyses <sup>d</sup>	P=0.649	P=0.775	P=0.513N	P=0.679
<b>Female</b>				
Animals initially in study	60	60	60	60
15-Month interim evaluation <sup>a</sup>	10	10	10	10
Moribund	19	16	14	16
Natural deaths	3	1	5	4
Animals surviving to study termination	28	33	30	30
Missexed <sup>a</sup>	0	0	1	0
Percent probability of survival at end of study	56	66	62	60
Mean survival (days)	649	665	636	657
Survival analyses	P=0.988	P=0.361N	P=0.958N	P=0.843N

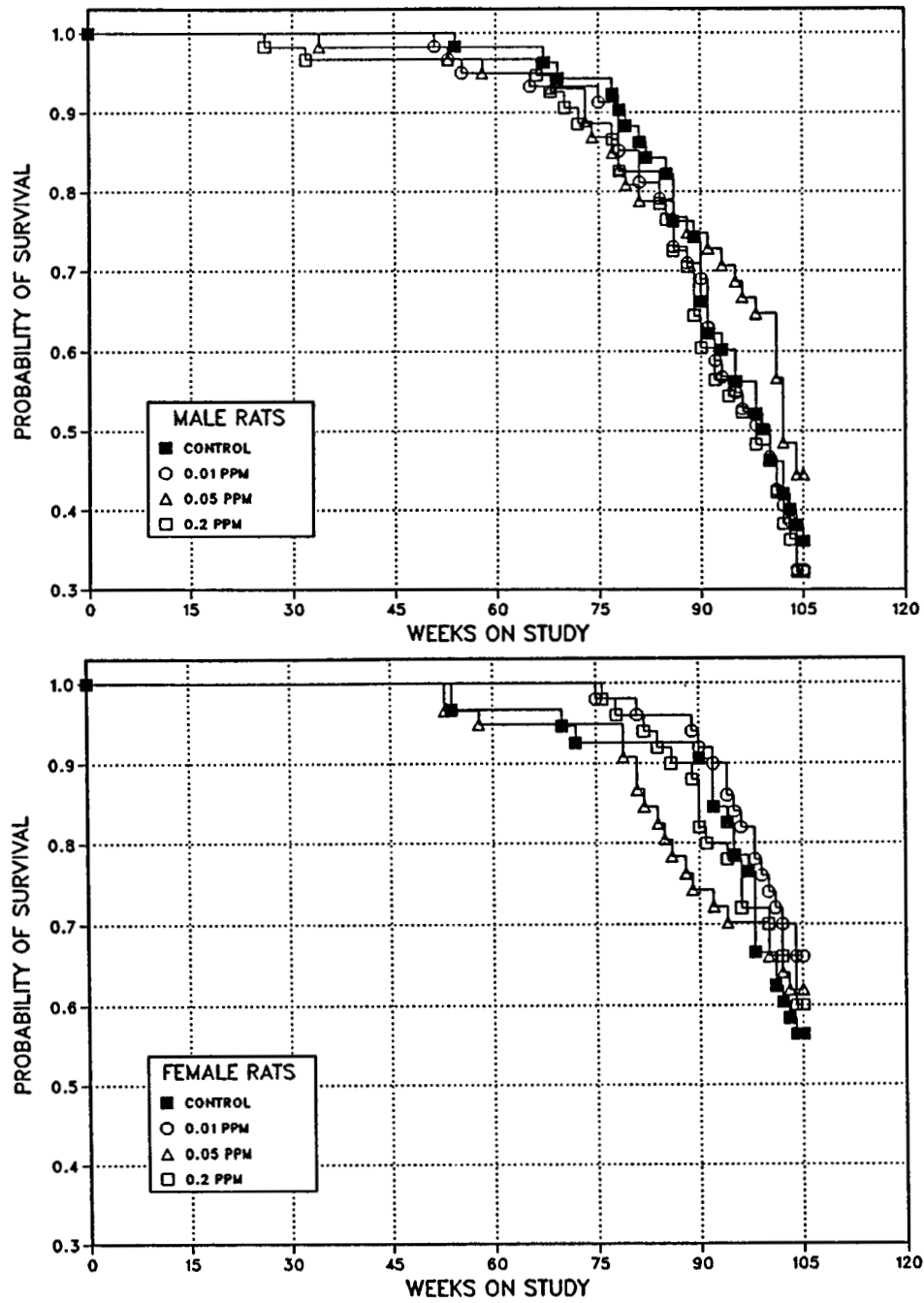
<sup>a</sup> Censored from survival analyses

<sup>b</sup> Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice

<sup>c</sup> Mean of all deaths (uncensored, censored, and terminal sacrifice)

<sup>d</sup> The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposure columns. A lower mortality in an exposure group is indicated by N.





**FIGURE 1**  
**Kaplan-Meier Survival Curves for Rats Administered Hexachlorocyclopentadiene by Inhalation for 2 Years**

**TABLE 5**  
**Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene**

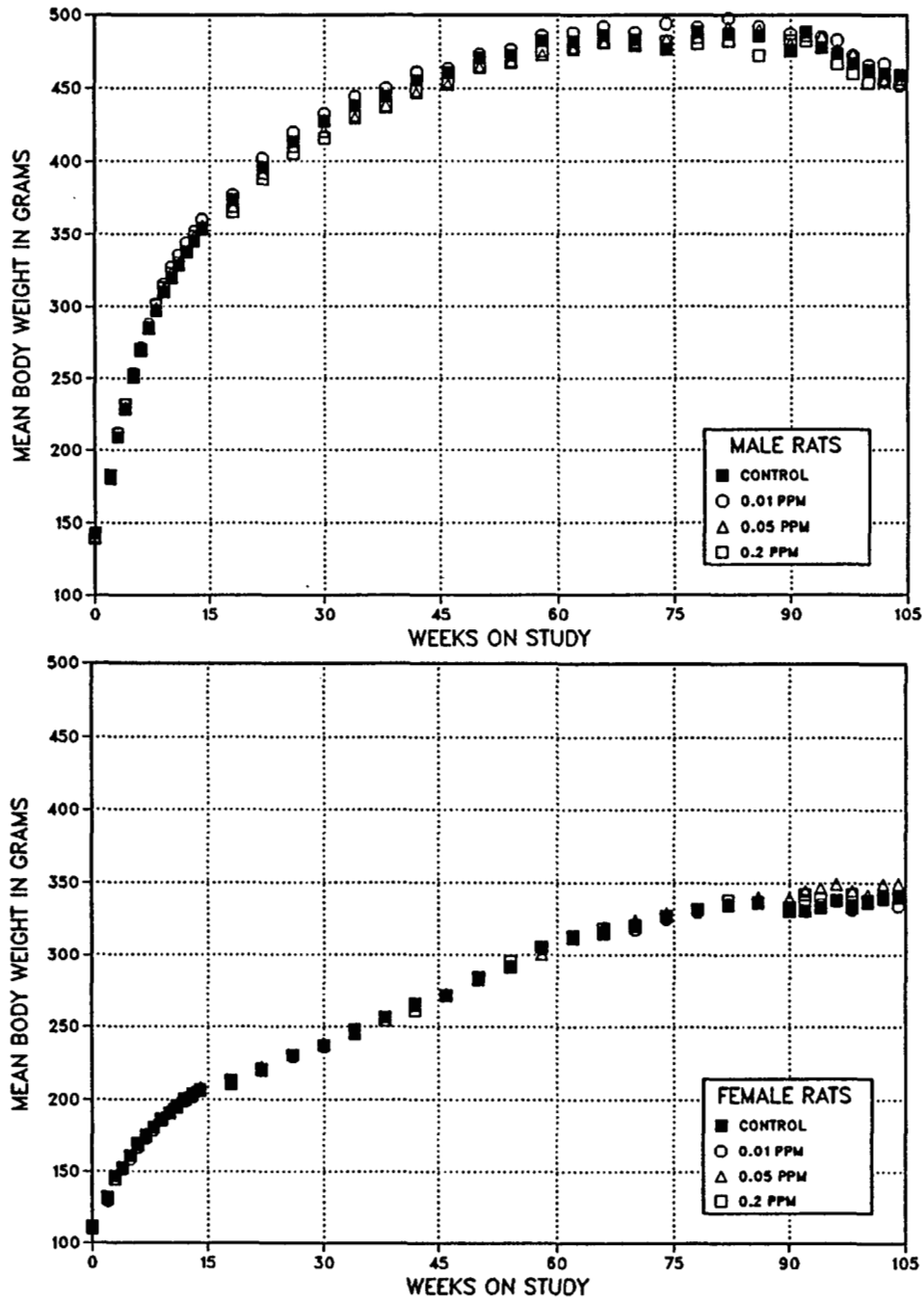
Weeks on Study	0 ppm		0.01 ppm			0.05 ppm			0.2 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	143	60	143	100	60	140	98	60	139	98	60
2	183	60	182	99	60	180	99	60	182	99	60
3	209	60	212	101	60	210	100	60	211	101	60
4	229	60	232	101	60	230	101	60	232	101	60
5	251	60	254	101	60	251	100	60	253	101	60
6	269	60	272	101	60	270	100	60	271	101	60
7	285	60	288	101	60	285	100	60	286	100	60
8	297	60	302	102	60	299	101	60	301	101	60
9	310	60	316	102	60	312	101	60	313	101	60
10	320	60	327	102	60	323	101	60	323	101	60
11	329	60	336	102	60	329	100	60	330	101	60
12	338	60	344	102	60	338	100	60	338	100	60
13	345	60	352	102	60	349	101	60	349	101	60
14	353	60	360	102	60	356	101	60	354	100	60
18	374	60	377	101	60	369	99	60	366	98	60
22	396	60	402	101	60	392	99	60	388	98	60
26	414	60	420	102	60	410	99	60	406	98	60
30	427	60	432	101	60	421	98	60	416	97	59
34	438	60	444	101	60	430	98	60	431	98	58
38	445	60	450	101	60	438	99	59	437	98	58
42	456	60	461	101	60	447	98	59	448	98	58
46	461	60	463	101	60	453	98	59	455	99	58
50	471	60	473	101	60	464	99	59	465	99	58
54	473	60	476	101	58	469	99	58	468	99	58
58	482	59	486	101	57	473	98	58	475	99	58
62	482	59	488	101	57	477	99	57	478	99	58
66 <sup>a</sup>	486	59	492	101	56	481	99	57	482	99	58
70	483	47	488	101	46	481	100	46	479	99	46
74	477	47	494	104	46	483	101	44	482	101	44
78	488	46	491	101	44	485	99	42	481	98	43
82	487	43	498	102	40	492	101	39	483	99	41
86	486	41	492	101	39	490	101	39	472	97	38
90	475	36	487	102	35	480	101	37	482	101	32
92	488	31	489	100	31	486	100	36	482	99	30
94	478	30	485	102	28	486	102	35	478	100	28
96	474	28	483	102	27	476	101	33	467	99	27
98	467	28	472	101	26	473	101	32	460	99	26
100	463	24	466	101	25	461	100	32	454	98	24
102	460	23	467	101	21	455	99	28	456	99	21
104	459	20	452	98	19	453	99	24	456	99	18
<b>Mean for weeks</b>											
1-13	270		274	101		270	100		271	100	
14-52	424		428	101		418	99		417	98	
53-104	477		483	101		477	100		473	99	

<sup>a</sup> Interim evaluation occurred during week 66.

**TABLE 6**  
**Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene**

Weeks on Study	0 ppm		0.01 ppm			0.05 ppm			0.2 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	112	60	111	100	60	110	98	60	111	99	60
2	132	60	129	98	60	130	99	60	130	99	60
3	147	60	144	98	60	144	98	60	145	98	60
4	153	60	151	99	60	152	100	60	153	100	60
5	161	60	159	99	60	161	100	60	161	100	60
6	169	60	166	99	60	170	101	59	170	101	60
7	175	60	173	99	60	176	101	59	175	100	60
8	181	60	179	99	60	183	101	59	181	100	60
9	187	60	185	99	60	188	101	59	186	100	60
10	190	60	191	101	60	194	102	59	191	101	60
11	194	60	196	101	60	198	102	59	196	101	60
12	200	60	199	99	60	202	101	59	200	100	60
13	203	60	202	99	60	206	101	59	204	100	60
14	206	60	206	100	60	208	101	59	207	100	60
18	213	60	212	99	60	213	100	59	211	99	60
22	221	60	220	100	60	222	101	59	220	100	60
26	230	60	229	99	60	230	100	59	230	100	60
30	237	60	236	100	60	239	101	59	237	100	60
34	248	60	247	99	60	249	100	59	245	99	60
38	256	60	254	99	60	255	99	59	254	99	60
42	266	60	265	100	60	264	99	59	261	98	60
46	272	60	272	100	60	273	100	59	272	100	60
50	285	60	283	99	60	283	99	59	284	100	60
54	291	60	293	100	60	293	101	57	296	101	60
58	306	58	304	100	60	301	98	57	306	100	60
62	312	58	312	100	60	312	100	56	314	101	60
66 <sup>a</sup>	315	58	317	101	60	320	102	56	319	101	60
70	321	48	318	99	50	325	101	46	321	100	50
74	327	46	326	100	50	330	101	46	328	100	50
78	332	46	330	100	49	333	100	46	332	100	49
82	335	46	336	100	48	336	100	42	339	101	48
86	337	46	337	100	48	341	101	39	337	100	45
90	331	46	333	101	47	340	103	36	334	101	44
92	331	45	339	102	45	345	104	36	343	103	40
94	334	42	336	101	45	347	104	34	340	102	40
96	338	39	338	100	42	350	103	34	339	100	39
98	334	37	332	100	41	345	103	34	343	103	36
100	337	33	338	101	37	342	102	34	339	101	36
102	340	31	339	100	36	349	103	32	340	100	35
104	340	29	334	98	35	350	103	30	341	100	33
<b>Mean for weeks</b>											
1-13	170		168	99		170	100		169	99	
14-52	243		242	100		244	100		242	100	
53-104	327		327	100		333	102		330	101	

<sup>a</sup> Interim evaluation occurred during week 66.



**FIGURE 2**  
**Growth Curves for Rats Administered Hexachlorocyclopentadiene by Inhalation for 2 Years**

### ***Pathology and Statistical Evaluation***

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the respiratory tract (nose, larynx, trachea, and lung) and neoplasms of the pituitary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

*Respiratory tract:* There were no chemical-related lesions observed in the respiratory tract of exposed rats at the 15-month interim evaluation. While the absolute lung weights of the 0.05 and 0.2 ppm males were significantly lower than that of the controls, the relative lung weights of these groups were similar (0.05 ppm males) or only marginally lower (0.2 ppm males) than that of the controls (Table G2). Thus, it seems likely that the lower absolute lung weights are related to lower body weights rather than to chemical exposure.

The principal alteration associated with the inhalation of hexachlorocyclopentadiene for up to 2 years was the accumulation of pale, yellow-brown, granular pigment in the respiratory epithelium of the nose, trachea, and bronchi and bronchioles of the lung (Tables 7, A5, and B4). Similar pigment was observed in a few cells, presumed to be macrophages, surrounding the bronchi and bronchioles of exposed rats, as well as in a small number of controls. Sections of lung from two male and two female rats were stained by a periodic acid-Schiff method for mucopolysaccharides, mucoproteins, and carbohydrates, a method for acid-fast substances, a modified Perls' method for iron, and Schmorl's method for reducing substances (lipofuscin and ceroid). The pigment within the cytoplasm of epithelial cells of the airways did not stain positively

by the periodic acid-Schiff, Perls', or acid-fast methods. The pigment within many, but not all, of the affected cells in the lungs stained positively for reducing substances. While a positive reaction with the Schmorl's method is consistent with lipofuscin or ceroid, it does not definitely identify the pigment as such.

In female rats, the incidences of squamous metaplasia of the larynx of the 0.01 and 0.2 ppm groups were significantly greater than that of the control group. The severity of squamous metaplasia was minimal in all groups. The apparent change diagnosed as squamous metaplasia consisted of stratified squamous epithelium several cell layers thick and was believed to be located in areas usually lined by columnar epithelium. A nonkeratinized squamous epithelium normally lines the upper posterior surface of the epiglottis, upper half of the laryngeal surface, a portion of the ventricular folds, and the true vocal cords, while a nonciliated columnar or pseudostratified, ciliated columnar epithelium lines the remainder of the laryngeal surface. Due to individual variation in determining where the transition from squamous to columnar epithelium occurs, as well as difficulties in obtaining consistent sections, the relevance of the higher incidences of squamous metaplasia in the 0.01 and 0.2 ppm groups is uncertain.

*Pituitary gland:* There was a statistically significant increased incidence of pars distalis adenoma in 0.2 ppm males (0 ppm, 23/50; 0.01 ppm, 23/39; 0.05 ppm, 23/38; 0.2 ppm 33/50; Table A3). The historical control incidence of pars distalis adenoma in male F344/N rats from recent NTP inhalation studies is 203/340 (60%), with a range of 45% to 68% (Table A4). The marginally increased incidence observed in the 0.2 ppm group was similar to the historical control mean and was not considered to be chemical related. The incidences of hyperplasia of the pituitary gland in the exposed groups were similar to that of the controls (Table A5).

**TABLE 7**  
**Incidences of Selected Nonneoplastic Lesions of the Respiratory Tract in Rats**  
**in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**

Dose (ppm)	0	0.01	0.05	0.2
<b>Male</b>				
<b>15-Month Interim Evaluation</b>				
Nose <sup>a</sup>	10	10	10	10
Pigmentation <sup>b</sup>	0	8** (1.0) <sup>c</sup>	10** (1.0)	7** (1.6)
Lung	10	10	10	10
Bronchiole Pigmentation	0	0	1 (1.0)	10** (1.1)
Peribronchiole Pigmentation	0	0	0	4* (1.3)
<b>2-Year Study</b>				
Nose	48	50	49	50
Pigmentation	1 (1.0)	46** (1.1)	48** (1.5)	48** (1.8)
Trachea	48	50	48	50
Inflammation, Suppurative	0	1 (2.0)	0	0
Pigmentation	0	0	0	5* (1.0)
Lung	50	50	50	50
Bronchiole Pigmentation	0	0	0	49** (1.4)
Peribronchiole Pigmentation	0	0	2 (1.0)	16** (1.5)
<b>(continued)</b>				

**TABLE 7**  
**Incidences of Selected Nonneoplastic Lesions of the Respiratory Tract in Rats**  
**in the 2-Year Inhalation Study of Hexachlorocyclopentadiene (continued)**

Dose (ppm)	0	0.01	0.05	0.2
<b>Female</b>				
<b>15-Month Interim Evaluation</b>				
Nose	10	10	10	10
Pigmentation	0	8** (1.0)	10** (1.0)	9** (1.2)
Lung	10	10	10	10
Bronchiole Pigmentation	0	1 (1.0)	6** (1.0)	10** (1.5)
Peribronchiole Pigmentation	0	0	1 (1.0)	8** (1.0)
<b>2-Year Study</b>				
Nose	50	50	49	50
Pigmentation	0	34** (1.0)	47** (1.7)	48** (1.7)
Larynx	50	50	48	50
Metaplasia, Squamous	9 (1.0)	20* (1.2)	15 (1.1)	24** (1.3)
Trachea	50	50	49	50
Pigmentation	0	0	0	1 (1.0)
Lung	50	50	49	50
Bronchiole Pigmentation	0	25** (1.0)	42** (1.1)	50** (1.8)
Peribronchiole Pigmentation	3 (1.0)	1 (1.0)	4 (1.0)	27** (1.0)

\* Significantly different ( $P \leq 0.05$ ) from the control group by Fisher's exact test (15-month interim evaluation) or by the logistic regression test (2-year study)

\*\*  $P \leq 0.01$

<sup>a</sup> Number of animals with organ examined microscopically

<sup>b</sup> Number of animals with lesion

<sup>c</sup> Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

## MICE

### 13-WEEK STUDY

All males and females exposed to 2 ppm hexachlorocyclopentadiene died during the first week (Table 8). All 1 ppm males and females died during the first 5 weeks of exposure. Five males and two females exposed to 0.4 ppm died during the first 2 weeks of exposure. In addition, two 0.04 ppm males, one 0.04 ppm female, and one 0.15 ppm female died before the end of the study. Six female controls died during week 8 due to a defective feeder. Final mean body weights of 0.15 and 0.4 ppm males and the body weight gain of 0.4 ppm males were significantly lower

than those of the controls. Final mean body weights and mean body weight gains of the other male and female exposure groups with survivors were similar to those of the controls. Treatment-related clinical findings included listlessness in 0.4 and 1 ppm males and females.

No chemical-related differences in hematology, clinical chemistry, or urinalysis parameters were noted in exposed males or females (Tables H4 and H5). No differences in these parameters could be attributed to duration of exposure. There were no chemical-related differences in organ weights (Table G3).

**TABLE 8**  
Survival and Body Weights of Mice in the 13-Week Inhalation Study of Hexachlorocyclopentadiene

Dose (ppm)	Survival <sup>a</sup>	Mean Body Weight <sup>b</sup> (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
<b>Male</b>					
0	10/10	21.9 ± 0.4	31.9 ± 0.5	10.0 ± 0.6	
0.04	8/10 <sup>c</sup>	19.4 ± 0.5**	31.9 ± 0.6	12.5 ± 0.8	100
0.15	10/10	21.4 ± 0.5	29.8 ± 0.5**	8.4 ± 0.4	93
0.4	5/10 <sup>d</sup>	21.4 ± 0.3	29.4 ± 0.6**	7.2 ± 0.7**	92
1	0/10 <sup>e</sup>	21.2 ± 0.3	—	—	—
2	0/10 <sup>f</sup>	21.1 ± 0.4	—	—	—
<b>Female</b>					
0	4/10 <sup>g</sup>	17.4 ± 0.4	26.0 ± 0.9	8.0 ± 0.7	
0.04	9/10 <sup>h</sup>	18.0 ± 0.4	27.4 ± 0.7	9.3 ± 0.5	106
0.15	9/10 <sup>h</sup>	17.4 ± 0.3	26.1 ± 0.4	8.8 ± 0.2	100
0.4	8/10 <sup>i</sup>	17.0 ± 0.4	25.6 ± 0.4	8.6 ± 0.5	99
1	0/10 <sup>j</sup>	16.9 ± 0.4	—	—	—
2	0/10 <sup>f</sup>	16.6 ± 0.3	—	—	—

\*\* Significantly different ( $P \leq 0.01$ ) from the control group by Williams' or Dunnett's test

<sup>a</sup> Number of animals surviving/number initially in group

<sup>b</sup> Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Final mean body weights were not calculated for groups with 100% mortality.

<sup>c</sup> Week of death: 5, 5

<sup>d</sup> Week of death: 1, 1, 1, 1, 2

<sup>e</sup> Week of death: 1, 1, 1, 2, 2, 2, 2, 2, 2, 5

<sup>f</sup> Week of death: 1, 1, 1, 1, 1, 1, 1, 1, 1

<sup>g</sup> Week of death: 8, 8, 8, 8, 8, 8 (due to defective feeder)

<sup>h</sup> Week of death: 1

<sup>i</sup> Week of death: 1, 2

<sup>j</sup> Week of death: 1, 1, 2, 2, 2, 2, 2, 2, 3, 5



Most male and female mice exposed to 2 ppm hexachlorocyclopentadiene exhibited extensive coagulation necrosis of the respiratory epithelium of the nose, larynx, trachea, and bronchi and bronchioles (Table 9). While some degree of vascular congestion, edema, serofibrinous exudate, or infiltration of neutrophils accompanied the necrosis, the degree of inflammation was not as great as that observed in rats exposed to 2 ppm. In mice exposed to 1 ppm, the severity of inflammation was generally greater than that observed in mice exposed to 2 ppm, presumably because of the longer survival of animals in the 1 ppm groups. Foci of suppurative inflammation not directly associated with necrosis of the epithelium were also observed in the nose of mice in the 0.4, 1, and 2 ppm groups. In some mice exposed to 1 or

2 ppm hexachlorocyclopentadiene, the necrotic epithelium at some sites was sloughed and replaced by a fibrinosuppurative exudate. Foci of regenerating epithelium characterized by flattened polygonal or low cuboidal cells were observed in the nose, larynx, trachea, and pulmonary airways. Some mice exposed to 0.15, 0.4, or 1 ppm exhibited small foci of squamous metaplasia in the larynx or trachea. This lesion was characterized by 3 to 4 poorly defined layers of nonkeratinized, flattened polygonal cells.

*Dose Selection Rationale:* Based on mortality, lower mean body weights, and chemical-related respiratory tract lesions, hexachlorocyclopentadiene exposure levels selected for the 2-year inhalation study in mice were 0.01, 0.05, and 0.2 ppm.

**TABLE 9**  
**Incidences of Selected Nonneoplastic Lesions of the Respiratory Tract in Mice**  
**in the 13-Week Inhalation Study of Hexachlorocyclopentadiene**

Dose (ppm)	0	0.04	0.15	0.4	1	2
<b>Male</b>						
Nose <sup>a</sup>	10	10	10	10	10	10
Necrosis, Acute <sup>b</sup>	0	0	0	0	1 (4.0) <sup>c</sup>	10** (4.0)
Inflammation, Serous	0	1 (2.0)	2 (2.0)	3 (3.3)	1 (4.0)	0
Inflammation, Suppurative	0	0	0	6** (2.0)	8** (2.8)	4* (2.5)
Larynx	9	10	10	10	10	10
Necrosis, Acute	0	0	0	0	3 (3.3)	10** (4.0)
Metaplasia, Squamous	0	0	0	2 (3.0)	1 (3.0)	0
Trachea	8	10	8	8	7	9
Necrosis, Acute	0	0	0	0	3 (3.7)	9** (4.0)
Inflammation, Necrotizing	0	0	0	0	1 (3.0)	0
Metaplasia, Squamous	0	0	1 (2.0)	4* (2.8)	4* (3.3)	0
Lung	10	10	10	10	10	10
Necrosis, Acute	0	0	0	0	3 (4.0)	10** (4.0)
Congestion	0	1 (2.0)	0	3 (2.7)	0	9** (2.9)
<b>Female</b>						
Nose	10	10	9	10	10	10
Necrosis, Acute	0	0	0	0	0	10** (4.0)
Inflammation, Serous	0	0	2 (2.0)	7** (3.1)	1 (4.0)	0
Inflammation, Suppurative	0	0	0	2 (2.5)	8** (3.0)	5* (2.6)
Larynx	10	10	9	10	10	10
Necrosis, Acute	0	0	0	0	0	9** <sup>d</sup> (4.0)
Metaplasia, Squamous	0	0	0	0	7** <sup>d</sup> (2.7)	0
Trachea	8	10	8	7	10	9
Necrosis, Acute	0	0	0	0	2 (4.0)	9** (4.0)
Inflammation, Necrotizing	0	0	0	0	2 (4.0)	0
Metaplasia, Squamous	0	0	0	2 (2.0)	7** (3.1)	0
Lung	10	10	9	10	10	10
Necrosis, Acute	0	0	0	0	1 (4.2)	10** (4.0)
Inflammation, Necrotizing	0	0	0	0	9** (3.8)	0
Congestion	0	0	0	0	0	9** (3.1)
Inflammation, Suppurative	0	0	0	0	0	1 (3.0)
Adenoma	0	0	1	0	0	0

\* Significantly different ( $P \leq 0.05$ ) from the control group by Fisher's exact test

\*\*  $P \leq 0.01$

<sup>a</sup> Number of animals with organ examined microscopically

<sup>b</sup> Number of animals with lesion

<sup>c</sup> Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe

<sup>d</sup> n=9

## 2-YEAR STUDY

### Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 10 and in the Kaplan-Meier curves in Figure 3. Survival of 0.2 ppm females was marginally lower than that of controls due to the higher incidence of ovarian inflammation in the 0.2 ppm females. Survival of exposed males and 0.01 and 0.05 ppm females was similar to that of the controls.

### Body Weights and Clinical Findings

Final mean body weights of males exposed to 0.01, 0.05, and 0.2 ppm hexachlorocyclopentadiene were within 5% of that of controls (Figure 4 and Table 11). However, the mean body weights of 0.2 ppm males were lower than those of the controls

during weeks 62 to 103. The mean body weights of 0.2 ppm females were lower than those of controls throughout the study. The final mean body weights of the remaining exposure groups were similar to those of the controls (Table 12 and Figure 4). No chemical-related clinical findings were observed in male or female mice during the 2-year study.

### Urinalysis

At the 15-month interim evaluation, the specific gravity of urine from males exposed to 0.05 and 0.2 ppm was slightly higher than that from the controls (Table H6). Urine volume in 0.2 ppm females was lower than that in the controls (Table H6). These differences did not represent an adverse change in renal function and were not chemical-related.

**TABLE 10**  
**Survival of Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**

Dose (ppm)	0	0.01	0.05	0.2
<b>Male</b>				
Animals initially in study	60 <sup>a</sup>	60	60	60
15-Month interim evaluation <sup>b</sup>	10	10	10	10
Accidental deaths <sup>b</sup>	1	2	0	0
Moribund	8	6	3	9
Natural deaths	6	9	5	7
Animals surviving to study termination	35	33	42	34
Percent probability of survival at end of study <sup>c</sup>	72	70	84	69
Mean survival (days) <sup>d</sup>	510	646	673	647
Survival analyses <sup>e</sup>	P=0.630	P=0.936	P=0.204N	P=0.794
<b>Female</b>				
Animals initially in study	60	60	60	60
15-Month interim evaluation <sup>b</sup>	10	10	10	10
Accidental deaths <sup>b</sup>	1	0	1	1
Moribund	8	10	11	15
Natural deaths	10	8	8	13
Animals surviving to study termination	31	32	30	21
Percent probability of survival at end of study	64	64	62	43
Mean survival (days)	638	651	645	610
Survival analyses	P=0.010	P=1.000N	P=0.942	P=0.053

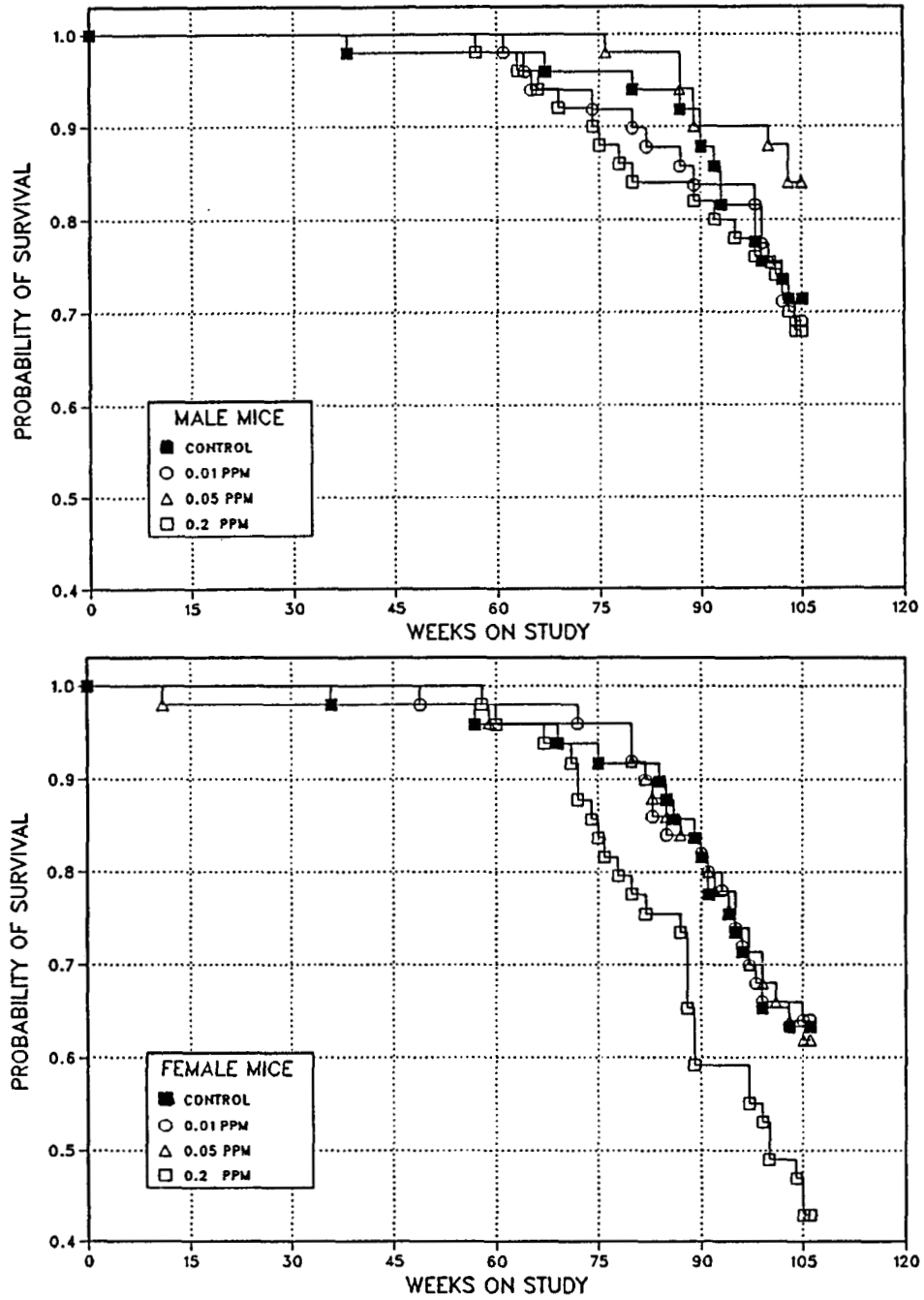
<sup>a</sup> Excludes the 30 male mice used as controls in the stop-exposure evaluation

<sup>b</sup> Censored from survival analyses

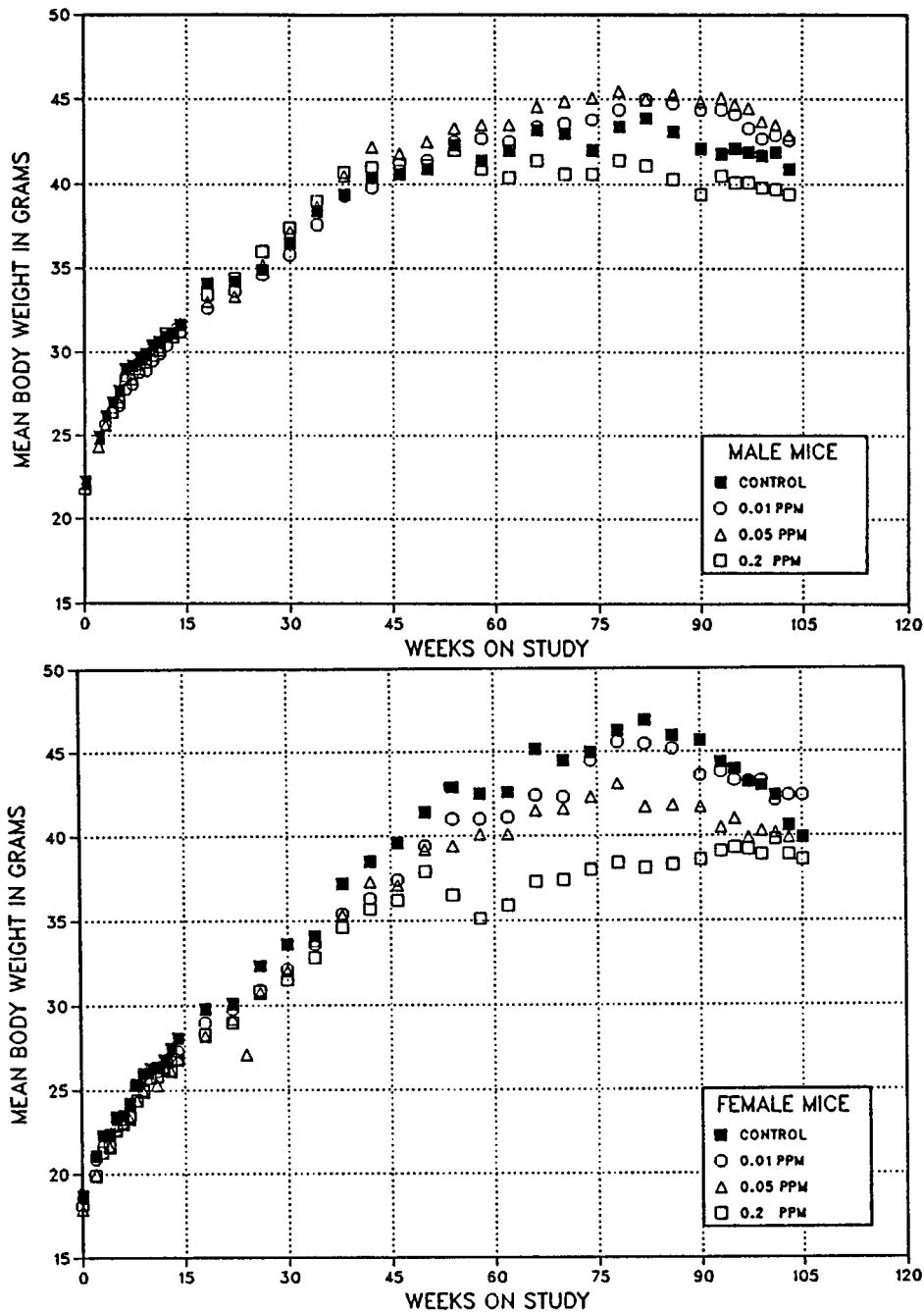
<sup>c</sup> Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice

<sup>d</sup> Mean of all deaths (uncensored, censored, and terminal sacrifice)

<sup>e</sup> The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposure columns. A lower mortality in an exposure group is indicated by N.



**FIGURE 3**  
**Kaplan-Meier Survival Curves for Mice Administered Hexachlorocyclopentadiene by Inhalation for 2 Years**



**FIGURE 4**  
Growth Curves for Mice Administered Hexachlorocyclopentadiene by Inhalation for 2 Years

**TABLE 11**  
**Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene**

Weeks on Study	0 ppm		0.01 ppm			0.05 ppm			0.2 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	22.2	90	22.1	100	60	22.1	100	60	21.8	98	60
2	24.9	90	24.9	100	60	24.3	98	60	24.8	100	60
3	26.2	90	25.7	98	60	25.6	98	60	26.2	100	60
4	27.0	90	26.4	98	60	26.7	99	60	26.4	98	60
5	27.7	90	26.8	97	60	27.0	98	60	27.3	99	60
6	29.0	89	27.8	96	60	28.6	99	60	28.4	98	60
7	29.2	89	28.1	96	60	28.4	97	60	28.7	98	60
8	29.7	89	28.8	97	60	29.0	98	60	29.3	99	60
9	29.9	89	28.9	97	60	29.6	99	60	29.4	98	60
10	30.4	89	29.5	97	60	30.1	99	60	29.8	98	60
11	30.6	89	29.9	98	60	30.1	98	60	30.3	99	60
12	30.9	89	30.4	98	60	30.9	100	60	31.1	101	60
13	31.1	89	30.9	99	60	31.4	101	60	30.9	99	60
14	31.6	89	31.2	99	60	31.7	100	60	31.2	99	60
18	34.1	89	32.6	96	60	33.0	97	60	33.4	98	60
22	34.2	89	33.6	98	60	33.3	97	60	34.4	101	60
26	34.9	89	34.6	99	60	35.2	101	60	36.1	103	60
30 <sup>a</sup>	36.5	79	35.8	98	60	37.2	102	60	37.4	103	60
34 <sup>a</sup>	38.4	69	37.6	98	60	38.7	101	60	39.0	102	60
38	39.4	69	39.3	100	60	40.5	103	60	40.7	103	60
42	40.4	68	39.8	99	60	42.2	105	60	41.0	102	60
46 <sup>a</sup>	40.6	58	40.8	101	60	41.8	103	60	41.2	102	60
50	40.9	58	41.4	101	59	42.6	104	60	41.1	101	60
54	42.3	58	42.5	101	59	43.3	102	60	42.0	99	60
58	41.4	58	42.7	103	59	43.5	105	60	40.9	99	59
62	42.0	58	42.5	101	58	43.5	104	60	40.4	96	59
66 <sup>a</sup>	43.2	58	43.5	101	56	44.6	103	60	41.4	96	58
70	43.0	47	43.6	101	46	44.9	104	50	40.6	94	46
74	42.0	47	43.8	104	46	45.1	107	50	40.6	97	46
78	43.4	47	44.4	102	45	45.5	105	49	41.4	95	43
82	43.9	46	45.0	103	43	45.0	103	49	41.1	94	42
86	43.1	46	44.8	104	43	45.3	105	48	40.3	94	42
90	42.1	45	44.4	106	41	44.9	107	45	39.4	94	41
93	41.8	42	44.4	106	41	45.1	108	45	40.5	97	40
95	42.1	40	44.1	105	40	44.7	106	45	40.1	95	40
97	41.9	40	43.3	103	40	44.5	106	45	40.1	96	39
99	41.7	38	42.7	102	38	43.7	105	45	39.8	95	38
101	41.9	37	42.9	102	36	43.5	104	44	39.7	95	38
103	40.9	36	42.6	104	34	42.9	105	43	39.4	96	36
<b>Mean for weeks</b>											
1-13	28.4		27.7	98		28.0	99		28.0	99	
14-52	37.1		36.7	99		37.6	101		37.6	101	
53-103	42.3		43.6	103		44.4	105		40.5	96	

<sup>a</sup> Interim evaluations occurred during weeks 27, 34, and 43 for the controls only, and during week 66 for all groups.

**TABLE 12**  
**Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene**

Weeks on Study	0 ppm		0.01 ppm			0.05 ppm			0.2 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.7	60	18.6	100	60	17.9	96	60	18.2	97	60
2	21.2	60	20.9	99	60	20.0	94	60	19.9	94	60
3	22.3	60	21.3	96	60	22.0	99	60	21.3	96	60
4	22.4	60	21.7	97	60	21.6	96	60	21.6	96	59
5	23.4	60	22.9	98	60	22.7	97	60	22.6	97	59
6	23.5	60	23.3	99	60	23.0	98	60	23.1	98	59
7	24.2	60	23.4	97	60	23.3	96	60	23.5	97	59
8	25.3	60	24.4	96	60	24.4	96	60	24.4	96	59
9	26.0	60	25.0	96	60	24.9	96	60	24.9	96	59
10	26.3	60	26.2	100	60	25.7	98	60	25.7	98	59
11	26.4	60	26.1	99	60	25.3	96	60	25.8	98	59
12	26.8	60	26.4	99	60	26.3	98	59	26.3	98	59
13	27.5	60	26.7	97	60	26.1	95	59	26.2	95	59
14	28.1	60	27.3	97	60	26.9	96	59	26.8	95	59
18	29.8	60	29.0	97	60	28.2	95	59	28.3	95	59
22	30.1	60	29.8	99	60	29.1	97	59	29.0	96	59
26	32.3	59	30.9	96	60	30.7	95	59	30.8	95	59
30	33.6	59	32.1	96	60	32.0	95	59	31.5	94	59
34	34.6	59	33.6	97	60	33.8	98	59	32.8	95	59
38	37.2	58	35.4	95	60	35.3	95	59	34.6	93	59
42	38.5	58	36.3	94	60	37.3	97	59	35.7	93	59
46	39.6	58	37.4	94	60	37.1	94	59	36.2	91	59
50	41.4	58	39.4	95	59	39.2	95	59	37.9	92	59
54	42.9	58	41.0	96	59	39.4	92	59	36.5	85	59
58	42.5	57	41.0	97	59	40.1	94	59	35.1	83	59
62	42.6	57	41.1	97	59	40.1	94	58	35.9	84	57
66 <sup>a</sup>	45.2	57	42.4	94	59	41.5	92	58	37.3	83	57
70	44.5	46	42.3	95	49	41.6	94	48	37.4	84	46
74	45.0	46	44.5	99	48	42.3	94	48	38.0	84	43
78	46.3	45	45.6	99	48	43.1	93	48	38.4	83	40
82	46.9	45	45.5	97	46	41.7	89	46	38.1	81	38
86	46.0	43	45.2	98	42	41.8	91	43	38.3	83	37
90	45.7	41	43.6	95	42	41.7	91	41	38.6	85	29
93	44.4	38	43.8	99	40	40.5	91	39	39.1	88	29
95	44.0	37	43.3	98	39	41.0	93	38	39.3	89	29
97	43.2	35	43.3	100	35	39.9	92	37	39.2	91	28
99	43.0	34	43.3	101	34	40.3	94	35	38.9	91	27
101	42.4	32	42.1	99	33	40.2	95	34	39.8	94	24
103	40.6	32	42.4	104	33	39.9	98	32	38.9	96	24
105	39.9	31	42.4	106	33	39.9	100	31	38.6	97	23
<b>Mean for weeks</b>											
1-13	24.2		23.6	98		23.3	96		23.3	96	
14-52	34.5		33.1	96		32.4	94		32.4	94	
53-105	43.8		43.1	98		40.9	93		38.1	87	

<sup>a</sup> Interim evaluation occurred during week 66.

### ***Pathology and Statistical Evaluation***

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the respiratory tract (nose, trachea, and lung) and ovary and neoplasms of the thyroid gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one dose group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and in Appendix D for female mice.

***Respiratory tract:*** Exposure of mice to hexachlorocyclopentadiene was associated with the occurrence of yellow-brown granular pigment within the cytoplasm of epithelial cells lining the nose, trachea, and lung similar to that in exposed rats (Tables 13, C5, and D5). In the nose, the pigment was generally located in the respiratory epithelium of the nasal septum. Sections of nose and lung from two male and two female mice were stained by a periodic acid-Schiff method for mucopolysaccharides, mucoproteins, and carbohydrates, a method for acid-fast substances, a modified Perls' method for iron, and Schmorl's method for reducing substances (lipofuscin and ceroid). The pigmented material in mice had the same staining characteristics as that in rats. Pigment within the cytoplasm of nasal epithelial cells and airways did not stain positively by the periodic acid-Schiff, Perls', or acid-fast methods. Pigment within many, but not all, of the affected cells stained positively for reducing substances.

Foci of suppurative inflammation were also observed in the nose of many mice exposed to 0.2 ppm. The inflammation was characterized by the infiltration of neutrophils and mononuclear cells in the lamina propria and the accumulation of neutrophils, fibrin, mucus, and cellular debris within the lumen of the nose.

***Ovary:*** There was a dose-related increase in the incidence of suppurative ovarian inflammation. The incidences of suppurative ovarian inflammation in 0.05 and 0.2 ppm females were significantly greater than that of the controls (0/49, 3/50, 6/50, 17/50; Table D5). The lesions occurred with marked severity in many of the affected mice and were a likely cause of early death.

***Thyroid gland:*** The incidence of follicular cell adenoma in 0.05 ppm females was slightly higher than that of the controls; however, the increase was not statistically significant and the incidences in the other exposure groups were similar to that of the controls (1/49, 1/50, 6/50, 0/50) (Tables D1 and D3). Although the incidence of follicular cell adenoma in 0.05 ppm females was greater than the historical control range (0% to 6%; Table D4) of this lesion in female B6C3F<sub>1</sub> mice from recent NTP inhalation studies, it was not considered to be related to hexachlorocyclopentadiene exposure.

No significantly increased incidences of site-specific neoplasms were observed in exposed groups of male or female mice.



**TABLE 13**  
**Incidences of Selected Nonneoplastic Lesions of the Respiratory Tract in Mice**  
**in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**

Dose (ppm)	0	0.01	0.05	0.2
<b>Male</b>				
<b>15-Month Interim Evaluation</b>				
Nose <sup>a</sup>	10	10	10	10
Inflammation, Suppurative <sup>b</sup>	0	0	1 (1.0) <sup>c</sup>	10** (2.5)
Mucosa, Pigmentation	0	7** (1.0)	10** (2.3)	10** (2.4)
Trachea	10	10	10	10
Mucosa, Pigmentation	0	0	10** (1.4)	10** (2.3)
Lung	10	10	10	10
Mucosa, Pigmentation	0	0	7** (1.0)	10** (2.5)
<b>2-Year Study</b>				
Nose	50	50	50	50
Inflammation, Suppurative	0	0	1 (2.0)	36** (2.3)
Mucosa, Pigmentation	0	45** (1.7)	50** (2.6)	44** (2.3)
Trachea	50	50	50	50
Mucosa, Pigmentation	0	29** (1.4)	48** (2.0)	48** (2.1)
Lung	49	50	50	50
Mucosa, Pigmentation	0	2 (1.0)	42** (1.5)	45** (2.1)
(continued)				

**TABLE 13**  
**Incidences of Selected Nonneoplastic Lesions of the Respiratory Tract in Mice**  
**in the 2-Year Inhalation Study of Hexachlorocyclopentadiene (continued)**

Dose (ppm)	0	0.01	0.05	0.2
<b>Female</b>				
<b>15-Month Interim Evaluation</b>				
Nose	10	10	10	9
Inflammation, Suppurative	0	1 (1.0)	0	8** (2.6)
Mucosa, Pigmentation	0	4* (1.0)	10** (1.8)	9** (1.3)
Trachea	10	10	10	10
Mucosa, Pigmentation	0	0	10** (1.4)	10** (2.0)
Lung	10	10	10	10
Mucosa, Pigmentation	0	0	4* (1.0)	10** (2.3)
<b>2-Year Study</b>				
Nose	49	50	50	48
Inflammation, Suppurative	4 (1.3)	0	3 (1.7)	40** (2.4)
Mucosa, Pigmentation	0	40** (1.1)	48** (2.6)	41** (1.9)
Trachea	49	50	48	47
Mucosa, Pigmentation	0	6* (1.2)	43** (1.7)	42** (2.0)
Lung	48	50	50	49
Mucosa, Pigmentation	0	0	27** (1.3)	44** (1.9)

\* Significantly different ( $P \leq 0.05$ ) from the control group by Fisher's exact test (15-month interim evaluation) or by the logistic regression test (2-year study)

\*\*  $P \leq 0.01$

<sup>a</sup> Number of animals with organ examined microscopically

<sup>b</sup> Number of animals with lesion

<sup>c</sup> Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

## STOP-EXPOSURE EVALUATION

The stop-exposure evaluation in male mice was conducted to determine the significance of exposure concentration versus exposure duration on the potential development of neoplasms or nonneoplastic lesions and to evaluate the regression or progression of the lesions after exposure was stopped. Exposure periods of 33 or 66 weeks for 0.2 ppm male mice and of 26 or 42 weeks for 0.5 ppm male mice were followed by recovery periods until the end of the study. Two sets of equivalent exposure groups (exposure level multiplied by exposure duration) were included to explore the effect of exposure duration on the incidence and severity of lesions. Exposure of male mice to 0.2 ppm for 66 weeks provides approximately the same total exposure as 0.5 ppm for 26 weeks (13 ppm · weeks) and exposure to 0.2 ppm for 104 weeks provides approximately the same total exposure as 0.5 ppm for 42 weeks (21 ppm · weeks).

## Survival

Estimates of the survival probability for male mice in the stop-exposure groups, as determined by comparison with the control group from the 2-year study, are shown in Table 14 and in the Kaplan-Meier survival curve in Figure 5. Two-year survival of stop-exposure groups was similar to that of the controls. However, there were a moderate number of early deaths among male mice exposed to 0.5 ppm for 42 weeks.

## Body Weights and Clinical Findings

During the exposure periods, mean body weights of 0.5 ppm mice were generally lower than those of the controls (Figure 6 and Table 15). However, during the recovery periods, stop-exposure mice gained weight and the final mean body weights of the stop-exposure groups were similar to that of the controls. No chemical-related clinical findings were observed in exposed male mice during the stop-exposure study.

**TABLE 14**  
**Survival of Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene**

Dose (ppm)	0	0.2 (33 weeks)	0.2 (66 weeks)	0.5 (26 weeks)	0.5 (42 weeks)
Animals initially in study	90 <sup>a</sup>	80	50	90	70
27-Week interim evaluation <sup>b</sup>	10	— <sup>c</sup>	—	10	—
34-Week interim evaluation <sup>b</sup>	10	10	—	10	—
43-Week interim evaluation <sup>b</sup>	10	10	—	10	10
15-Month interim evaluation <sup>b</sup>	10	10	—	10	10
Accidental deaths <sup>b</sup>	1	1	1	0	0
Moribund	8	7	6	5	10
Natural deaths	6	7	10	4	7
Animals surviving to study termination	35	35	33	41	33
Percent probability of survival at end of study <sup>d</sup>	72	71	67	82	70
Mean survival (days) <sup>e</sup>	509	555	673	522	554
Survival analyses <sup>f</sup>		P=1.000	P=0.652	P=0.311N	P=0.500

<sup>a</sup> Includes 60 controls from the core study

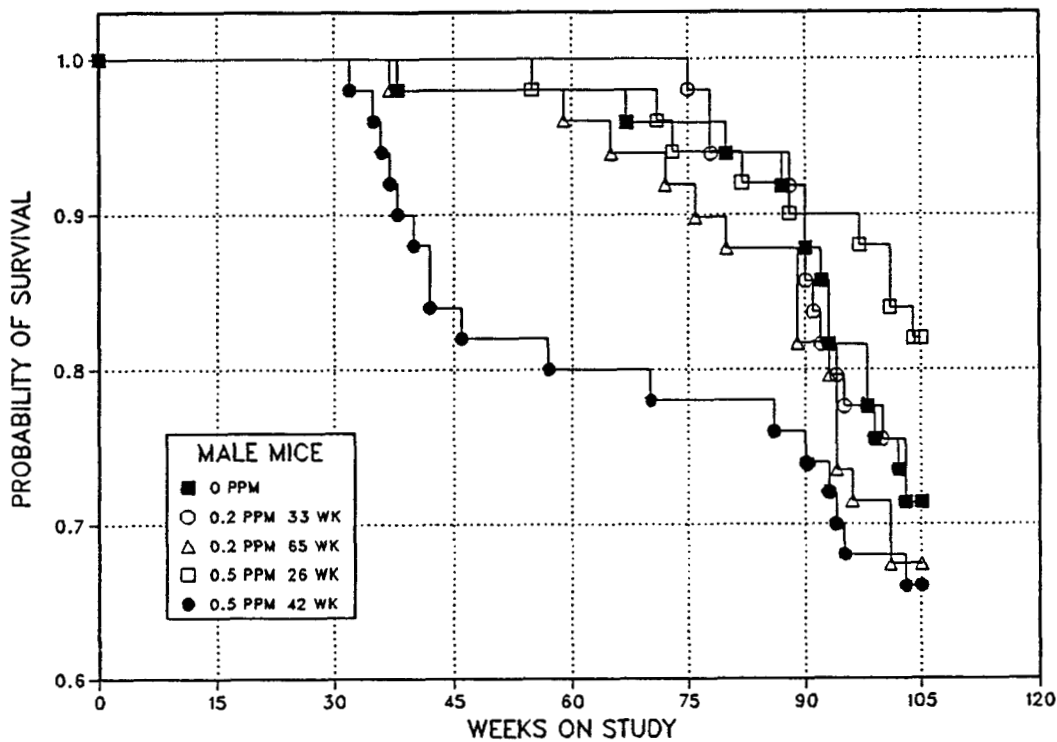
<sup>b</sup> Censored from survival analyses

<sup>c</sup> No interim evaluation scheduled for this group

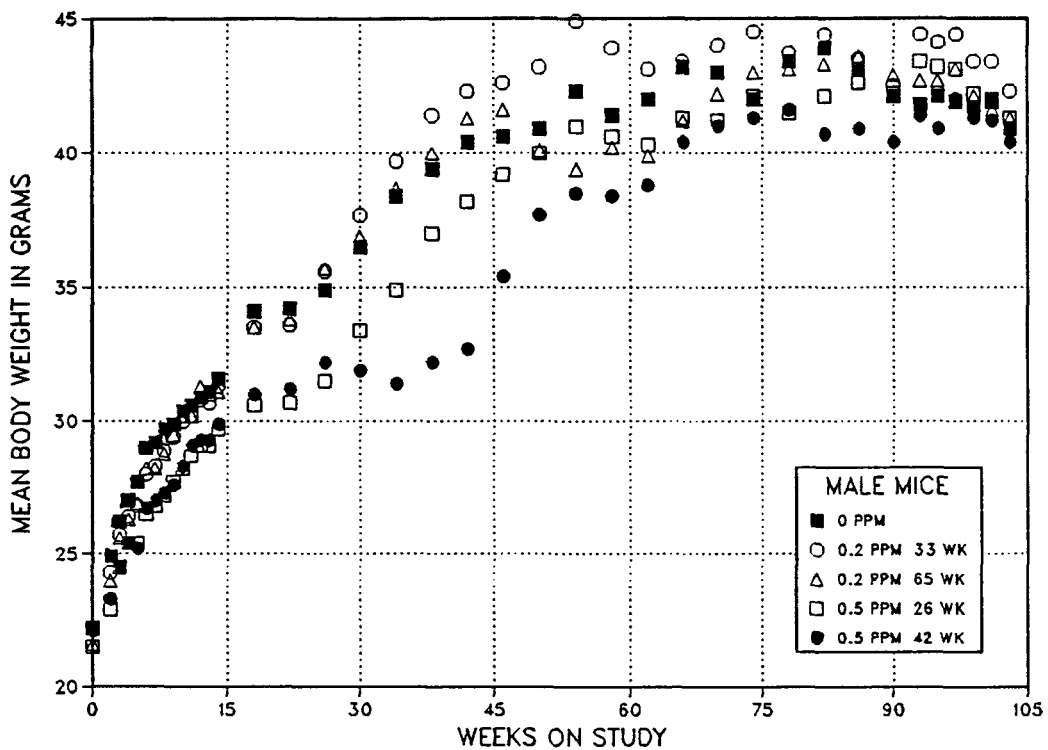
<sup>d</sup> Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice

<sup>e</sup> Mean of all deaths (uncensored, censored, and terminal sacrifice)

<sup>f</sup> The results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposure columns. A lower mortality in an exposure group is indicated by N.



**FIGURE 5**  
**Kaplan-Meier Survival Curves for Male Stop-Exposure Mice Administered Hexachlorocyclopentadiene by Inhalation**



**FIGURE 6**  
**Growth Curves for Male Stop-Exposure Mice Administered Hexachlorocyclopentadiene by Inhalation**

**TABLE 15**  
**Mean Body Weights and Survival of Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene**

Weeks on Study	0 ppm		0.2 ppm (33 weeks)			0.2 ppm (66 weeks)		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
1	22.2	90	22.2	100	80	21.6	97	50
2	24.9	90	24.3	98	80	24.0	96	50
3	26.2	90	25.7	98	80	25.6	98	50
4	27.0	90	26.4	98	80	26.3	97	50
5	27.7	90	26.8	97	80	26.9	97	50
6	29.0	89	28.1	97	80	28.2	97	50
7	29.2	89	28.3	97	80	28.2	97	50
8	29.7	89	28.9	97	80	28.8	97	50
9	29.9	89	29.4	98	80	29.5	99	50
10	30.4	89	30.0	99	80	30.2	99	50
11	30.6	89	30.2	99	80	30.2	99	50
12	30.9	89	30.8	100	80	31.3	101	50
13	31.1	89	30.7	99	80	31.0	100	50
14	31.6	89	31.3	99	80	31.1	98	50
18	34.1	89	33.5	98	80	33.5	98	50
22	34.2	89	33.6	98	80	33.8	99	50
26	34.9	89	35.6	102	80	35.7	102	50
30 <sup>a</sup>	36.5	79	37.7	103	80	36.9	101	50
34 <sup>a</sup>	38.4	69	39.7	103	69	38.7	101	50
38	39.4	69	41.4	105	69	40.0	102	49
42	40.4	68	42.3	105	69	41.3	102	49
46 <sup>a</sup>	40.6	58	42.6	105	59	41.6	103	49
50	40.9	58	43.2	106	59	40.1	98	48
54	42.3	58	44.9	106	59	39.4	93	48
58	41.4	58	43.9	106	59	40.2	97	48
62	42.0	58	43.1	103	59	39.9	95	47
66 <sup>a</sup>	43.2	58	43.4	101	59	41.2	95	46
70	43.0	47	44.0	102	49	42.2	98	46
74	42.0	47	44.5	106	49	43.0	102	45
78	43.4	47	43.7	101	48	43.1	99	44
82	43.9	46	44.4	101	46	43.3	99	43
86	43.1	46	43.5	101	46	43.6	101	43
90	42.1	45	42.5	101	45	42.9	102	40
93	41.8	42	44.4	106	40	42.7	102	40
95	42.1	40	44.1	105	39	42.7	101	36
97	41.9	40	44.4	106	38	43.1	103	35
99	41.7	38	43.4	104	38	42.1	101	35
101	41.9	37	43.4	104	37	41.6	99	35
103	40.9	36	42.3	103	37	41.3	101	33
<b>Mean for weeks</b>								
1-13	28.4		27.8	98		27.8	98	
14-52	37.1		38.1	103		37.3	101	
53-103	42.3		43.7	103		42.0	99	

(continued)

**TABLE 15**  
**Mean Body Weights and Survival of Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene (continued)**

Weeks on Study	0 ppm		0.5 ppm (26 weeks)			0.5 ppm (42 weeks)		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
1	22.2	90	21.5	97	90	22.1	100	70
2	24.9	90	22.9	92	90	23.3	94	70
3	26.2	90	24.5	94	90	24.5	94	70
4	27.0	90	25.4	94	90	25.4	94	70
5	27.7	90	25.4	92	90	25.2	91	70
6	29.0	89	26.5	91	90	26.7	92	70
7	29.2	89	26.8	92	90	27.0	93	70
8	29.7	89	27.2	92	90	27.3	92	70
9	29.9	89	27.7	93	90	27.6	92	70
10	30.4	89	28.2	93	90	28.3	93	70
11	30.6	89	28.7	94	90	29.1	95	70
12	30.9	89	29.1	94	90	29.3	95	70
13	31.1	89	29.1	94	90	29.3	94	70
14	31.6	89	29.7	94	90	29.9	95	70
18	34.1	89	30.6	90	90	31.0	91	70
22	34.2	89	30.7	90	90	31.2	91	70
26	34.9	89	31.5	90	90	32.2	92	70
30 <sup>a</sup>	36.5	79	33.4	92	80	31.9	87	70
34 <sup>a</sup>	38.4	69	34.9	91	70	31.4	82	69
38	39.4	69	37.0	94	70	32.2	82	65
42	40.4	68	38.2	95	70	32.7	81	64
46 <sup>a</sup>	40.6	58	39.2	97	60	35.4	87	52
50	40.9	58	40.0	98	60	37.7	92	51
54	42.3	58	41.0	97	60	38.5	91	51
58	41.4	58	40.6	98	59	38.4	93	50
62	42.0	58	40.3	96	59	38.8	92	50
66 <sup>a</sup>	43.2	58	41.3	96	49	40.4	94	40
70	43.0	47	41.2	96	49	41.0	95	40
74	42.0	47	42.1	100	47	41.3	98	39
78	43.4	47	41.5	96	47	41.6	96	39
82	43.9	46	42.1	96	47	40.7	93	39
86	43.1	46	42.6	99	46	40.9	95	39
90	42.1	45	42.2	100	45	40.4	96	38
93	41.8	42	43.4	104	45	41.4	99	37
95	42.1	40	43.2	103	45	40.9	97	35
97	41.9	40	43.1	103	44	42.0	100	34
99	41.7	38	42.2	101	44	41.3	99	34
101	41.9	37	42.0	100	43	41.2	98	34
103	40.9	36	41.3	101	42	40.4	99	34
<b>Mean for weeks</b>								
1-13	28.4		26.4	93		26.5	93	
14-52	37.1		34.5	93		32.6	88	
53-103	42.3		41.9	99		40.6	96	

<sup>a</sup> Interim evaluations occurred during week 27 (control and 26-week 0.5 ppm), week 34 (control, 33-week 0.2 ppm, and 26-week 0.5 ppm), and weeks 43 and 66 (control, 33-week 0.2 ppm, 26-week 0.5 ppm, and 42-week 0.5 ppm). No interim evaluations were conducted for the 66-week 0.2 ppm group.

### Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the respiratory tract. Summaries of the incidences of neoplasms and nonneoplastic lesions of male mice in the stop-exposure groups are shown in Tables E1 and E3. For statistical analyses, comparisons were made between controls and 0.2 ppm groups exposed for 33, 66, or 104 weeks (Table E2a); between controls and 0.5 ppm groups exposed for 26 or 42 weeks (Table E2b); and between equivalent exposure groups (Tables E2c and E2d).

*Comparison of Groups Exposed to 0 ppm versus 0.2 ppm for 33, 66, or 104 Weeks:* Pigmentation of

the mucosa of the nose, trachea, and lung were present in most animals exposed to 0.2 ppm, independent of exposure duration (Tables 16 and E3). Mucosal pigmentation was not observed in controls. The incidences and severity of mucosal pigmentation in these organs were similar among 0.2 ppm groups. The incidences of suppurative inflammation of the nose of male mice exposed to 0.2 ppm for 66 or 104 weeks were significantly greater than those of the controls, and the increase was exposure related.

Exposed groups had incidences of alveolar/bronchiolar adenoma or carcinoma (combined) that were slightly but not significantly greater than those of the controls (Tables 16 and E2a).

**TABLE 16**  
**Incidences of Selected Neoplasms and Nonneoplastic Lesions of the Respiratory Tract in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene: 0 ppm versus 0.2 ppm for 33, 66, or 104 Weeks**

Dose (ppm)	0	0.2 (33 weeks)	0.2 (66 weeks)	0.2 (104 weeks)
Nose <sup>a</sup>	50	50	49	50
Inflammation, Suppurative <sup>b</sup>	0	2 (2.5) <sup>c</sup>	17** (2.5)	36** (2.3)
Mucosa, Pigmentation	0	50** (2.2)	46** (2.1)	44** (2.3)
Trachea	50	50	49	50
Mucosa, Pigmentation	0	50** (2.0)	48** (2.0)	48** (2.1)
Lung	49	50	49	50
Inflammation, Suppurative	0	0	0	4* (4.0)
Mucosa, Pigmentation	0	46** (2.0)	45** (1.9)	45** (2.1)
Alveolar Epithelial Hyperplasia	0	4 (2.8)	2 (2.5)	5* (2.4)
Alveolar/bronchiolar Adenoma	11	9	15	15
Alveolar/bronchiolar Carcinoma	0	4	2	1
Alveolar/bronchiolar Adenoma or Carcinoma <sup>d</sup>	11	13	17	16

\* Significantly different ( $P \leq 0.05$ ) from the control group by the logistic regression test

\*\*  $P \leq 0.01$

<sup>a</sup> Number of animals with organ examined microscopically

<sup>b</sup> Number of animals with lesion

<sup>c</sup> Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

<sup>d</sup> Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean  $\pm$  standard deviation): 139/624 (22.3%  $\pm$  9.4%), range 10%-42%



*Comparison of Groups Exposed to 0 ppm versus 0.5 ppm for 26 or 42 Weeks:* The incidences of focal suppurative inflammation of the nose in male mice exposed to 0.5 ppm hexachlorocyclopentadiene for 26 or 42 weeks were significantly greater than that of the controls, and the incidence and severity in the group exposed for 42 weeks were greater than those in the 26-week stop-exposure group (Tables 17 and E3). Focal suppurative inflammation of the lung and trachea occurred only in male mice exposed to 0.5 ppm for 42 weeks. The incidences of pigmentation in the nose, trachea, and lung in males exposed to 0.5 ppm for 42 weeks were lower than those of the group exposed to 0.5 ppm for 26 weeks. Hyperplasia of the alveolar epithelium of the lung occurred in mice exposed to 0.5 ppm hexachlorocyclopentadiene for 26 or 42 weeks, and the incidence in the 42-week

0.5 ppm stop-exposure group was significantly greater than that of the controls.

There was a significant exposure-related increase in the incidence of alveolar/bronchiolar carcinoma, and the incidences of alveolar/bronchiolar carcinoma in 0.5 ppm groups were significantly greater than that of the controls by pairwise comparison (Tables 17 and E2b). However, the overall incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 0.5 ppm groups were similar to that of the controls. All mice in the 0.5 ppm groups with alveolar/bronchiolar carcinoma survived until the end of the study except for one mouse in the 26-week 0.5 ppm group which died on day 725 and two mice in the 42-week 0.5 ppm group which died on days 395 and 661.

**TABLE 17**  
**Incidences of Selected Neoplasms and Nonneoplastic Lesions of the Respiratory Tract in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene: 0 ppm versus 0.5 ppm for 26 or 42 Weeks**

Dose (ppm)	0	0.5 (26 weeks)	0.5 (42 weeks)
Nose <sup>a</sup>	50	50	50
Inflammation, Suppurative <sup>b</sup>	0	7* (2.0) <sup>c</sup>	24** (2.5)
Mucosa, Pigmentation	0	35** (1.4)	29** (1.6)
Trachea	50	49	50
Inflammation, Suppurative	0	0	8* (2.5)
Mucosa, Pigmentation	0	48** (2.0)	27** (1.8)
Lung	49	50	50
Inflammation, Suppurative	0	0	16** (3.5)
Mucosa, Pigmentation	0	48** (1.9)	33** (2.0)
Alveolar Epithelial Hyperplasia	0	4 (2.5)	5* (2.4)
Alveolar/bronchiolar Adenoma	11	10	10
Alveolar/bronchiolar Carcinoma <sup>d</sup>	0	5*	6*
Alveolar/bronchiolar Adenoma or Carcinoma <sup>e</sup>	11	14	14

\* Significantly different ( $P \leq 0.05$ ) from the control group by the logistic regression test

\*\*  $P \leq 0.01$

<sup>a</sup> Number of animals with organ examined microscopically

<sup>b</sup> Number of animals with lesion

<sup>c</sup> Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

<sup>d</sup> Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean  $\pm$  standard deviation): 45/624 (7.2%  $\pm$  5.5%), range 0%-16%

<sup>e</sup> Historical incidence: 139/624 (22.3%  $\pm$  9.4%), range 10%-42%

Focal hyperplasia of the alveolar epithelium, alveolar/bronchiolar adenoma, and alveolar/bronchiolar carcinoma constitute a morphologic continuum in the development and progression of the most common form of spontaneous and chemical-induced pulmonary neoplasia in the B6C3F<sub>1</sub> mouse. Focal hyperplasia is characterized by an increase in the number of cuboidal or low columnar cells lining the alveoli with no or minimal distortion of the normal architecture of the lung. Alveolar/bronchiolar adenoma is a circumscribed expansile lesion distorting the underlying alveolar architecture. The neoplastic epithelium is generally arranged in complex, irregular papillary patterns, but it is uniform and comprises a single layer of cuboidal to columnar epithelium. Some cells have cytoplasmic vacuoles characteristic of type II pneumocytes, while others have an appearance more typical of bronchiolar cells. Alveolar/bronchiolar carcinoma is usually diagnosed on the basis of heterogeneity in cellular morphology and growth pattern, areas of solid growth (loss of basement membrane dependency), and cellular anaplasia.

*Comparison of Groups Exposed to 0.2 ppm for 66 Weeks or 0.5 ppm for 26 Weeks:* The incidence and severity of mucosal pigmentation of the nose were lower in males exposed to 0.5 ppm hexachlorocyclopentadiene for 26 weeks (35/50, 1.4) than in the 66-week 0.2 ppm stop-exposure group (46/49, 2.1) (Table E3). However, incidences and severity of mucosal pigmentation of the lung (48/50, 1.9; 45/49, 1.9) and trachea (48/49, 2.0; 48/49, 2.0) were similar in both groups. The incidence and severity of suppurative inflammation of the nose were lower in the 26-week 0.5 ppm stop-exposure group (7/50, 2.0) than in the 66-week 0.2 ppm stop-exposure group (17/49, 2.5). The incidences of alveolar/bronchiolar neoplasms in male mice exposed to 0.5 ppm for 26 weeks [adenoma, 10/50; carcinoma, 5/50; adenoma or carcinoma (combined), 14/50] were not significantly different from those in males exposed to 0.2 ppm for 66 weeks [adenoma, 15/49; carcinoma, 2/49; adenoma or carcinoma (combined), 17/49] (Table E2c).

*Comparison of Groups Exposed to 0.2 ppm for 104 Weeks or 0.5 ppm for 42 Weeks:* The incidence and severity of mucosal pigmentation in the 104-week 0.2 ppm group (nose: 44/50, 2.3; trachea: 48/50, 2.1; lung: 45/50, 2.1) were greater than those of the

42-week 0.5 ppm stop-exposure group (nose: 29/50, 1.6; trachea: 27/50, 1.8; lung: 33/50, 2.0) (Table E3). The incidence of suppurative inflammation of the nose was also greater in the 104-week 0.2 ppm group (36/50, 2.3) than that in the 42-week 0.5 ppm stop-exposure group (24/50, 2.5), but the severity of this lesion was similar in both groups. The incidence, but not the severity, of suppurative inflammation of the lung was lower in the 104-week 0.2 ppm group (4/50, 4.0) than in the 42-week 0.5 ppm stop-exposure group (16/50, 3.5). The incidence of alveolar/bronchiolar carcinoma in male mice exposed to 0.5 ppm for 42 weeks (6/50) was significantly greater than that of males exposed to 0.2 ppm for 104 weeks (1/50) (Table E2d). However, the overall incidence of alveolar/bronchiolar adenoma or carcinoma (combined) was similar between the two groups (0.2 ppm for 104 weeks, 16/50; 0.5 ppm for 42 weeks, 14/50).

## GENETIC TOXICOLOGY

Hexachlorocyclopentadiene (0.03 to 100 µg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested by a preincubation protocol, with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table F1; Haworth *et al.*, 1983). In cytogenetic assays with cultured Chinese hamster ovary cells, hexachlorocyclopentadiene induced both sister chromatid exchanges and aberrations with and without S9 (Tables F2 and F3; Galloway *et al.*, 1987). Although no cell cycle delay was evident in either of these Chinese hamster ovary cell studies, toxicity was a problem in the aberrations test where fewer than the desired number of 200 cells per dose level were available for scoring at the highest doses tested, with and without S9. In the sister chromatid exchange test, no clear dose-response relationship was evident.

*In vivo*, no genetic effects were observed. No induction of sex-linked recessive lethal mutations was noted in germ cells of male *Drosophila melanogaster* treated with hexachlorocyclopentadiene by feeding or injection (Table F4; Zimmering *et al.*, 1985; Mason *et al.*, 1992). No increase in the frequency of micronucleated erythrocytes was observed in peripheral blood samples obtained from male and female B6C3F<sub>1</sub> mice exposed to hexachlorocyclopentadiene by inhalation for 13 weeks (Table F5).

## DISCUSSION AND CONCLUSIONS

Hexachlorocyclopentadiene, a pale yellow liquid, is used as a chemical intermediate in the synthesis of chlorinated cyclodiene pesticides (chlordane, aldrin, dieldrin, heptachlor, mirex, endosulfan, and pentac) (Bell *et al.*, 1979) and flame retardants (chlorendic acid and other derivatives) (Sanders, 1978). The National Cancer Institute nominated hexachlorocyclopentadiene for study because it has a large production volume, which suggests the potential for significant human exposure; because it has a structural relationship to compounds identified as hepatocarcinogens such as heptachlor, aldrin, and dieldrin (NCI, 1977a, 1978); and because of the lack of information on its chronic toxicity. Thirteen-week and 2-year toxicology and carcinogenicity studies were conducted by exposing groups of male and female F344/N rats and B6C3F<sub>1</sub> mice to hexachlorocyclopentadiene (approximately 98% pure) by inhalation for 6 hours per day, 5 days per week. Because hexachlorocyclopentadiene has no end use of its own, occupational exposure is the most serious human health hazard. Workplace exposure occurs primarily via inhalation, therefore this route of exposure was chosen for use in the NTP studies.

During the 13-week studies, 1 ppm was the lowest exposure level at which chemical-related deaths occurred in rats; in mice the lowest clearly lethal exposure level was 0.4 ppm. Treon *et al.* (1955) reported previously that acute hexachlorocyclopentadiene inhalation exposure (1.5 ppm for 7 hours) caused 100% mortality in mice and 5% mortality in rats. The somewhat greater sensitivity of mice could also be due to the small size of their airways relative to those of the rats and the ease with which the mouse airways occlude. Respiratory distress occurred in rats exposed to 1 or 2 ppm hexachlorocyclopentadiene in the 13-week study. Respiratory distress and impaired respiratory function were also observed in Sprague-Dawley rats exposed to 0.5 ppm hexachlorocyclopentadiene for 6 hours per day, 5 days per week for 14 weeks (Rand *et al.*, 1982a).

Histopathologic evaluation of the tissues of rats and mice in the 13-week studies clearly showed that the respiratory tract is the target of hexachlorocyclo-

pentadiene toxicity in both species. In the 13-week studies, inflammation and epithelial necrosis of the respiratory tract (nose, larynx, trachea, or lung) and squamous metaplasia of the respiratory epithelium occurred in rats exposed to 0.4 ppm or more. Mice exposed to 0.4 ppm or more also had inflammation and metaplasia of the respiratory tract. Mild nasal inflammation and tracheal epithelial metaplasia (males) occurred in some mice exposed to 0.15 ppm hexachlorocyclopentadiene. Generally, the severity of the pulmonary lesions was related to exposure level.

The exposure levels of 0.01, 0.05, or 0.2 ppm (equivalent to 0.11, 0.56, or 2.28 mg/m<sup>3</sup>) used in the present 2-year studies were selected based on body weight depression, mortality, and the incidence and severity of chemical-related respiratory tract lesions in the 13-week rat and mouse studies. The 0.2 ppm exposure level was chosen as the highest concentration for rats and mice, because this exposure level is one-half of the lowest exposure level (0.4 ppm) that caused death in mice, body weight depression in rats and mice, and significant respiratory lesions in rats and mice in the 13-week studies.

In the 2-year studies, pigmentation in the respiratory epithelial lining of the nose, trachea (males), and bronchi and bronchioles of the lung; respiratory epithelial hyperplasia of the nose; and squamous metaplasia of the laryngeal epithelium (females) occurred with increased incidence and severity in exposed rats. Mice exposed to hexachlorocyclopentadiene had increased incidences and severity of mucosal pigmentation of the nose, trachea, and lung and suppurative inflammation of the nose. Similar lesions were observed in male mice in the stop-exposure evaluation.

It is evident that hexachlorocyclopentadiene is highly toxic to the respiratory tract. Its toxicity is comparable to other known respiratory toxicants such as methyl isocyanate, glutaraldehyde, and formaldehyde. Mice exposed to 30 ppm methyl isocyanate for 2 hours had extensive necrosis and erosion of the respiratory and olfactory epithelium of the nose, trachea, and mainstem bronchi (Boorman *et al.*,

1987). Changes observed in rats similarly exposed included erosion and separation of the olfactory and respiratory epithelia from the basement membrane (Bucher *et al.*, 1987). Rats exposed to 3 ppm methyl isocyanate for 6 hours per day for up to 8 days had inflammatory and squamous metaplastic lesions of the respiratory tract (Fowler and Dodd, 1987). Hyperplasia and squamous metaplasia of the nose occurred in rats exposed to 500 ppb glutaraldehyde for 6 hours per day, 5 days per week, for 13 weeks. Mice exposed similarly to 1,000 ppb of glutaraldehyde had squamous metaplasia of the laryngeal epithelium and necrosis and suppurative inflammation of the nasal cavity (NTP, 1993).

The brown pigment observed in the mucosa and submucosa of the respiratory tract of rats and mice exposed to hexachlorocyclopentadiene was not reported with any of the other irritants, and it appears to be a unique response to this chemical. Lipid peroxidation has been implicated in the pathogenesis of this brown pigment (Chio *et al.*, 1969). Whether metabolism of hexachlorocyclopentadiene by rats and mice leads to the generation of intracellular free radicals and peroxides is unknown. Hexachlorocyclopentadiene is a highly reactive chemical. It reacts readily with olefinic and aromatic compounds (Ungnade and McBee, 1958). It also binds to whole blood and plasma (El Dareer *et al.*, 1983) and to epithelial lung tissue, extracellular lung lining, and bronchiolar Clara cells (Rand *et al.*, 1982a).

Although the respiratory tract was the only site identified for hexachlorocyclopentadiene toxicity in these NTP studies, Treon *et al.* (1955) identified the adrenal gland, brain, heart, liver, and kidney as additional sites in rats exposed to 0.15 ppm or more for 3.5 hours. The apparent greater toxicity (as indicated by the increased number of sites affected) of hexachlorocyclopentadiene observed by Treon *et al.* (1955) could have been caused by tissue autolysis rather than impurities in the batch of chemical used. The degenerative changes in these organs occurred at doses where high mortality was encountered. As for chemical purity, the batch used by Treon *et al.* (1955) was 89.5% pure whereas those used by Rand *et al.* (1982a) and NTP were 97.7% and approximately 98% pure, respectively. The major contaminants known to be associated with industrial preparation of hexachlorocyclopentadiene include octachlorocyclopentadiene, hexachloro-1,3-butadiene, tetrachloroethane, hexachlorobenzene, and pentachlorobenzene (BUA, 1988). All of these contami-

nants except octachlorocyclopentadiene are known to cause liver and/or kidney damage (NTP, 1983; 1991a,b). However, much higher concentrations of these contaminants are required for toxicity than those that would have been achieved in the Treon *et al.* (1955) studies.

Several conclusions concerning the respiratory lesions (mucosal pigmentation and suppurative inflammation of the respiratory epithelium) emerged from the stop-exposure evaluation. Pigmentation of the respiratory tract epithelium caused by exposure to hexachlorocyclopentadiene is persistent as indicated by its presence in the respiratory tract of the majority of the male mice after a long recovery period (62 to 78 weeks). This suggests that the pigment could be a reaction product between the chemical and an intracellular component of the respiratory tissue that has a very slow turnover rate. The results of the stop-exposure evaluation clearly show that incidence and severity of the respiratory lesions are positively related to exposure concentration and duration. In addition there appears to be a critical burden (concentration times weeks) below which suppurative inflammation of the trachea and lung does not occur. The critical burden was estimated at 20 to 21 ppm · weeks. This conclusion is supported by the finding that no chemical-related inflammatory lesions occurred in the trachea and lung of male mice exposed to 0.5 ppm for 26 weeks or 0.2 ppm for 66 weeks, or male or female mice exposed to 0.01 or 0.05 ppm for 104 weeks. Exposure concentration of 0.5 ppm has an inhibitory effect on mucosal pigmentation of the respiratory tract. Pigmentation incidences at this concentration, whether the exposure was for 26 or 42 weeks, were 35% lower than that observed in the other exposure groups, except the 0.01 ppm core group.

The pigmentation could be secondary to the chronic inflammation observed in part of the respiratory tract. However, the pigmentation was observed in the respiratory tract of mice exposed to lower concentrations of the chemical, which did not cause inflammatory lesions, and was also observed in the respiratory tract of exposed rats that had little evidence of inflammation. This also suggests that the pigmentation may have been the result of a direct reaction between the chemical or one of its metabolites and the respiratory tissue. Hexachlorocyclopentadiene could, under reductive dehalogenation, form free radicals, which could then react with the respiratory epithelium thus causing pigmentation.

There was a dose-related increase in the incidence of suppurative ovarian inflammation in mice. The incidences of suppurative ovarian inflammation in 0.05 and 0.2 ppm females were significantly greater than that of the controls (0/49, 3/50, 6/50, 17/50). The lesions occurred with marked severity in many of the affected females and were a likely cause of early death. The increase may have been due to the reduced immunity of exposed mice as a result of stress. This condition is similar to the utero-ovarian infections observed in mice in other NTP studies and apparently caused by *Klebsiella* species.

In the 2-year core studies, there were no increased neoplasm incidences in rats or mice that could be attributed to the whole-body exposure to hexachlorocyclopentadiene vapors. The incidences of alveolar/bronchiolar carcinoma in male mice exposed to 0.5 ppm for 26 (5/50) or 42 (6/50) weeks in the stop-exposure evaluation were significantly greater than that of the controls (0/49). However, this increase could not be clearly related to hexachlorocyclopentadiene exposure because the incidences of this neoplasm in these stop-exposure groups were within the historical control range (0% to 16%), and the combined incidence of alveolar/bronchiolar adenoma or carcinoma in these stop-exposure groups was similar to that of the controls. This lack of a carcinogenic response to hexachlorocyclopentadiene exposure contrasts with the positive carcinogenic response to cyclodiene pesticides such as chlordane, heptachlor, aldrin, and dieldrin. Oral administration of these compounds produced liver neoplasms in

mice, but the results were inconclusive in rats (NCI, 1977a,b; 1978). These compounds were found to cause peroxisome proliferation in the liver of rats (Ortega *et al.*, 1957; Wright *et al.*, 1972). No reports of peroxisome proliferation due to hexachlorocyclopentadiene were found. Because there were no chemical-related increases in liver weights or liver lesions in either the 13-week or 2-year inhalation studies, it is unlikely that hexachlorocyclopentadiene would cause proliferation of the endoplasmic reticulum. The lack of carcinogenic activity of hexachlorocyclopentadiene coincides with its lack of mutagenic activity (Litton Bionetics, 1978a,b; Haworth *et al.*, 1983). However, hepatocarcinogen cyclodiene pesticides also lack mutagenic activity (Wildemaue *et al.*, 1983).

## CONCLUSIONS

Under the conditions of these 2-year studies, there was *no evidence of carcinogenic activity\** of hexachlorocyclopentadiene in male or female F344/N rats or B6C3F<sub>1</sub> mice exposed to 0.01, 0.05, or 0.2 ppm.

Exposure of rats to hexachlorocyclopentadiene produced pigmentation of the respiratory epithelium of the nose, trachea (males), and bronchi and bronchioles of the lung. Squamous metaplasia of the laryngeal epithelium occurred in female rats exposed to hexachlorocyclopentadiene. Suppurative inflammation of the nose as well as pigmentation of the respiratory mucosal epithelium occurred in mice exposed to hexachlorocyclopentadiene.

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\* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

## REFERENCES

- Abdo, K.M., Montgomery, C.A., Kluwe, W.M., Farnell, D.R., and Prejean, J.D. (1984). Toxicity of hexachlorocyclopentadiene: Subchronic (13-week) administration by gavage to F344 rats and B6C3F<sub>1</sub> mice. *J. Appl. Toxicol.* **4**, 75-81.
- American Conference of Governmental Industrial Hygienists (ACGIH) (1991). Threshold limit values and biological exposure indices for 1991-1992. Cincinnati, OH.
- Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.
- Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity, and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* **257**, 229-306.
- Atallah, Y.H., Whitacre, D.M., and Butz, R.G. (1981). Fate of hexachlorocyclopentadiene in the environment. In *Toxicology of Halogenated Hydrocarbons: Health and Ecological Effects* (M.A.Q. Khan and R.H. Stanton, Eds.), pp. 344-355. Pergamon Press, New York.
- Bell, M.A., Ewing, R.A., and Lutz, G.A. (1979). Reviews of the environmental effects of pollutants: XII. Hexachlorocyclopentadiene (EPA 600/1-78-047). U.S. Environmental Protection Agency, Cincinnati, OH.
- Beratergremium für Umweltrelevante Altstoffe (BUA) (1988). Hexachlorocyclopentadiene. BUA Report No. 25. VCH Verlagsgesellschaft, Weinheim, Germany.
- Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.
- Boorman, G.A., Uraih, L.C., Gupta, B.N., and Bucher, J.R. (1987). Two-hour methyl isocyanate inhalation and 90-day recovery study in B6C3F<sub>1</sub> mice. *Environ. Health Perspect.* **72**, 63-69.
- Brooks, T.M., Hodson-Walker, G., and Wiggins, D.E. (1983). Genotoxicity studies with hexachlorocyclopentadiene (HEX) (Report No. SBGR 83.251). Shell Research Ltd., Sittingbourne Research Centre, Tunstall, United Kingdom (unpublished report).
- Bucher, J.R., Boorman, G.A., Gupta, B.N., Uraih, L.C., Hall, L.B., and Stefanski, S.A. (1987). Two-hour methyl isocyanate inhalation exposure and 91-day recovery: A preliminary description of pathologic changes in F344 rats. *Environ. Health Perspect.* **72**, 71-75.
- Buncher, C.R., Moomaw, C., and Sirkoski, E. (1980). Mortality study of Mantague Plant - Hooker Chemical. Division of Epidemiology and Biostatistics, University of Cincinnati Medical Center, Cincinnati, OH (unpublished report).
- Chernoff, N., and Kavlock, R.J. (1982). An *in vivo* teratology screen utilizing pregnant mice. *J. Toxicol. Environ. Health* **10**, 541-550.
- Chio, K.S., Reiss, U., Fletcher, B., and Tappel, A.L. (1969). Peroxidation of subcellular organelles: Formation of lipofuscinlike fluorescent pigments. *Science* **166**, 1535-1536.
- Chou, S.F.J., and Griffin, R.A. (1983). Soil, clay, and caustic soda effects on solubility, sorption, and mobility of hexachlorocyclopentadiene. *Environmental Geology Notes* **104**. Illinois Department of Energy and Natural Resources, State Geological Survey Division, Champaign, IL.

- Clark, D.G., Blair, D., Martin, J., Hendy, R., Pilcher, A., and Wiggins, D. (1982). Thirty-week chronic inhalation study of hexachlorocyclopentadiene (HEX) in rats (Experiment No. 1760, Report No. SGBR 82.051). Shell Toxicology Laboratory, Tunstall, United Kingdom (unpublished report).
- Code of Federal Regulations (CFR) 21, Part 58.
- Cox, D.R. (1972). Regression models and life-tables. *J. R. Stat. Soc.* B34, 187-220.
- Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology: Mechanisms and Toxicity of Chemical Carcinogens and Mutagens* (M.A. Mehlman, W.G. Flamm, and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Company, Inc., Princeton, NJ.
- Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* 6, 44-52.
- Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* 32, 236-248.
- Dorough, H.W. (1979). The accumulation, distribution and dissipation of hexachlorocyclopentadiene (C56) in tissues of rats and mice. Velsicol, Inc., Chicago, IL (unpublished report).
- Dorough, H.W., and Ranieri, T.A. (1984). Distribution and elimination of hexachlorocyclopentadiene in rats and mice. *Drug Chem. Toxicol.* 7, 73-89.
- Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* 6, 241-252.
- Dunnnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* 50, 1096-1121.
- El Dareer, S.M., Noker, P.E., Tillery, K.F., and Hill, D.L. (1983). Investigations on the basis for the differential toxicity of hexachlorocyclopentadiene administered to rats by various routes. *J. Toxicol. Environ. Health* 12, 203-211.
- Elia, V.J., Clark, C.S., Majeti, V.A., Gartside, P.S., MacDonald, T., Richdale, N., Meyer, C.R., Van Meer, G.L., and Hunninen, K. (1983). Hazardous chemical exposure at a municipal wastewater treatment plant. *Environ. Res.* 32, 360-371.
- Fowler, E.H., and Dodd, D.E. (1987). Eighty-five day postexposure follow-up study in Fischer 344 rats after repeated exposures to methyl isocyanate vapor. *Environ. Health Perspect.* 72, 125-132.
- Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.* 10 (Suppl. 10), 1-175.
- Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *J. Natl. Cancer Inst.* 62, 957-974.
- Goggelman, W., Bonse, G., Henschler, D., and Creim, H. (1978). Mutagenicity of chlorinated cyclopentadienes due to metabolic activation. *Biochem. Pharmacol.* 27, 2927-2929.
- Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* 58, 385-392.
- Haseman, J.K., Huff, J., and Boorman, G.A. (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol. Pathol.* 12, 126-135.
- Haseman, J.K., Huff, J.E., Rao, G.N., Arnold, J.E., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F<sub>1</sub> (B6C3F<sub>1</sub>) mice. *JNCI* 75, 975-984.
- Hawley, G.G., Ed. (1977). *The Condensed Chemical Dictionary*, 9th ed., p. 436. Van Nostrand Reinhold Company, New York.
- Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutagen.* 5 (Suppl. 1), 3-142.

- Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.
- Jonckheere, A.R. (1954). A distribution-free *k*-sample test against ordered alternatives. *Biometrika* **41**, 133-145.
- Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457-481.
- Kilzer, L., Scheunert, I., Geyer, H., Klein, W., and Korte, F. (1979). Laboratory screening of the volatilization rates of organic chemicals from water and soil. *Chemosphere* **10**, 751-761.
- Kirk-Othmer Encyclopedia of Chemical Technology* (1979). 3rd ed., Vol. 5, pp. 791-797. John Wiley and Sons, New York.
- Kloskowski, R., Scheunert, I., Klein, W., and Korte, F. (1981). Laboratory screening of distribution, conversion and mineralization of chemicals in the soil-plant-system and comparison to outdoor experimental data. *Chemosphere* **10**, 1089-1100.
- Kominsky, J.R., and Wisseman, C.L., III (1978). Hazard Evaluation and Technical Assistance Report No. TA-77-39, Morris Forman Wastewater Treatment Plant, Metropolitan Sewer District, Louisville, Kentucky. U.S. Department of Health, Education, and Welfare, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH.
- Lawrence, L.J., and Dorough, H.W. (1982). Fate of inhaled hexachlorocyclopentadiene in albino rats and comparison to the oral and IV routes of administration. *Fundam. Appl. Toxicol.* **2**, 235-240.
- Litton Bionetics (1978a). Mutagenicity evaluation of hexachlorocyclopentadiene in the mouse lymphoma forward assay: Final report. Litton Bionetics, Inc., Kensington, MD.
- Litton Bionetics (1978b). Mutagenicity evaluation of hexachlorocyclopentadiene in the mouse dominant lethal assay: Final report. Litton Bionetics, Inc., Kensington, MD.
- Lu, P.-Y., Metcalf, R.L., Hirwe, A.S., and Williams, J.W. (1975). Evaluation of environmental distribution and fate of hexachlorocyclopentadiene, chlordene, heptachlor, and heptachlor epoxide in a laboratory model ecosystem. *J. Agric. Food Chem.* **23**, 967-973.
- McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.
- MacGregor, J.T., Wehr, C.M., and Langlois, R.G. (1983). A simple fluorescent staining procedure for micronuclei and RNA in erythrocytes using Hoechst 33258 and pyronin Y. *Mutat. Res.* **120**, 269-275.
- MacGregor, J.T., Wehr, C.M., Henika, P.R., and Shelby, M.D. (1990). The *in vivo* erythrocyte micronucleus test: Measurement at steady state increases assay efficiency and permits integration with toxicity studies. *Fundam. Appl. Toxicol.* **14**, 513-522.
- McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **79**, 639-648.
- Margolin, B.H., Collings, B.J., and Mason, J.M. (1983). Statistical analysis and sample-size determinations for mutagenicity experiments with binomial responses. *Environ. Mutagen.* **5**, 705-716.
- Maronpot, R.R., and Boorman, G.A. (1982). Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* **10**, 71-80.
- Mason, J.M., Valencia, R., and Zimmering, S. (1992). Chemical mutagenesis testing in *Drosophila*. VIII. Reexamination of equivocal results. *Environ. Mol. Mutagen.* **19**, 227-234.
- Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.



- Morse, D.L., Landrigan, P.J., and Flint, J.W. (1978). CDC report concerning hexachlorocyclopentadiene contamination of a municipal sewage treatment plant, Louisville, Kentucky. Centers for Disease Control, Atlanta, GA.
- Morse, D.L., Kominsky, J.R., Wisseman, C.L., III, and Landrigan, P.J. (1979). Occupational exposure to hexachlorocyclopentadiene: How safe is sewage? *JAMA* **241**, 2177-2179.
- Murray, F.J., Schwetz, B.A., Balmer, M.F., and Staples, R.E. (1980). Teratogenic potential of hexachlorocyclopentadiene in mice and rabbits. *Toxicol. Appl. Pharmacol.* **53**, 497-500.
- National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.
- National Cancer Institute (NCI) (1977a). Bioassay of Heptachlor for Possible Carcinogenicity (CAS No. 76-44-8). Technical Report Series No. 9. NIH Publication No. 77-809. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.
- National Cancer Institute (NCI) (1977b). Bioassay of Chlordane for Possible Carcinogenicity (CAS No. 57-74-9). Technical Report Series No. 8. NIH Publication No. 77-808. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.
- National Cancer Institute (NCI) (1978). Bioassays of Aldrin and Dieldrin for Possible Carcinogenicity (CAS Nos. 309-00-2 and 60-57-1). Technical Report Series No. 21. NIH Publication No. 78-821. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.
- National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.
- National Toxicology Program (NTP) (1983). Carcinogenesis Studies of 1,1,1,2-Tetrachloroethane (CAS No. 630-20-6) in F344/N Rats and B6C3F<sub>1</sub> Mice (Gavage Studies). Technical Report Series No. 237. NIH Publication No. 83-1793. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.
- National Toxicology Program (NTP) (1991a). Toxicity Studies of Hexachloro-1,3-butadiene in B6C3F<sub>1</sub> Mice (Feed Studies). NTP Toxicity Report No. 6. NIH Publication No. 91-3120. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.
- National Toxicology Program (NTP) (1991b). Toxicity Studies of Pentachlorobenzene in F344/N Rats and B6C3F<sub>1</sub> Mice (Feed Studies). NTP Toxicity Report No. 1. NIH Publication No. 91-3125. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.
- National Toxicology Program (NTP) (1993). Toxicity Studies of Glutaraldehyde (CAS No. 111-30-8) Administered by Inhalation to F344/N Rats and B6C3F<sub>1</sub> Mice. NTP Toxicity Report No. 25. NIH Publication No. 93-3348. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.
- Ortega, P., Hayes, W.J., Jr., and Durham, W.F. (1957). Pathologic changes in the liver of rats after feeding low levels of various insecticides. *AMA Arch. Pathol.* **64**, 614-622.
- Rand, G.M., Nees, P.O., Calo, C.J., Alexander, D.J., and Clark, G.C. (1982a). Effects of inhalation exposure to hexachlorocyclopentadiene on rats and monkeys. *J. Toxicol. Environ. Health* **9**, 743-760.
- Rand, G.M., Nees, P.O., Calo, C.J., Clarke, G.C., and Edmondson, N.A. (1982b). The Clara cell: An electron microscopy examination of the terminal bronchioles of rats and monkeys following inhalation of hexachlorocyclopentadiene. *J. Toxicol. Environ. Health* **10**, 59-72.

- Rieck, C.E. (1979a). Effect of hexachlorocyclopentadiene on soil microbe populations. Agronomy Department, University of Kentucky, Lexington, KY (unpublished report).
- Rieck, C.E. (1979b). Soil metabolism of  $^{14}\text{C}$ -hexachlorocyclopentadiene. Agronomy Department, University of Kentucky, Lexington, KY (unpublished report).
- Sadtler Standard Spectra*. IR No. 5142; UV No. 1397. Sadtler Research Laboratories, Philadelphia, PA.
- Sanders, H.J. (1978). Flame retardants: Government regulations and public emphasis on safety provide the impetus for an expanding industry. *Chem. Eng. News* April 24, 22-36.
- Schmid, W. (1976). The micronucleus test for cytogenetic analysis. In *Chemical Mutagens: Principles and Methods for their Detection* (A. Hollaender, Ed.), Vol. 4, pp. 31-53. Plenum Press, New York.
- Shell Research Limited (1982). Toxicology of insecticide intermediates: The skin sensitizing potential of hexachlorocyclopentadiene (HEX). Report No. SBGR 82.225. Shell Research Ltd., Sittingbourne Research Centre, Tunstall, United Kingdom (unpublished report).
- Shindell and Associates (1981). Report of epidemiologic study of the employees of Velsicol Chemical Corporation plant, Memphis, Tennessee, January 1952-December, 1979. Shindell and Associates, Milwaukee, WI (unpublished report).
- Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* 33, 386-389.
- Southern Research Institute (SRI) (1980). Acute toxicity report on hexachlorocyclopentadiene (C55607) in Fischer F344 rat and B6C3F<sub>1</sub> mice. Southern Research Institute, Birmingham, AL (unpublished report).
- Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* 67, 233.
- Tarone, R.E. (1975). Tests for trend in life table analysis. *Biometrika* 62, 679-682.
- Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* 236, 933-941.
- Treon, J.F., Cleveland, F.P., and Cappel, J. (1955). The toxicity of hexachlorocyclopentadiene. *Arch. Ind. Health* 11, 459-472.
- Ungnade, H.E., and McBee, E.T. (1958). The chemistry of perchlorocyclopentenes and cyclopentadienes. *Chem. Rev.* 58, 249-320.
- U.S. Environmental Protection Agency (USEPA) (1977). Chemical Hazard Information Profile: Hexachlorocyclopentadiene. United States Environmental Protection Agency, Washington, DC.
- U.S. Environmental Protection Agency (USEPA) (1980). Ambient water quality criteria for hexachlorocyclopentadiene. Report EPA-44/5-80-055. Office of Water Regulations and Standards, United States Environmental Protection Agency, Washington, DC.
- Verschueren, K. (1977). *Handbook of Environmental Data on Organic Chemicals*, pp. 211, 365-366. Van Nostrand Reinhold Company, New York.
- Wang, H.H., and MacMahon, B. (1979). Mortality of workers employed in the manufacture of chlordane and heptachlor. *J. Occup. Med.* 21, 745-748.
- Weber, J.B. (1979). Adsorption of HEX by Cape Fear loam soil. North Carolina State University, Raleigh, NC (unpublished report).
- Wildemauwe, C., Lontie, J.-F., Schoofs, L., and van Larebeke, N. (1983). The mutagenicity in prokaryotes of insecticides, acaricides, and nematocides. *Residue Rev.* 89, 129-178.
- Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* 27, 103-117.
- Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* 28, 519-531.

Wolfe, N.L., Zepp, R.G., Schlotzhauer, P., and Sink, M. (1982). Transformation pathways of hexachlorocyclopentadiene in the aquatic environment. *Chemosphere* 11, 91-101.

Wright, A.S., Potter, D., Wooder, M.F., Donninger, C., and Greenland, R.D. (1972). The effects of dieldrin on the subcellular structure and function of mammalian liver cells. *Food Cosmet. Toxicol.* 10, 311-332.

Yu, C.C., and Atallah, Y.H. (1977). Hexhydrolysis at various pHs and temperatures. Project No. V82428, Report No. 8. Velsicol Chemical Corporation, Chicago, IL.

Yu, C.C., and Atallah, Y.H. (1981). Pharmacokinetics and metabolism of hexachlorocyclopentadiene in rats. Project No. V82428, Report No. 10. Velsicol Chemical Corporation, Chicago, IL.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four *in vitro* genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* 16 (Suppl. 18), 1-14.

Zimmering, S., Mason, J.M., Valencia, R., and Woodruff, R.C. (1985). Chemical mutagenesis testing in *Drosophila*. II. Results of 20 coded compounds tested for the National Toxicology Program. *Environ. Mutagen.* 7, 87-100.



**APPENDIX A**  
**SUMMARY OF LESIONS IN MALE RATS**  
**IN THE 2-YEAR INHALATION STUDY**  
**OF HEXACHLOROCYCLOPENTADIENE**

<b>TABLE A1</b>	<b>Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene . . . . .</b>	<b>71</b>
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**TABLE A1**  
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Disposition Summary</b>				
Animals initially in study	60	60	60	60
<i>15-Month interim evaluation</i>	10	10	10	10
Early deaths				
Moribund	27	30	23	31
Natural deaths	5	4	5	3
Survivors				
Terminal sacrifice	18	16	22	16
Animals examined microscopically	60	60	60	60
<b>15-Month Interim Evaluation</b>				
<b>Alimentary System</b>				
None				
<b>Cardiovascular System</b>				
None				
<b>Endocrine System</b>				
Adrenal cortex	(10)			(10)
Bilateral, adenoma				1 (10%)
Adrenal medulla	(10)			(10)
Pheochromocytoma benign				1 (10%)
Islets, pancreatic	(10)			(10)
Adenoma	1 (10%)			1 (10%)
Pituitary gland	(10)			(9)
Pars distalis, adenoma	4 (40%)			3 (33%)
Thyroid gland	(10)		(1)	(10)
C-cell, carcinoma			1 (100%)	
<b>General Body System</b>				
None				
<b>Genital System</b>				
Testes	(10)	(2)	(1)	(10)
Interstitial cell, adenoma	2 (20%)	2 (100%)		5 (50%)
Interstitial cell, adenoma, multiple	7 (70%)		1 (100%)	5 (50%)
<b>Hematopoietic System</b>				
None				
<b>Integumentary System</b>				
None				

**TABLE A1**  
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation (continued)</b>				
<b>Musculoskeletal System</b>				
Skeletal muscle			(1)	
Sarcoma			1 (100%)	
<b>Nervous System</b>				
None				
<b>Respiratory System</b>				
Lung	(10)	(10)	(10)	(10)
Sarcoma, metastatic, skeletal muscle			1 (10%)	
<b>Special Senses System</b>				
None				
<b>Urinary System</b>				
Urinary bladder	(10)			(10)
Papilloma	1 (10%)			
<b>2-Year Study</b>				
<b>Alimentary System</b>				
Intestine large, colon	(47)	(34)	(25)	(49)
Intestine large, rectum	(47)	(34)	(24)	(50)
Sarcoma				1 (2%)
Intestine large, cecum	(48)	(32)	(23)	(49)
Intestine small, duodenum	(47)	(34)	(26)	(50)
Intestine small, jejunum	(46)	(33)	(23)	(48)
Adenocarcinoma, mucinous	1 (2%)			
Fibroma	1 (2%)			
Intestine small, ileum	(46)	(32)	(24)	(48)
Liver	(50)	(39)	(36)	(50)
Hepatocellular adenoma	1 (2%)	1 (3%)	1 (3%)	3 (6%)
Mesentery	(12)	(11)	(8)	(14)
Oral mucosa				(1)
Squamous cell carcinoma				1 (100%)
Pancreas	(50)	(34)	(30)	(50)
Pharynx			(3)	
Papilloma			1 (33%)	
Squamous cell carcinoma			1 (33%)	
Stomach, forestomach	(50)	(36)	(30)	(50)
Stomach, glandular	(50)	(35)	(30)	(50)
<b>Cardiovascular System</b>				
Heart	(50)	(34)	(27)	(50)

TABLE A1

Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene  
(continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study</b> (continued)				
<b>Endocrine System</b>				
Adrenal cortex	(50)	(33)	(27)	(50)
Adenoma	1 (2%)			
Carcinoma			1 (4%)	
Adrenal medulla	(50)	(34)	(28)	(49)
Pheochromocytoma malignant	2 (4%)	1 (3%)	1 (4%)	1 (2%)
Pheochromocytoma benign	12 (24%)	7 (21%)	6 (21%)	13 (27%)
Pheochromocytoma benign, multiple	1 (2%)			
Bilateral, pheochromocytoma benign	2 (4%)	3 (9%)	5 (18%)	4 (8%)
Islets, pancreatic	(50)	(34)	(29)	(50)
Adenoma	7 (14%)	5 (15%)	5 (17%)	10 (20%)
Carcinoma	4 (8%)	2 (6%)	1 (3%)	2 (4%)
Parathyroid gland	(47)	(30)	(25)	(46)
Pituitary gland	(50)	(39)	(38)	(50)
Carcinoma, metastatic, Zymbal's gland		1 (3%)		
Pars distalis, adenoma	23 (46%)	23 (59%)	23 (61%)	33 (66%)
Thyroid gland	(49)	(35)	(32)	(50)
C-cell, adenoma	5 (10%)	3 (9%)	5 (16%)	3 (6%)
C-cell, carcinoma		1 (3%)	2 (6%)	3 (6%)
Follicular cell, adenoma		1 (3%)		3 (6%)
<b>General Body System</b>				
None				
<b>Genital System</b>				
Epididymis	(50)	(35)	(27)	(50)
Preputial gland	(50)	(38)	(30)	(48)
Carcinoma	6 (12%)	2 (5%)	1 (3%)	2 (4%)
Testes	(50)	(48)	(48)	(50)
Bilateral, interstitial cell, adenoma	23 (46%)	21 (44%)	19 (40%)	19 (38%)
Interstitial cell, adenoma	12 (24%)	11 (23%)	13 (27%)	15 (30%)
Interstitial cell, adenoma, multiple	3 (6%)	2 (4%)	1 (2%)	
<b>Hematopoietic System</b>				
Bone marrow	(50)	(34)	(27)	(50)
Lymph node	(2)	(6)	(11)	(8)
Lymph node, bronchial	(49)	(32)	(28)	(48)
Lymph node, mandibular	(48)	(32)	(30)	(50)
Squamous cell carcinoma, metastatic, skin				1 (2%)
Lymph node, mesenteric	(49)	(35)	(31)	(50)
Lymph node, mediastinal	(48)	(32)	(28)	(48)
Carcinoma, metastatic, thyroid gland			1 (4%)	
Spleen	(50)	(41)	(37)	(50)
Thymus	(48)	(32)	(28)	(49)
Carcinoma, metastatic, thyroid gland				1 (2%)



**TABLE A1**  
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Integumentary System</b>				
Skin	(50)	(38)	(34)	(50)
Basal cell carcinoma				1 (2%)
Fibroma	2 (4%)	1 (3%)	2 (6%)	3 (6%)
Fibrosarcoma	1 (2%)	1 (3%)		
Neurofibroma				1 (2%)
Neurofibrosarcoma			1 (3%)	1 (2%)
Sarcoma			1 (3%)	
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma	1 (2%)	1 (3%)		1 (2%)
Sebaceous gland, carcinoma		1 (3%)		1 (2%)
<b>Musculoskeletal System</b>				
Skeletal muscle	(1)		(1)	(2)
Rhabdomyosarcoma	1 (100%)			
<b>Nervous System</b>				
Brain	(50)	(35)	(29)	(50)
Glioma malignant				1 (2%)
Granular cell tumor malignant			1 (3%)	
<b>Respiratory System</b>				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	2 (4%)	2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma				2 (4%)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Carcinoma, metastatic, Zymbal's gland		2 (4%)		
Hemangiosarcoma, metastatic, uncertain primary site			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Squamous cell carcinoma, metastatic, skin				1 (2%)
Nose	(48)	(50)	(49)	(50)
Adenoma, papillary				1 (2%)
Squamous cell carcinoma, metastatic, oral mucosa				1 (2%)
<b>Special Senses System</b>				
Harderian gland		(1)	(2)	(2)
Adenoma				1 (50%)
Duct, carcinoma		1 (100%)		
Zymbal's gland	(2)	(2)	(1)	(1)
Carcinoma	2 (100%)	2 (100%)	1 (100%)	

**TABLE A1**  
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study</b> (continued)				
<b>Urinary System</b>				
Kidney	(50)	(37)	(36)	(50)
Nephroblastoma		1 (3%)		
Urinary bladder	(50)	(34)	(27)	(50)
<b>Systemic Lesions</b>				
Multiple organs <sup>b</sup>	(50)	(50)	(50)	(50)
Leukemia mononuclear	29 (58%)	33 (66%)	26 (52%)	29 (58%)
Mesothelioma malignant	1 (2%)	5 (10%)		2 (4%)
<b>Neoplasm Summary</b>				
Total animals with primary neoplasms <sup>c</sup>				
15-Month interim evaluation	10	2	3	10
2-Year study	50	49	49	49
Total primary neoplasms				
15-Month interim evaluation	15	2	3	17
2-Year study	146	131	120	161
Total animals with benign neoplasms				
15-Month interim evaluation	10	2	1	10
2-Year study	46	45	46	47
Total benign neoplasms				
15-Month interim evaluation	15	2	1	17
2-Year study	99	81	83	113
Total animals with malignant neoplasms				
15-Month interim evaluation			2	
2-Year study	36	38	32	34
Total malignant neoplasms				
15-Month interim evaluation			2	
2-Year study	47	50	37	48
Total animals with metastatic neoplasms				
15-Month interim evaluation			1	
2-Year study	1	3	3	3
Total metastatic neoplasms				
15-Month interim evaluation			1	
2-Year study	1	5	3	4
Total animals with malignant neoplasms of uncertain primary site				
2-Year study			1	

<sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

<sup>b</sup> Number of animals with any tissue examined microscopically

<sup>c</sup> Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2 Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0 ppm

Table with 3 columns: Category (Number of Days on Study, Carcass ID Number, Alimentary System, Cardiovascular System, Endocrine System, General Body System) and 28 columns of data (individual rat IDs). Symbols include '+', 'A', 'X', 'M', and 'I'.

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined









**TABLE A2**  
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0 ppm (continued)**

<b>Number of Days on Study</b>	6 6 7	
	9 9 1 1 1 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	
	4 8 2 2 9 4 9 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	
<b>Carcass ID Number</b>	0 0	
	1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1	Total
	1 3 7 9 7 3 8 1 1 1 2 2 3 4 6 6 8 8 9 0 2 3 4 4 5	Tissues/
	2 1 4 1 1 2 3 1 2 4 1 3 4 3 1 4 1 2 4 2 3 3 2 4 3	Tumors
<b>Special Senses System</b>		
Eye		4
Zymbal's gland	+	2
Carcinoma	X	2
<b>Urinary System</b>		
Kidney	+ +	50
Urinary bladder	+ +	50
<b>Systemic Lesions</b>		
Multiple organs	+ +	50
Leukemia mononuclear	X X X X X X   X   X X   X   X   X X X	29
Mesothelioma malignant	X	1



























**TABLE A2**  
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.05 ppm (continued)**

<b>Number of Days on Study</b>	7 7	
	1 2 2 3	
	2 3 4 1	
<b>Carcass ID Number</b>	0 0	<b>Total Tissues/ Tumors</b>
	7 6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7	
	0 1 5 2 2 2 3 4 5 7 7 8 8 9 0 1 1 2 2 3 3 4 5 5 5	
	4 3 3 1 2 4 1 3 1 3 4 1 4 2 2 1 3 2 4 2 4 1 1 2 4	
<b>Special Senses System</b>		
Ear		1
Eye	+ +	7
Harderian gland		2
Zymbal's gland		1
Carcinoma		1
<b>Urinary System</b>		
Kidney	+ +	36
Urethra		1
Urinary bladder	+ + +	27
<b>Systemic Lesions</b>		
Multiple organs	+ +	50
Leukemia mononuclear	X X	26







**TABLE A2**  
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.2 ppm (continued)**

Number of Days on Study	6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7																		Total Tissues/ Tumors
	8 9 0 0 0 1 1 2 2 3 3 3 3 3 3 3 3 3 3 3 3																		
Carcass ID Number	3 5 4 4 9 2 9 3 4 0 0 0 0 0 0 0 0 0 0 0 0																		
	0 0 0 1 0 1 1 0 1 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1																		
																			9 9 9 0 9 0 0 9 0 9 9 9 9 9 9 0 0 0 0 0 0 0 0
																			9 1 8 1 6 5 5 9 3 1 2 2 4 5 6 8 1 1 2 2 3 4 4 5 5
																			2 4 4 4 2 1 3 4 1 1 1 4 2 2 4 2 2 3 1 4 3 1 4 2 4
<b>Genital System</b>																			
Epididymis	+ +																		50
Preputial gland	+ + + + + + + + M + + + + + + + + + + + + + + + +																		48
Carcinoma																			2
Prostate	+ +																		50
Seminal vesicle	+ +																		50
Testes	+ +																		50
Bilateral, interstitial cell, adenoma	X X																		19
Interstitial cell, adenoma	X X																		15
<b>Hematopoietic System</b>																			
Bone marrow	+ +																		50
Lymph node	+ +																		8
Lymph node, bronchial	+ +																		48
Lymph node, mandibular	+ +																		50
Squamous cell carcinoma, metastatic, skin																			1
Lymph node, mesenteric	+ +																		50
Lymph node, mediastinal	+ +																		48
Spleen	+ +																		50
Thymus	+ +																		49
Carcinoma, metastatic, thyroid gland	X																		1
<b>Integumentary System</b>																			
Mammary gland	+ +																		50
Skin	+ +																		50
Basal cell carcinoma																			1
Fibroma	X X																		3
Neurofibroma																			1
Neurofibrosarcoma																			1
Squamous cell carcinoma																			1
Squamous cell papilloma	X																		1
Sebaceous gland, carcinoma	X																		1
<b>Musculoskeletal System</b>																			
Bone	+ +																		50
Skeletal muscle	+ +																		2
<b>Nervous System</b>																			
Brain	+ +																		50
Glioma malignant																			1
Spinal cord																			1







**TABLE A3**  
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Adrenal Medulla: Benign Pheochromocytoma</b>				
Overall rate <sup>a</sup>	15/50 (30%)	10/50 (20%)	11/50 (22%)	17/50 (34%)
Adjusted rate <sup>b</sup>	58.2%	31.8%	31.4%	60.7%
Terminal rate <sup>c</sup>	8/18 (44%)	1/16 (6%)	1/22 (5%)	6/16 (38%)
First incidence (days)	628	565	471	617
Life table test <sup>d</sup>	P=0.109	P=0.247N	P=0.148N	P=0.314
Logistic regression test <sup>d</sup>	P=0.108	P=0.203N	P=0.225N	P=0.311
Cochran-Armitage test <sup>d</sup>	P=0.145			
Fisher exact test <sup>d</sup>		P=0.178N	P=0.247N	P=0.415
<b>Liver: Hepatocellular Adenoma</b>				
Overall rate	1/50 (2%)	1/39 (3%) <sup>e</sup>	1/36 (3%) <sup>e</sup>	3/50 (6%)
Adjusted rate	4.3%			12.0%
Terminal rate	0/18 (0%)			0/16 (0%)
First incidence (days)	712			617
Life table test				P=0.281
Logistic regression test				P=0.284
Cochran-Armitage test				
Fisher exact test				P=0.309
<b>Lung: Alveolar/bronchiolar Adenoma</b>				
Overall rate	5/50 (10%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rate	23.5%	12.5%	9.1%	15.4%
Terminal rate	3/18 (17%)	2/16 (13%)	2/22 (9%)	2/16 (13%)
First incidence (days)	694	730 (T)	730 (T)	639
Life table test	P=0.577N	P=0.258N	P=0.145N	P=0.413N
Logistic regression test	P=0.569N	P=0.233N	P=0.150N	P=0.397N
Cochran-Armitage test	P=0.522N			
Fisher exact test		P=0.218N	P=0.218N	P=0.357N
<b>Lung: Alveolar/bronchiolar Adenoma or Carcinoma</b>				
Overall rate	5/50 (10%)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted rate	23.5%	12.5%	9.1%	26.1%
Terminal rate	3/18 (17%)	2/16 (13%)	2/22 (9%)	3/16 (19%)
First incidence (days)	694	730 (T)	730 (T)	639
Life table test	P=0.258	P=0.258N	P=0.145N	P=0.561
Logistic regression test	P=0.266	P=0.233N	P=0.150N	P=0.583
Cochran-Armitage test	P=0.320			
Fisher exact test		P=0.218N	P=0.218N	P=0.630N
<b>Pancreatic Islets: Adenoma</b>				
Overall rate	7/50 (14%)	5/34 (15%) <sup>e</sup>	5/29 (17%) <sup>e</sup>	10/50 (20%)
Adjusted rate	32.9%			43.0%
Terminal rate	5/18 (28%)			5/16 (31%)
First incidence (days)	651			620
Life table test				P=0.230
Logistic regression test				P=0.235
Cochran-Armitage test				
Fisher exact test				P=0.298

TABLE A3

Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene  
(continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Pancreatic Islets: Carcinoma</b>				
Overall rate	4/50 (8%)	2/34 (6%) <sup>e</sup>	1/29 (3%) <sup>e</sup>	2/50 (4%)
Adjusted rate	15.6%			11.1%
Terminal rate	1/18 (6%)			0/16 (0%)
First incidence (days)	626			723
Life table test				P=0.395N
Logistic regression test				P=0.367N
Cochran-Armitage test				
Fisher exact test				P=0.339N
<b>Pancreatic Islets: Adenoma or Carcinoma</b>				
Overall rate	11/50 (22%)	7/34 (21%) <sup>e</sup>	6/29 (21%) <sup>e</sup>	12/50 (24%)
Adjusted rate	44.7%			49.4%
Terminal rate	6/18 (33%)			5/16 (31%)
First incidence (days)	626			620
Life table test				P=0.398
Logistic regression test				P=0.420
Cochran-Armitage test				
Fisher exact test				P=0.500
<b>Pituitary Gland (Pars Distalis): Adenoma</b>				
Overall rate	23/50 (46%)	23/39 (59%) <sup>e</sup>	23/38 (61%) <sup>e</sup>	33/50 (66%)
Adjusted rate	66.8%			93.9%
Terminal rate	8/18 (44%)			14/16 (88%)
First incidence (days)	464			485
Life table test				P=0.037
Logistic regression test				P=0.016
Cochran-Armitage test				
Fisher exact test				P=0.035
<b>Preputial Gland: Carcinoma</b>				
Overall rate	6/50 (12%)	2/38 (5%) <sup>e</sup>	1/30 (3%) <sup>e</sup>	2/48 (4%)
Adjusted rate	21.9%			12.5%
Terminal rate	2/18 (11%)			2/16 (13%)
First incidence (days)	464			730 (T)
Life table test				P=0.168N
Logistic regression test				P=0.162N
Cochran-Armitage test				
Fisher exact test				P=0.148N
<b>Skin: Fibroma</b>				
Overall rate	2/50 (4%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	6.8%	6.3%	8.5%	16.7%
Terminal rate	0/18 (0%)	1/16 (6%)	1/22 (5%)	2/16 (13%)
First incidence (days)	536	730 (T)	723	709
Life table test	P=0.261	P=0.524N	P=0.656N	P=0.454
Logistic regression test	P=0.275	P=0.504N	P=0.694N	P=0.476
Cochran-Armitage test	P=0.302			
Fisher exact test		P=0.500N	P=0.691N	P=0.500

**TABLE A3**  
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Skin: Squamous Cell Papilloma, Basal Cell Carcinoma, or Squamous Cell Carcinoma</b>				
Overall rate	1/50 (2%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	5.6%	3.6%	0.0%	14.5%
Terminal rate	1/18 (6%)	0/16 (0%)	0/22 (0%)	2/16 (13%)
First incidence (days)	730 (T)	662	- <sup>f</sup>	534
Life table test	P=0.097	P=0.747	P=0.460N	P=0.268
Logistic regression test	P=0.110	P=0.754	P=0.460N	P=0.287
Cochran-Armitage test	P=0.118			
Fisher exact test		P=0.753N	P=0.500N	P=0.309
<b>Testes: Adenoma</b>				
Overall rate	38/50 (76%)	34/48 (71%)	33/48 (69%)	34/50 (68%)
Adjusted rate	100.0%	100.0%	100.0%	93.7%
Terminal rate	18/18 (100%)	14/14 (100%)	21/21 (100%)	14/16 (88%)
First incidence (days)	536	355	402	474
Life table test	P=0.542	P=0.517	P=0.072N	P=0.528N
Logistic regression test	P=0.393N	P=0.499N	P=0.254N	P=0.374N
Cochran-Armitage test	P=0.300N			
Fisher exact test		P=0.363N	P=0.282N	P=0.252N
<b>Thyroid Gland (C-cell): Adenoma</b>				
Overall rate	5/49 (10%)	3/35 (9%) <sup>e</sup>	5/32 (16%) <sup>e</sup>	3/50 (6%)
Adjusted rate	20.2%			15.2%
Terminal rate	2/18 (11%)			2/16 (13%)
First incidence (days)	626			621
Life table test				P=0.413N
Logistic regression test				P=0.381N
Cochran-Armitage test				
Fisher exact test				P=0.346N
<b>Thyroid Gland (C-cell): Carcinoma</b>				
Overall rate	0/49 (0%)	1/35 (3%) <sup>e</sup>	2/32 (6%) <sup>e</sup>	3/50 (6%)
Adjusted rate	0.0%			16.0%
Terminal rate	0/18 (0%)			1/16 (6%)
First incidence (days)	-			709
Life table test				P=0.103
Logistic regression test				P=0.103
Cochran-Armitage test				
Fisher exact test				P=0.125
<b>Thyroid Gland (C-cell): Adenoma or Carcinoma</b>				
Overall rate	5/49 (10%)	3/35 (9%) <sup>e</sup>	7/32 (22%) <sup>e</sup>	6/50 (12%)
Adjusted rate	20.2%			29.4%
Terminal rate	2/18 (11%)			3/16 (19%)
First incidence (days)	626			621
Life table test				P=0.428
Logistic regression test				P=0.460
Cochran-Armitage test				
Fisher exact test				P=0.514

**TABLE A3**  
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Thyroid Gland (Follicular Cell): Adenoma</b>				
Overall rate	0/49 (0%)	1/35 (3%) <sup>e</sup>	0/32 (0%) <sup>e</sup>	3/50 (6%)
Adjusted rate	0.0%			15.4%
Terminal rate	0/18 (0%)			2/16 (13%)
First incidence (days)	--			639
Life table test				P=0.106
Logistic regression test				P=0.110
Cochran-Armitage test				
Fisher exact test				P=0.125
<b>All Organs: Mononuclear Cell Leukemia</b>				
Overall rate	29/50 (58%)	33/50 (66%)	26/50 (52%)	29/50 (58%)
Adjusted rate	72.6%	79.2%	65.2%	76.1%
Terminal rate	8/18 (44%)	8/16 (50%)	9/22 (41%)	8/16 (50%)
First incidence (days)	536	370	506	460
Life table test	P=0.484	P=0.258	P=0.210N	P=0.416
Logistic regression test	P=0.473N	P=0.241	P=0.349N	P=0.536
Cochran-Armitage test	P=0.429N			
Fisher exact test		P=0.268	P=0.344N	P=0.580N
<b>All Organs: Malignant Mesothelioma</b>				
Overall rate	1/50 (2%)	5/50 (10%)	0/50 (0%)	2/50 (4%)
Adjusted rate	4.3%	20.6%	0.0%	5.9%
Terminal rate	0/18 (0%)	1/16 (6%)	0/22 (0%)	0/16 (0%)
First incidence (days)	712	597	--	542
Life table test	P=0.546N	P=0.093	P=0.476N	P=0.466
Logistic regression test	P=0.517N	P=0.094	P=0.480N	P=0.510
Cochran-Armitage test	P=0.509N			
Fisher exact test		P=0.102	P=0.500N	P=0.500
<b>All Organs: Benign Neoplasms</b>				
Overall rate	46/50 (92%)	45/50 (90%)	46/50 (92%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	18/18 (100%)	16/16 (100%)	22/22 (100%)	16/16 (100%)
First incidence (days)	464	355	402	220
Life table test	P=0.195	P=0.439	P=0.237N	P=0.250
Logistic regression test	P=0.048	P=0.586	P=0.413	P=0.115
Cochran-Armitage test	P=0.201			
Fisher exact test		P=0.500N	P=0.643N	P=0.339
<b>All Organs: Malignant Neoplasms</b>				
Overall rate	36/50 (72%)	38/50 (76%)	32/50 (64%)	34/50 (68%)
Adjusted rate	79.1%	84.0%	76.9%	79.5%
Terminal rate	9/18 (50%)	9/16 (56%)	13/22 (59%)	8/16 (50%)
First incidence (days)	373	370	471	180
Life table test	P=0.531	P=0.347	P=0.169N	P=0.505
Logistic regression test	P=0.318N	P=0.429	P=0.262N	P=0.382N
Cochran-Armitage test	P=0.319N			
Fisher exact test		P=0.410	P=0.260N	P=0.414N

**TABLE A3**  
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>All Organs: Benign or Malignant Neoplasms</b>				
Overall rate	50/50 (100%)	49/50 (98%)	48/50 (96%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	18/18 (100%)	16/16 (100%)	22/22 (100%)	16/16 (100%)
First incidence (days)	373	355	402	180
Life table test	P=0.289	P=0.436	P=0.176N	P=0.339
Logistic regression test	P=0.142	P=0.630N	— <sup>g</sup>	—
Cochran-Armitage test	P=0.471			
Fisher exact test		P=0.500N	P=0.247N	P=1.000N

(T) Terminal sacrifice

- <sup>a</sup> Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for bone marrow, brain, epididymis, heart, kidney, larynx, liver, lung, nose, pancreas, pancreatic islets, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
- <sup>b</sup> Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
- <sup>c</sup> Observed incidence at terminal kill
- <sup>d</sup> Beneath the control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
- <sup>e</sup> Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not appropriate.
- <sup>f</sup> Not applicable; no neoplasms in animal group
- <sup>g</sup> Value of statistic cannot be computed.

**TABLE A4**  
**Historical Incidence of Pituitary Gland Neoplasms in Untreated Male F344/N Rats<sup>a</sup>**

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
<b>Historical Incidence at Battelle Pacific Northwest Laboratories</b>			
<i>o</i> -Chlorobenzalmalononitrile	25/47	1/47	26/47
2-Chloroacetophenone	31/47	1/47	32/47
Epinephrine hydrochloride	34/50	0/50	34/50
Ethyl chloride	31/49	1/49	32/49
<b>Overall Historical Incidence</b>			
Total	203/340 (59.7%)	6/340 (1.8%)	208/340 (61.2%)
Standard deviation	8.1%	2.1%	8.6%
Range	45%-68%	0%-6%	45%-68%

<sup>a</sup> Data as of 20 August 1992. Incidences cited are for pituitary gland pars distalis or unspecified site.



**TABLE A5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Disposition Summary</b>				
Animals initially in study	60	60	60	60
<i>15-Month interim evaluation</i>	10	10	10	10
Early deaths				
Moribund	27	30	23	31
Natural deaths	5	4	5	3
Survivors				
Terminal sacrifice	18	16	22	16
Animals examined microscopically	60	60	60	60
<b>15-Month Interim Evaluation</b>				
<b>Alimentary System</b>				
Liver	(10)	(3)		(10)
Basophilic focus	2 (20%)			2 (20%)
Clear cell focus	1 (10%)	1 (33%)		
Granuloma, multifocal	2 (20%)			2 (20%)
Hepatodiaphragmatic nodule		2 (67%)		
Infarct	1 (10%)			
Biliary tract, hyperplasia				1 (10%)
Pancreas	(10)			(10)
Inflammation, chronic	1 (10%)			
Acinus, atrophy	6 (60%)			4 (40%)
Artery, inflammation	1 (10%)			
<b>Cardiovascular System</b>				
Heart	(10)			(10)
Cardiomyopathy	4 (40%)			3 (30%)
<b>Endocrine System</b>				
Thyroid gland	(10)		(1)	(10)
Ultimobranchial cyst	1 (10%)			1 (10%)
C-cell, hyperplasia	1 (10%)			
Follicular cell, cyst	1 (10%)			
<b>General Body System</b>				
None				
<b>Genital System</b>				
Preputial gland	(10)			(10)
Cyst				2 (20%)
Seminal vesicle	(10)			(10)
Inflammation, suppurative	5 (50%)			3 (30%)
Testes	(10)	(2)	(1)	(10)
Seminiferous tubule, atrophy				1 (10%)

**TABLE A5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation (continued)</b>				
<b>Hematopoietic System</b>				
Lymph node	(1)			
Renal, hemorrhage	1 (100%)			
Lymph node, mediastinal	(10)			(10)
Hemorrhage	1 (10%)			
Spleen	(10)			(10)
Ectopic tissue				1 (10%)
<b>Integumentary System</b>				
Skin	(10)			(10)
Cyst epithelial inclusion	1 (10%)			
Ulcer	1 (10%)			
<b>Musculoskeletal System</b>				
None				
<b>Nervous System</b>				
None				
<b>Respiratory System</b>				
Larynx	(10)	(10)	(10)	(10)
Foreign body		1 (10%)		
Hyperplasia	1 (10%)			
Inflammation, chronic	1 (10%)			
Inflammation, suppurative		1 (10%)		1 (10%)
Metaplasia, squamous		2 (20%)		
Lung	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia	2 (20%)		1 (10%)	1 (10%)
Alveolus, hemorrhage	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Alveolus, infiltration cellular, multifocal, histiocyte	3 (30%)	1 (10%)	2 (20%)	1 (10%)
Artery, mineralization	1 (10%)	1 (10%)	5 (50%)	1 (10%)
Bronchiole, pigmentation			1 (10%)	10 (100%)
Peribronchiolar, pigmentation				4 (40%)
Nose	(10)	(10)	(10)	(10)
Hemorrhage	1 (10%)	2 (20%)	2 (20%)	3 (30%)
Inflammation, suppurative	1 (10%)			1 (10%)
Pigmentation		8 (80%)	10 (100%)	7 (70%)
Nasolacrimal duct, hemorrhage	6 (60%)	1 (10%)	7 (70%)	6 (60%)
Respiratory epithelium, hyperplasia	1 (10%)	1 (10%)	1 (10%)	2 (20%)
Trachea	(10)	(10)	(10)	(10)
Inflammation, chronic			1 (10%)	
<b>Special Senses System</b>				
Eye		(2)		
Cataract		1 (50%)		

**TABLE A5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene** (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation</b> (continued)				
<b>Urinary System</b>				
Kidney	(10)	(1)		(10)
Nephropathy, chronic	9 (90%)	1 (100%)		10 (100%)
<b>2-Year Study</b>				
<b>Alimentary System</b>				
Intestine large, colon	(47)	(34)	(25)	(49)
Mineralization				1 (2%)
Intestine large, rectum	(47)	(34)	(24)	(50)
Ulcer				1 (2%)
Intestine large, cecum	(48)	(32)	(23)	(49)
Inflammation, suppurative	1 (2%)			
Ulcer	1 (2%)			
Intestine small, ileum	(46)	(32)	(24)	(48)
Inflammation, suppurative		1 (3%)		
Liver	(50)	(39)	(36)	(50)
Angiectasis	1 (2%)		1 (3%)	
Basophilic focus	8 (16%)	3 (8%)	2 (6%)	2 (4%)
Clear cell focus	3 (6%)	3 (8%)	3 (8%)	5 (10%)
Eosinophilic focus		1 (3%)		
Granuloma, multifocal	1 (2%)			
Hematopoietic cell proliferation	1 (2%)			
Hepatodiaphragmatic nodule	3 (6%)	5 (13%)	1 (3%)	1 (2%)
Hyperplasia				3 (6%)
Necrosis, focal		1 (3%)		
Thrombosis			1 (3%)	
Vacuolization cytoplasmic	1 (2%)	2 (5%)		3 (6%)
Biliary tract, hyperplasia	9 (18%)	2 (5%)	1 (3%)	1 (2%)
Hepatocyte, hyperplasia	1 (2%)	1 (3%)	4 (11%)	
Mesentery	(12)	(11)	(8)	(14)
Hemorrhage	2 (17%)			
Inflammation, granulomatous	2 (17%)	1 (9%)		2 (14%)
Fat, mineralization			1 (13%)	
Fat, necrosis	9 (75%)	7 (64%)	7 (88%)	12 (86%)
Pancreas	(50)	(34)	(30)	(50)
Fibrosis	2 (4%)			1 (2%)
Acinus, atrophy	23 (46%)	13 (38%)	9 (30%)	18 (36%)
Acinus, hyperplasia			1 (3%)	
Artery, inflammation			2 (7%)	
Pharynx			(3)	
Developmental malformation			1 (33%)	
Stomach, forestomach	(50)	(36)	(30)	(50)
Acanthosis	6 (12%)	6 (17%)	6 (20%)	6 (12%)
Edema			1 (3%)	1 (2%)
Erosion			1 (3%)	
Hyperkeratosis	3 (6%)	4 (11%)	3 (10%)	1 (2%)
Inflammation, suppurative	3 (6%)	2 (6%)	1 (3%)	2 (4%)
Mineralization	1 (2%)		2 (7%)	1 (2%)
Ulcer	2 (4%)	3 (8%)	2 (7%)	1 (2%)
Muscularis, hypoplasia		1 (3%)	1 (3%)	4 (8%)

**TABLE A5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Alimentary System (continued)</b>				
Stomach, glandular	(50)	(35)	(30)	(50)
Edema			1 (3%)	1 (2%)
Erosion	1 (2%)	2 (6%)		2 (4%)
Hemorrhage	1 (2%)			
Inflammation, suppurative	3 (6%)	2 (6%)	1 (3%)	2 (4%)
Mineralization	1 (2%)	2 (6%)	1 (3%)	1 (2%)
Necrosis		1 (3%)		
Serosa, fibrosis				1 (2%)
Tooth	(1)	(1)		(1)
Inflammation, suppurative	1 (100%)	1 (100%)		1 (100%)
<b>Cardiovascular System</b>				
Blood vessel	(5)	(3)	(2)	(2)
Atherosclerosis, diffuse	1 (20%)			1 (50%)
Mineralization	2 (40%)			
Mineralization, diffuse		1 (33%)		1 (50%)
Polyarteritis, diffuse		1 (33%)	1 (50%)	
Thrombosis	1 (20%)			
Aorta, atherosclerosis	1 (20%)			
Aorta, mineralization			1 (50%)	
Mesenteric artery, developmental malformation		1 (33%)		
Heart	(50)	(34)	(27)	(50)
Cardiomyopathy	13 (26%)	9 (26%)	4 (15%)	16 (32%)
Mineralization	1 (2%)	2 (6%)	1 (4%)	1 (2%)
Thrombosis	1 (2%)	1 (3%)	1 (4%)	3 (6%)
Myocardium, hemorrhage		1 (3%)		
<b>Endocrine System</b>				
Adrenal cortex	(50)	(33)	(27)	(50)
Cytomegaly	9 (18%)	4 (12%)	4 (15%)	10 (20%)
Hemorrhage		1 (3%)		
Hyperplasia	2 (4%)	3 (9%)	1 (4%)	
Metaplasia, osseous			1 (4%)	
Necrosis		1 (3%)		
Adrenal medulla	(50)	(34)	(28)	(49)
Hyperplasia	10 (20%)	8 (24%)	7 (25%)	13 (27%)
Bilateral, hyperplasia	3 (6%)	3 (9%)	3 (11%)	6 (12%)
Islets, pancreatic	(50)	(34)	(29)	(50)
Hyperplasia	3 (6%)			
Parathyroid gland	(47)	(30)	(25)	(46)
Hyperplasia	2 (4%)	2 (7%)	3 (12%)	4 (9%)
Pituitary gland	(50)	(39)	(38)	(50)
Cyst		1 (3%)	3 (8%)	3 (6%)
Hemorrhage	1 (2%)	2 (5%)	1 (3%)	1 (2%)
Necrosis	1 (2%)		1 (3%)	
Pars distalis, hyperplasia	10 (20%)	4 (10%)	3 (8%)	6 (12%)
Pars intermedia, hyperplasia				1 (2%)

TABLE A5

**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Endocrine System (continued)</b>				
Thyroid gland	(49)	(35)	(32)	(50)
Ultimobranchial cyst		2 (6%)		2 (4%)
C-cell, hyperplasia	6 (12%)	1 (3%)		8 (16%)
Follicular cell, hyperplasia	1 (2%)			1 (2%)
<b>General Body System</b>				
None				
<b>Genital System</b>				
Epididymis	(50)	(35)	(27)	(50)
Granuloma sperm			1 (4%)	
Preputial gland	(50)	(38)	(30)	(48)
Cyst	7 (14%)	3 (8%)	1 (3%)	2 (4%)
Hyperplasia	1 (2%)	2 (5%)		
Inflammation, suppurative	6 (12%)	2 (5%)		3 (6%)
Prostate	(50)	(35)	(30)	(50)
Inflammation, suppurative	15 (30%)	13 (37%)	14 (47%)	13 (26%)
Epithelium, hyperplasia	6 (12%)	3 (9%)	1 (3%)	3 (6%)
Seminal vesicle	(50)	(35)	(29)	(50)
Inflammation, suppurative	6 (12%)	3 (9%)	5 (17%)	2 (4%)
Epithelium, hyperplasia			2 (7%)	
Testes	(50)	(48)	(48)	(50)
Arteriole, inflammation	4 (8%)		2 (4%)	5 (10%)
Interstitial cell, hyperplasia	5 (10%)	12 (25%)	8 (17%)	11 (22%)
Seminiferous tubule, atrophy	9 (18%)	8 (17%)	10 (21%)	11 (22%)
<b>Hematopoietic System</b>				
Bone marrow	(50)	(34)	(27)	(50)
Hyperplasia, reticulum cell	1 (2%)			
Myelofibrosis	1 (2%)	2 (6%)	2 (7%)	4 (8%)
Lymph node	(2)	(6)	(11)	(8)
Pancreatic, hemorrhage			1 (9%)	
Renal, hemorrhage			1 (9%)	
Renal, hyperplasia, lymphoid			1 (9%)	1 (13%)
Renal, pigmentation			1 (9%)	
Lymph node, bronchial	(49)	(32)	(28)	(48)
Hemorrhage	1 (2%)		1 (4%)	
Pigmentation	1 (2%)			1 (2%)
Lymph node, mandibular	(48)	(32)	(30)	(50)
Hemorrhage		1 (3%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (6%)	4 (13%)	3 (6%)
Inflammation, chronic				1 (2%)
Lymph node, mesenteric	(49)	(35)	(31)	(50)
Hemorrhage	1 (2%)	1 (3%)	2 (6%)	1 (2%)
Inflammation	1 (2%)			
Lymph node, mediastinal	(48)	(32)	(28)	(48)
Hemorrhage		1 (3%)		
Mineralization	1 (2%)			
Pigmentation	2 (4%)	2 (6%)		3 (6%)

**TABLE A5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Hematopoietic System (continued)</b>				
Spleen	(50)	(41)	(37)	(50)
Ectopic tissue	1 (2%)		1 (3%)	2 (4%)
Fibrosis	5 (10%)	9 (22%)	9 (24%)	7 (14%)
Hyperplasia, reticulum cell	1 (2%)			
Necrosis	3 (6%)	1 (2%)		
<b>Integumentary System</b>				
Mammary gland	(50)	(34)	(27)	(50)
Galactocele		1 (3%)		2 (4%)
Hyperplasia	1 (2%)			3 (6%)
Inflammation, suppurative				3 (6%)
Skin	(50)	(38)	(34)	(50)
Abscess	1 (2%)	1 (3%)		1 (2%)
Acanthosis	2 (4%)	3 (8%)	1 (3%)	
Cyst epithelial inclusion	4 (8%)	2 (5%)	4 (12%)	2 (4%)
Hyperkeratosis	1 (2%)	3 (8%)	1 (3%)	
Ulcer	1 (2%)	2 (5%)		
<b>Musculoskeletal System</b>				
Bone	(50)	(34)	(27)	(50)
Fibrous osteodystrophy	1 (2%)			
Inflammation, suppurative			1 (4%)	
Skeletal muscle	(1)		(1)	(2)
Mineralization				1 (50%)
<b>Nervous System</b>				
Brain	(50)	(35)	(29)	(50)
Compression	6 (12%)	5 (14%)	9 (31%)	8 (16%)
Gliosis	1 (2%)			
Hemorrhage	6 (12%)	6 (17%)	5 (17%)	6 (12%)
Hemorrhage, multifocal		1 (3%)		
Hydrocephalus	4 (8%)	5 (14%)	10 (34%)	4 (8%)
Mineralization			1 (3%)	
Necrosis	1 (2%)		1 (3%)	
<b>Respiratory System</b>				
Larynx	(48)	(50)	(47)	(49)
Foreign body	1 (2%)	1 (2%)		
Inflammation, chronic	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative	7 (15%)	3 (6%)	2 (4%)	3 (6%)
Metaplasia, squamous	1 (2%)	2 (4%)	6 (13%)	4 (8%)
Mineralization	1 (2%)		1 (2%)	

**TABLE A5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Respiratory System (continued)</b>				
<b>Lung</b>	(50)	(50)	(50)	(50)
Congestion		1 (2%)	1 (2%)	
Infiltration cellular, histiocyte	1 (2%)			
Thrombosis			1 (2%)	
Alveolar epithelium, hyperplasia	7 (14%)	6 (12%)	5 (10%)	3 (6%)
Alveolus, hemorrhage	8 (16%)	13 (26%)	14 (28%)	12 (24%)
Alveolus, infiltration cellular, multifocal, histiocyte	7 (14%)	6 (12%)	8 (16%)	14 (28%)
Alveolus, inflammation, suppurative	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Artery, mineralization	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Bronchiole, pigmentation				49 (98%)
Peribronchiolar, pigmentation			2 (4%)	16 (32%)
Pleura, fibrosis				1 (2%)
<b>Nose</b>	(48)	(50)	(49)	(50)
Foreign body	2 (4%)	5 (10%)	8 (16%)	7 (14%)
Hemorrhage	6 (13%)	6 (12%)	5 (10%)	6 (12%)
Inflammation, suppurative	9 (19%)	7 (14%)	6 (12%)	12 (24%)
Pigmentation	1 (2%)	46 (92%)	48 (98%)	48 (96%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Respiratory epithelium, hyperplasia	7 (15%)	10 (20%)	8 (16%)	13 (26%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	2 (4%)		2 (4%)
<b>Trachea</b>	(48)	(50)	(48)	(50)
Inflammation, suppurative		1 (2%)		
Pigmentation				5 (10%)
<b>Special Senses System</b>				
<b>Eye</b>	(4)	(2)	(7)	(7)
Atrophy	1 (25%)			
Cataract	2 (50%)	1 (50%)	5 (71%)	2 (29%)
Anterior chamber, hemorrhage				1 (14%)
Anterior chamber, inflammation, suppurative	1 (25%)	1 (50%)		
Choroid, iris, inflammation, chronic	2 (50%)			1 (14%)
Cornea, inflammation	1 (25%)			1 (14%)
<b>Urinary System</b>				
<b>Kidney</b>	(50)	(37)	(36)	(50)
Cyst	1 (2%)		2 (6%)	1 (2%)
Mineralization	1 (2%)	3 (8%)	1 (3%)	2 (4%)
Nephropathy, chronic	47 (94%)	36 (97%)	33 (92%)	49 (98%)
Cortex, necrosis	1 (2%)			
Papilla, necrosis		1 (3%)		
Pelvis, dilatation		2 (5%)		1 (2%)
Pelvis, transitional epithelium, hyperplasia				1 (2%)
Renal tubule, hyperplasia				2 (4%)

**TABLE A5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<i>2-Year Study (continued)</i>				
<b>Urinary System (continued)</b>				
Urethra			(1)	
Inflammation, suppurative			1 (100%)	
Urinary bladder	(50)	(34)	(27)	(50)
Inflammation, suppurative	1 (2%)	1 (3%)	3 (11%)	1 (2%)
Transitional epithelium, hyperplasia	2 (4%)		1 (4%)	1 (2%)

<sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion



**APPENDIX B**  
**SUMMARY OF LESIONS IN FEMALE RATS**  
**IN THE 2-YEAR INHALATION STUDY**  
**OF HEXACHLOROCYCLOPENTADIENE**

<b>TABLE B1</b>	<b>Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene . . . . .</b>	<b>117</b>
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**TABLE B1**  
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Disposition Summary</b>				
Animals initially in study	60	60	60	60
<i>15-Month interim evaluation</i>	10	10	10	10
Early deaths				
Moribund	19	16	14	16
Natural deaths	3	1	5	4
Survivors				
Terminal sacrifice	28	33	30	30
Missexed			1	
Animals examined microscopically	60	60	59	60
<b>15-Month Interim Evaluation</b>				
<b>Alimentary System</b>				
Liver	(10)	(3)		(10)
Hepatocellular adenoma		1 (33%)		
<b>Cardiovascular System</b>				
None				
<b>Endocrine System</b>				
Pituitary gland	(10)		(5)	(10)
Pars distalis, adenoma	1 (10%)		2 (40%)	2 (20%)
<b>General Body System</b>				
None				
<b>Genital System</b>				
Uterus	(10)		(10)	(10)
Polyp stromal			1 (10%)	
<b>Hematopoietic System</b>				
None				
<b>Integumentary System</b>				
Mammary gland	(10)	(1)	(1)	(10)
Fibroadenoma	1 (10%)	1 (100%)	1 (100%)	
<b>Musculoskeletal System</b>				
None				

**TABLE B1**  
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation</b> (continued)				
<b>Nervous System</b>				
None				
<b>Respiratory System</b>				
None				
<b>Special Senses System</b>				
None				
<b>Urinary System</b>				
None				
<b>2-Year Study</b>				
<b>Alimentary System</b>				
Esophagus	(50)	(18)	(19)	(50)
Carcinoma, metastatic, thyroid gland				1 (2%)
Liver	(50)	(31)	(32)	(50)
Hepatocellular carcinoma			1 (3%)	
Hepatocellular adenoma	1 (2%)	1 (3%)		
Hepatocellular adenoma, multiple				1 (2%)
Mesentery	(9)	(6)	(6)	(3)
Pancreas	(50)	(17)	(19)	(50)
Carcinoma, metastatic, kidney	1 (2%)			
Pharynx	(3)		(1)	
Squamous cell carcinoma	1 (33%)		1 (100%)	
Tongue	(1)	(1)	(1)	
Carcinoma	1 (100%)	1 (100%)		
Squamous cell carcinoma, metastatic, pharynx			1 (100%)	
<b>Cardiovascular System</b>				
Heart	(50)	(17)	(19)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (5%)	

TABLE B1

Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene  
(continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study</b> (continued)				
<b>Endocrine System</b>				
Adrenal cortex	(50)	(21)	(19)	(50)
Carcinoma		1 (5%)		
Adrenal medulla	(47)	(19)	(20)	(50)
Pheochromocytoma malignant		1 (5%)	1 (5%)	
Pheochromocytoma benign	5 (11%)	2 (11%)	3 (15%)	2 (4%)
Bilateral, pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(50)	(18)	(19)	(50)
Adenoma	2 (4%)	1 (6%)		1 (2%)
Pituitary gland	(50)	(39)	(33)	(50)
Pars distalis, adenoma	31 (62%)	30 (77%)	23 (70%)	38 (76%)
Pars intermedia, adenoma	2 (4%)	1 (3%)		1 (2%)
Pars nervosa, hamartoma		1 (3%)		
Thyroid gland	(50)	(19)	(19)	(50)
C-cell, adenoma	6 (12%)	3 (16%)	1 (5%)	5 (10%)
C-cell, carcinoma		1 (5%)	3 (16%)	4 (8%)
Follicular cell, adenoma	1 (2%)			
Follicular cell, carcinoma		1 (5%)		
<b>General Body System</b>				
None				
<b>Genital System</b>				
Clitoral gland	(49)	(22)	(27)	(50)
Carcinoma	5 (10%)	5 (23%)	3 (11%)	4 (8%)
Ovary	(50)	(18)	(24)	(49)
Granulosa cell tumor benign	1 (2%)			1 (2%)
Thecoma malignant				1 (2%)
Uterus	(50)	(22)	(49)	(50)
Adenocarcinoma				1 (2%)
Polyp stromal	3 (6%)	5 (23%)	4 (8%)	8 (16%)
Sarcoma stromal	1 (2%)			
Bilateral, polyp stromal	1 (2%)			
<b>Hematopoietic System</b>				
Bone marrow	(50)	(17)	(19)	(50)
Lymph node		(2)	(1)	(3)
Lymph node, bronchial	(42)	(17)	(16)	(48)
Carcinoma, metastatic, thyroid gland				1 (2%)
Lymph node, mandibular	(48)	(17)	(18)	(49)
Carcinoma, metastatic, thyroid gland				1 (2%)
Lymph node, mesenteric	(50)	(17)	(18)	(49)
Lymph node, mediastinal	(47)	(17)	(17)	(44)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (6%)	
Spleen	(50)	(21)	(26)	(50)
Thymus	(47)	(17)	(16)	(45)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (6%)	

**TABLE B1**  
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Integumentary System</b>				
Mammary gland	(50)	(33)	(28)	(50)
Adenoacanthoma		1 (3%)		
Adenocarcinoma	2 (4%)	1 (3%)	4 (14%)	1 (2%)
Adenocarcinoma, multiple	1 (2%)			
Fibroadenoma	12 (24%)	13 (39%)	12 (43%)	8 (16%)
Fibroadenoma, multiple		6 (18%)	1 (4%)	5 (10%)
Sarcoma				1 (2%)
Skin	(50)	(17)	(19)	(50)
Basal cell carcinoma				1 (2%)
Neurofibrosarcoma			1 (5%)	
Squamous cell papilloma			1 (5%)	
Subcutaneous tissue, sarcoma	1 (2%)			1 (2%)
<b>Musculoskeletal System</b>				
Bone	(50)	(17)	(19)	(50)
Mandible, squamous cell carcinoma, metastatic, pharynx			1 (5%)	
<b>Nervous System</b>				
None				
<b>Respiratory System</b>				
Larynx	(50)	(50)	(48)	(50)
Carcinoma, metastatic, thyroid gland				1 (2%)
Lung	(50)	(50)	(49)	(50)
Adenocarcinoma, metastatic, mammary gland	1 (2%)			
Alveolar/bronchiolar adenoma	1 (2%)			
Alveolar/bronchiolar carcinoma			1 (2%)	
Carcinoma, metastatic, thyroid gland		1 (2%)		1 (2%)
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Carcinoma, metastatic, adrenal cortex		1 (2%)		
Pheochromocytoma malignant, metastatic			1 (2%)	
Trachea	(50)	(50)	(49)	(50)
Carcinoma, metastatic, thyroid gland				1 (2%)
<b>Special Senses System</b>				
Eye	(4)	(1)	(5)	(4)
Lids, fibroma			1 (20%)	
Harderian gland	(1)	(1)		
Adenoma	1 (100%)			
Duct, carcinoma		1 (100%)		
Zymbal's gland	(1)	(1)		
Carcinoma	1 (100%)	1 (100%)		

**TABLE B1**  
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study</b> (continued)				
<b>Urinary System</b>				
Kidney	(50)	(50)	(49)	(50)
Carcinoma	1 (2%)			
<b>Systemic Lesions</b>				
Multiple organs <sup>b</sup>	(50)	(50)	(50)	(50)
Leukemia mononuclear	16 (32%)	14 (28%)	18 (36%)	21 (42%)
<b>Neoplasm Summary</b>				
Total animals with primary neoplasms <sup>c</sup>				
15-Month interim evaluation	2	2	3	2
2-Year study	47	48	41	49
Total primary neoplasms				
15-Month interim evaluation	2	2	4	2
2-Year study	98	91	79	105
Total animals with benign neoplasms				
15-Month interim evaluation	2	2	3	2
2-Year study	44	42	36	46
Total benign neoplasms				
15-Month interim evaluation	2	2	4	2
2-Year study	68	63	46	70
Total animals with malignant neoplasms				
2-Year study	29	26	27	28
Total malignant neoplasms				
2-Year study	30	28	33	35
Total animals with metastatic neoplasms				
2-Year study	3	2	3	1
Total metastatic neoplasms				
2-Year study	3	2	6	6

<sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

<sup>b</sup> Number of animals with any tissue examined microscopically

<sup>c</sup> Primary neoplasms: all neoplasms except metastatic neoplasms

**TABLE B2**  
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0 ppm**

	3	3	4	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	
Number of Days on Study	7	7	8	0	2	3	3	4	5	6	6	7	8	8	8	8	8	8	0	0	0	0	1	2	3	3	
	6	6	8	2	5	9	9	0	3	0	3	7	0	1	1	3	6	3	5	9	9	6	3	3	3		
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	2	3	2	2	2	2	2	1	2	3	2	1	1	2	2	2	1	2	2	2	1	1	1	1	1		
	5	0	2	1	1	3	5	9	7	0	0	1	7	6	5	6	4	8	4	7	9	9	6	6	6		
	2	2	2	1	4	4	1	3	3	3	4	3	2	2	4	1	2	4	1	1	4	3	1	3	4		
<b>Alimentary System</b>																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular adenoma																		X									
Mesentery	+		+																	+						+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma, metastatic, kidney	X																										
Pharynx																										+	
Squamous cell carcinoma																										X	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tongue																										+	
Carcinoma																										X	
<b>Cardiovascular System</b>																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>Endocrine System</b>																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal medulla	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma benign																		X			X						
Bilateral, pheochromocytoma benign																											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																											
Parathyroid gland	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pars intermedia, adenoma																											
Thyroid gland																											
C-cell, adenoma																										+	
Follicular cell, adenoma																										X	
<b>General Body System</b>																											
None																											

+: Tissue examined microscopically  
A: Autolysis precludes examination

M: Missing tissue  
I: Insufficient tissue

X: Lesion present  
Blank: Not examined











**TABLE B2**  
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0 ppm (continued)**

<b>Number of Days on Study</b>	7 7	
	3 3	
	3 3	
<b>Carcass ID Number</b>	0 0	Total Tissues/ Tumors
	1 1 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 3 3	
	7 7 8 9 9 0 2 2 3 3 3 4 4 5 6 6 7 7 8 8 8 9 9 0 0	
	1 4 3 1 2 1 3 4 1 2 3 3 4 3 2 3 3 4 1 2 4 1 2 1 3	
<b>Special Senses System</b>		
Eye	+	4
Harderian gland		1
Adenoma		1
Zymbal's gland		1
Carcinoma		1
<b>Urinary System</b>		
Kidney	+ +	50
Carcinoma		1
Urinary bladder	+ +	50
<b>Systemic Lesions</b>		
Multiple organs	+ +	50
Leukemia mononuclear	X          X          X  X          X          X	16





**TABLE B2**  
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.01 ppm (continued)**

<b>Number of Days on Study</b>	5 5 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7
	2 6 2 2 3 5 5 5 6 8 8 9 9 0 0 2 2 3 3 3 3 3 3 3 3
	1 5 1 5 8 4 4 9 8 1 3 1 4 5 9 4 4 2 2 2 2 2 2 2 2
<b>Carcass ID Number</b>	0 0
	4 5 5 5 5 5 5 5 5 4 5 4 5 5 5 6 4 4 4 4 4 4 4 4
	8 6 7 9 3 1 2 1 2 1 8 9 6 2 5 9 0 6 7 7 7 7 8 9 9
	1 1 4 4 4 4 3 3 2 2 3 1 3 4 3 3 1 2 1 2 3 4 2 1 4
<b>Hematopoietic System</b>	
Bone marrow	+ + + + + + + + + + + + + + + + +
Lymph node	+ + + + + + + + + + + + + + + + +
Lymph node, bronchial	+ + + + + + + + + + + + + + + + +
Lymph node, mandibular	+ + + + + + + + + + + + + + + + +
Lymph node, mesenteric	+ + + + + + + + + + + + + + + + +
Lymph node, mediastinal	+ + + + + + + + + + + + + + + + +
Spleen	+ + + + + + + + + + + + + + + + +
Thymus	+ + + + + + + + + + + + + + + + +
<b>Integumentary System</b>	
Mammary gland	+ + + + + + + + + + + + + + + + +
Adenoacanthoma	+ + + + + + + + + + + + + + + + +
Adenocarcinoma	+ + + + + + + + + + + + + + + + +
Fibroadenoma	+ + + + + + + + + + + + + + + + +
Fibroadenoma, multiple	+ + + + + + + + + + + + + + + + +
Skin	+ + + + + + + + + + + + + + + + +
<b>Musculoskeletal System</b>	
Bone	+ + + + + + + + + + + + + + + + +
<b>Nervous System</b>	
Brain	+ + + + + + + + + + + + + + + + +
<b>Respiratory System</b>	
Larynx	+ + + + + + + + + + + + + + + + +
Lung	+ + + + + + + + + + + + + + + + +
Carcinoma, metastatic, thyroid gland	+ + + + + + + + + + + + + + + + +
Carcinoma, metastatic, adrenal cortex	+ + + + + + + + + + + + + + + + +
Nose	+ + + + + + + + + + + + + + + + +
Trachea	+ + + + + + + + + + + + + + + + +
<b>Special Senses System</b>	
Eye	+ + + + + + + + + + + + + + + + +
Harderian gland	+ + + + + + + + + + + + + + + + +
Duct, carcinoma	+ + + + + + + + + + + + + + + + +
Zymbal's gland	+ + + + + + + + + + + + + + + + +
Carcinoma	+ + + + + + + + + + + + + + + + +
<b>Urinary System</b>	
Kidney	+ + + + + + + + + + + + + + + + +
Urinary bladder	+ + + + + + + + + + + + + + + + +
<b>Systemic Lesions</b>	
Multiple organs	+ + + + + + + + + + + + + + + + +
Leukemia mononuclear	X X X X X X X X X X X X X X X X X







**TABLE B2**  
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.05 ppm (continued)**

<b>Number of Days on Study</b>	7 7	
	3 3	
	1 1	
<b>Carcass ID Number</b>	0 0	Total Tissues/ Tumors
	7 8 9	
	9 0 0 0 0 2 2 2 3 3 4 4 5 5 6 6 7 7 7 8 8 9 9 0	
	3 1 2 3 4 1 3 4 1 3 1 3 1 2 1 2 1 2 4 2 4 1 2 3 4	
<b>Alimentary System</b>		
Esophagus		19
Intestine large, colon		18
Intestine large, rectum		18
Intestine large, cecum		15
Intestine small, duodenum		18
Intestine small, jejunum		16
Intestine small, ileum		16
Liver	+ + + + +	32
Hepatocellular carcinoma		1
Mesentery		6
Pancreas		19
Pharynx		1
Squamous cell carcinoma		1
Salivary glands		18
Stomach, forestomach	+ +	21
Stomach, glandular	+ +	21
Tongue		1
Squamous cell carcinoma, metastatic, pharynx		1
Tooth		1
<b>Cardiovascular System</b>		
Heart		19
Alveolar/bronchiolar carcinoma, metastatic, lung		1
<b>Endocrine System</b>		
Adrenal cortex		19
Adrenal medulla		20
Pheochromocytoma malignant		1
Pheochromocytoma benign		3
Islets, pancreatic		19
Parathyroid gland		19
Pituitary gland	+ + + + + + + +	33
Pars distalis, adenoma	X X X X X X X X	23
Thyroid gland		19
C-cell, adenoma		1
C-cell, carcinoma		3
<b>General Body System</b>		
None		

**TABLE B2**  
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.05 ppm (continued)**

Number of Days on Study	3 3 4 5 5 5 5 5 5 5 5 6 6 6 6 6 6 7 7 7 7 7 7 7
	6 6 0 4 5 6 6 6 8 9 9 1 1 4 5 9 9 0 1 3 3 3 3 3
	6 7 2 9 0 1 2 9 5 0 7 1 8 2 2 5 5 9 8 1 1 1 1 1 1
Carcass ID Number	0 0
	9 7 8 8 7 9 8 7 8 8 8 7 9 7 7 8 8 7 8 7 7 7 7 7
	0 6 4 8 8 0 6 8 3 1 5 7 0 9 6 2 4 9 1 7 7 8 8 9
	1 3 4 3 1 3 3 3 2 2 3 4 2 4 2 2 2 1 3 1 3 2 4 2
<b>Genital System</b>	
Clitoral gland	+ + + + + + + + + + M + + + + + + + + + +
Carcinoma	+ + + + + + + + + + + + + + + + + + + X + +
Ovary	+ +
Uterus	+ +
Polyp stromal	+ +
Vagina	+ +
<b>Hematopoietic System</b>	
Bone marrow	+ +
Lymph node	+ +
Lymph node, bronchial	+ + M + + + + + M M + + + + + + + + + +
Lymph node, mandibular	+ + + + + + + + + + M + + + + + + + + + +
Lymph node, mesenteric	+ +
Lymph node, mediastinal	+ M + + + + + + + M + + + + + + + + + +
Alveolar/bronchiolar carcinoma, metastatic, lung	+ +
Spleen	+ +
Thymus	+ M + + + + + + + M + + + + + + + M + + + +
Alveolar/bronchiolar carcinoma, metastatic, lung	+ +
<b>Integumentary System</b>	
Mammary gland	+ + + + + + + + + + M + + + + + + + + + +
Adenocarcinoma	+ +
Fibroadenoma	+ +
Fibroadenoma, multiple	+ +
Skin	+ + + + + + + + + + M + + + + + + + + + +
Neurofibrosarcoma	+ +
Squamous cell papilloma	+ +
<b>Musculoskeletal System</b>	
Bone	+ +
Mandible, squamous cell carcinoma, metastatic, pharynx	+ +
<b>Nervous System</b>	
Brain	+ +
<b>Respiratory System</b>	
Larynx	+ +
Lung	+ +
Alveolar/bronchiolar carcinoma	+ +
Pheochromocytoma malignant, metastatic	+ +
Nose	+ +
Trachea	+ +





**TABLE B2**  
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.05 ppm (continued)**

<b>Number of Days on Study</b>	7 7	
	3 3	
	1 1	
<b>Carcass ID Number</b>	0 0	<b>Total Tissues/ Tumors</b>
	7 8 9	
	9 0 0 0 0 2 2 2 3 3 4 4 5 5 6 6 7 7 7 8 8 9 9 9 0	
	3 1 2 3 4 1 3 4 1 3 1 3 1 2 1 2 1 2 4 2 4 1 2 3 4	
<b>Special Senses System</b>		
Eye	+	5
Lids, fibroma		1
<b>Urinary System</b>		
Kidney	+ +	49
Urinary bladder		19
<b>Systemic Lesions</b>		
Multiple organs	+ +	49
Leukemia mononuclear	X X X X X X X X	18

**TABLE B2**  
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.2 ppm**

	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	2	4	6	8	9	1	2	2	2	3	5	6	6	6	9	1	1	2	2	2	3	3	3	3	3	3	3	3	3
Carcass ID Number	8	1	9	8	7	7	5	6	8	5	8	7	7	8	6	0	0	4	6	6	0	0	0	0	0	0	0	0	0
<b>Alimentary System</b>																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																													
Intestine large, colon	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma, multiple																													
Mesentery								+	+												+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>Cardiovascular System</b>																													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>Endocrine System</b>																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																													
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pars intermedia, adenoma																													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X													X	
C-cell, carcinoma																											X		X
<b>General Body System</b>																													
None																													
<b>Genital System</b>																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X											X														
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																													
Thecoma malignant																											X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																													
Polyp stromal											X		X	X												X		X	

**TABLE B2**  
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.2 ppm (continued)**

Number of Days on Study	7 7	
Carcass ID Number	3 3	
	0 0	
	1 1	
	0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 1 1 2 2	Total
	7 7 7 8 8 8 9 9 9 0 2 3 3 5 5 6 6 7 8 8 8 9 9 0 0	Tissues/
	2 3 4 1 2 3 1 2 3 1 2 1 3 1 2 3 4 3 1 2 4 1 3 1 2	Tumors
<b>Alimentary System</b>		
Esophagus	+ +	50
Carcinoma, metastatic, thyroid gland		1
Intestine large, colon	+ +	48
Intestine large, rectum	+ +	49
Intestine large, cecum	+ +	48
Intestine small, duodenum	+ +	49
Intestine small, jejunum	+ +	48
Intestine small, ileum	+ +	47
Liver	+ +	50
Hepatocellular adenoma, multiple		1
X		
Mesentery		3
Pancreas	+ +	50
Salivary glands	+ +	50
Stomach, forestomach	+ +	50
Stomach, glandular	+ +	50
Tooth		1
<b>Cardiovascular System</b>		
Heart	+ +	50
<b>Endocrine System</b>		
Adrenal cortex	+ +	50
Adrenal medulla	+ +	50
Pheochromocytoma benign		2
X		
Islets, pancreatic	+ +	50
Adenoma		1
X		
Parathyroid gland	+ M + + + + M + + + + + + + + + M + + + + + + +	45
Pituitary gland	+ +	50
Pars distalis, adenoma	X X	38
Pars intermedia, adenoma		1
X		
Thyroid gland	+ +	50
C-cell, adenoma		5
X		
C-cell, carcinoma	X X	4
<b>General Body System</b>		
None		
<b>Genital System</b>		
Clitoral gland	+ +	50
Carcinoma		4
X		
Ovary	+ + + M + + + + + + + + + + + + + + + + + + +	49
Granulosa cell tumor benign		1
Thecoma malignant		1
Uterus	+ +	50
Adenocarcinoma		1
X		
Polyp stromal	X X	8



**TABLE B2**  
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.2 ppm (continued)**

<b>Number of Days on Study</b>	5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7
	2 4 6 8 9 1 2 2 2 3 5 6 6 6 9 1 1 2 2 2 3 3 3 3
	8 1 9 8 7 7 5 6 8 5 8 7 7 8 6 0 0 4 6 6 0 0 0 0
<b>Carcass ID Number</b>	1 1
	1 1 1 1 2 1 0 1 1 1 1 1 1 0 1 1 1 1 1 1 0 0 0 0
	7 6 2 9 0 2 8 3 9 1 1 5 7 9 4 0 4 1 1 7 6 6 6 7
	4 1 4 4 3 1 4 2 2 2 3 4 2 4 2 3 4 1 4 1 1 2 3 4
<b>Hematopoietic System</b>	
Bone marrow	+ +
Lymph node	+ +
Lymph node, bronchial	+ +
Carcinoma, metastatic, thyroid gland	+ +
Lymph node, mandibular	+ +
Carcinoma, metastatic, thyroid gland	+ +
Lymph node, mesenteric	M +
Lymph node, mediastinal	+ + + + + + + M + + + + + + + + + + + + + + + + +
Spleen	+ +
Thymus	+ + + + + + + + + + M + + + + + + M + + + + + + +
<b>Integumentary System</b>	
Mammary gland	+ +
Adenocarcinoma	+ +
Fibroadenoma	X X +
Fibroadenoma, multiple	+ + + + + + + + + + X X + + + + + + + + + + +
Sarcoma	+ +
Skin	+ +
Basal cell carcinoma	+ +
Subcutaneous tissue, sarcoma	+ +
<b>Musculoskeletal System</b>	
Bone	+ +
<b>Nervous System</b>	
Brain	+ +
<b>Respiratory System</b>	
Larynx	+ +
Carcinoma, metastatic, thyroid gland	+ +
Lung	+ +
Carcinoma, metastatic, thyroid gland	+ +
Nose	+ +
Trachea	+ +
Carcinoma, metastatic, thyroid gland	+ +
<b>Special Senses System</b>	
Eye	+ +
<b>Urinary System</b>	
Kidney	+ +
Urinary bladder	+ +
<b>Systemic Lesions</b>	
Multiple organs	+ +
Leukemia mononuclear	+ + + + + + + + + + X X X X X X X X X X X X



TABLE B3

## Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Adrenal Medulla: Benign Pheochromocytoma</b>				
Overall rate <sup>a</sup>	6/50 (12%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate <sup>b</sup>	19.2%	5.1%	7.9%	5.5%
Terminal rate <sup>c</sup>	4/28 (14%)	0/33 (0%)	0/30 (0%)	1/30 (3%)
First incidence (days)	681	681	562	617
Life table test <sup>d</sup>	P=0.247N	P=0.099N	P=0.250N	P=0.124N
Logistic regression test <sup>d</sup>	P=0.237N	P=0.115N	P=0.256N	P=0.128N
Cochran-Armitage test <sup>d</sup>	P=0.237N			
Fisher exact test <sup>d</sup>		P=0.134N	P=0.243N	P=0.134N
<b>Clitoral Gland: Carcinoma</b>				
Overall rate	5/49 (10%)	5/22 (23%) <sup>e</sup>	3/27 (11%) <sup>e</sup>	4/50 (8%)
Adjusted rate	17.1%			11.0%
Terminal rate	4/28 (14%)			2/30 (7%)
First incidence (days)	709			569
Life table test				P=0.460N
Logistic regression test				P=0.478N
Cochran-Armitage test				
Fisher exact test				P=0.487N
<b>Mammary Gland: Fibroadenoma</b>				
Overall rate	12/50 (24%)	19/50 (38%)	13/50 (26%)	13/50 (26%)
Adjusted rate	37.4%	52.0%	35.8%	34.7%
Terminal rate	9/28 (32%)	16/33 (48%)	8/30 (27%)	8/30 (27%)
First incidence (days)	488	654	549	528
Life table test	P=0.373N	P=0.209	P=0.530	P=0.554
Logistic regression test	P=0.348N	P=0.136	P=0.446	P=0.501
Cochran-Armitage test	P=0.355N			
Fisher exact test		P=0.097	P=0.500	P=0.500
<b>Mammary Gland: Carcinoma</b>				
Overall rate	3/50 (6%)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted rate	9.6%	3.0%	12.8%	2.3%
Terminal rate	2/28 (7%)	1/33 (3%)	3/30 (10%)	0/30 (0%)
First incidence (days)	680	730 (T)	709	626
Life table test	P=0.342N	P=0.257N	P=0.521	P=0.304N
Logistic regression test	P=0.336N	P=0.276N	P=0.460	P=0.305N
Cochran-Armitage test	P=0.335N			
Fisher exact test		P=0.309N	P=0.500	P=0.309N
<b>Mammary Gland: Fibroadenoma or Carcinoma</b>				
Overall rate	14/50 (28%)	19/50 (38%)	15/50 (30%)	14/50 (28%)
Adjusted rate	44.0%	52.0%	41.6%	36.2%
Terminal rate	11/28 (39%)	16/33 (48%)	10/30 (33%)	8/30 (27%)
First incidence (days)	488	654	549	528
Life table test	P=0.360N	P=0.370	P=0.540	P=0.529N
Logistic regression test	P=0.333N	P=0.267	P=0.426	P=0.586N
Cochran-Armitage test	P=0.341N			
Fisher exact test		P=0.198	P=0.500	P=0.588N

TABLE B3

Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Pancreatic Islets: Adenoma</b>				
Overall rate	2/50 (4%)	1/18 (6%) <sup>e</sup>	0/19 (0%) <sup>e</sup>	1/50 (2%)
Adjusted rate	7.1%			3.3%
Terminal rate	2/28 (7%)			1/30 (3%)
First incidence (days)	730 (T)			730 (T)
Life table test				P=0.476N
Logistic regression test				P=0.476N
Cochran-Armitage test				
Fisher exact test				P=0.500N
<b>Pituitary Gland (Pars Distalis): Adenoma</b>				
Overall rate	31/50 (62%)	30/39 (77%) <sup>e</sup>	23/33 (70%) <sup>e</sup>	38/50 (76%)
Adjusted rate	73.1%			86.0%
Terminal rate	17/28 (61%)			24/30 (80%)
First incidence (days)	502			541
Life table test				P=0.237
Logistic regression test				P=0.114
Cochran-Armitage test				
Fisher exact test				P=0.097
<b>Thyroid Gland (C-cell): Adenoma</b>				
Overall rate	6/50 (12%)	3/19 (16%) <sup>e</sup>	1/19 (5%) <sup>e</sup>	5/50 (10%)
Adjusted rate	19.6%			15.7%
Terminal rate	5/28 (18%)			4/30 (13%)
First incidence (days)	625			668
Life table test				P=0.467N
Logistic regression test				P=0.486N
Cochran-Armitage test				
Fisher exact test				P=0.500N
<b>Thyroid Gland (C-cell): Carcinoma</b>				
Overall rate	0/50 (0%)	1/19 (5%) <sup>e</sup>	3/19 (16%) <sup>e</sup>	4/50 (8%)
Adjusted rate	0.0%			12.8%
Terminal rate	0/28 (0%)			3/30 (10%)
First incidence (days)	— <sup>f</sup>			726
Life table test				P=0.074
Logistic regression test				P=0.072
Cochran-Armitage test				
Fisher exact test				P=0.059
<b>Thyroid Gland (C-cell): Adenoma or Carcinoma</b>				
Overall rate	6/50 (12%)	4/19 (21%) <sup>e</sup>	4/19 (21%) <sup>e</sup>	9/50 (18%)
Adjusted rate	19.6%			27.7%
Terminal rate	5/28 (18%)			7/30 (23%)
First incidence (days)	625			668
Life table test				P=0.328
Logistic regression test				P=0.301
Cochran-Armitage test				
Fisher exact test				P=0.288

TABLE B3

Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene  
(continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Thyroid Gland (Follicular Cell): Adenoma or Carcinoma</b>				
Overall rate	1/50 (2%)	1/19 (5%) <sup>e</sup>	0/19 (0%) <sup>e</sup>	0/50 (0%)
Adjusted rate	3.6%			0.0%
Terminal rate	1/28 (4%)			0/30 (0%)
First incidence (days)	730 (1)			—
Life table test				P=0.486N
Logistic regression test				P=0.486N
Cochran-Armitage test				
Fisher exact test				P=0.500N
<b>Uterus: Stromal Polyp</b>				
Overall rate	4/50 (8%)	5/50 (10%)	4/50 (8%)	8/50 (16%)
Adjusted rate	13.3%	14.2%	12.0%	22.2%
Terminal rate	3/28 (11%)	4/33 (12%)	2/30 (7%)	4/30 (13%)
First incidence (days)	686	659	652	628
Life table test	P=0.120	P=0.592	P=0.628N	P=0.209
Logistic regression test	P=0.121	P=0.550	P=0.603	P=0.186
Cochran-Armitage test	P=0.119			
Fisher exact test		P=0.500	P=0.643N	P=0.178
<b>Uterus: Stromal Polyp or Stromal Sarcoma</b>				
Overall rate	5/50 (10%)	5/50 (10%)	4/50 (8%)	8/50 (16%)
Adjusted rate	16.8%	14.2%	12.0%	22.2%
Terminal rate	4/28 (14%)	4/33 (12%)	2/30 (7%)	4/30 (13%)
First incidence (days)	686	659	652	628
Life table test	P=0.165	P=0.533N	P=0.482N	P=0.314
Logistic regression test	P=0.167	P=0.577N	P=0.548N	P=0.288
Cochran-Armitage test	P=0.165			
Fisher exact test		P=0.630N	P=0.500N	P=0.277
<b>All Organs: Mononuclear Cell Leukemia</b>				
Overall rate	16/50 (32%)	14/50 (28%)	18/50 (36%)	21/50 (42%)
Adjusted rate	40.6%	30.1%	43.6%	55.8%
Terminal rate	6/28 (21%)	3/33 (9%)	8/30 (27%)	14/30 (47%)
First incidence (days)	639	521	366	569
Life table test	P=0.135	P=0.306N	P=0.414	P=0.290
Logistic regression test	P=0.102	P=0.485N	P=0.401	P=0.221
Cochran-Armitage test	P=0.103			
Fisher exact test		P=0.414N	P=0.417	P=0.204
<b>All Organs: Benign Neoplasms</b>				
Overall rate	44/50 (88%)	42/50 (84%)	36/50 (72%)	46/50 (92%)
Adjusted rate	91.7%	93.3%	79.9%	95.7%
Terminal rate	24/28 (86%)	30/33 (91%)	21/30 (70%)	28/30 (93%)
First incidence (days)	488	521	366	528
Life table test	P=0.257	P=0.130N	P=0.148N	P=0.557
Logistic regression test	P=0.171	P=0.214N	P=0.072N	P=0.427
Cochran-Armitage test	P=0.153			
Fisher exact test		P=0.387N	P=0.039N	P=0.370

**TABLE B3**  
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>All Organs: Malignant Neoplasms</b>				
Overall rate	29/50 (58%)	26/50 (52%)	27/50 (54%)	28/50 (56%)
Adjusted rate	65.5%	52.7%	60.5%	67.8%
Terminal rate	13/28 (46%)	10/33 (30%)	13/30 (43%)	17/30 (57%)
First incidence (days)	376	521	366	569
Life table test	P=0.496	P=0.214N	P=0.451N	P=0.415N
Logistic regression test	P=0.507	P=0.432N	P=0.422N	P=0.478N
Cochran-Armitage test	P=0.511			
Fisher exact test		P=0.344N	P=0.420N	P=0.500N
<b>All Organs: Benign or Malignant Neoplasms</b>				
Overall rate	47/50 (94%)	48/50 (96%)	41/50 (82%)	49/50 (98%)
Adjusted rate	95.9%	96.0%	87.2%	98.0%
Terminal rate	26/28 (93%)	31/33 (94%)	24/30 (80%)	29/30 (97%)
First incidence (days)	376	521	366	528
Life table test	P=0.355	P=0.249N	P=0.223N	P=0.549N
Logistic regression test	P=0.246	P=0.584	P=0.109N	P=0.358
Cochran-Armitage test	P=0.221			
Fisher exact test		P=0.500	P=0.061N	P=0.309

(T)Terminal sacrifice

- <sup>a</sup> Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for bone marrow, brain, clitoral gland, heart, kidney, larynx, liver, lung, nose, ovary, pancreas, pancreatic islets, parathyroid gland, pituitary gland, salivary gland, spleen, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
- <sup>b</sup> Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
- <sup>c</sup> Observed incidence at terminal kill
- <sup>d</sup> Beneath the control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
- <sup>e</sup> Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not appropriate.
- <sup>f</sup> Not applicable; no neoplasms in animal group

**TABLE B4**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Disposition Summary</b>				
Animals initially in study	60	60	60	60
<b>15-Month interim evaluation</b>				
Early deaths				
Moribund	19	16	14	16
Natural deaths	3	1	5	4
Survivors				
Terminal sacrifice	28	33	30	30
Missexed			1	
Animals examined microscopically	60	60	59	60
<b>15-Month Interim Evaluation</b>				
<b>Alimentary System</b>				
Liver	(10)	(3)		(10)
Basophilic focus	3 (30%)			
Clear cell focus		1 (33%)		
Granuloma, multifocal	2 (20%)			2 (20%)
Hepatodiaphragmatic nodule	3 (30%)	2 (67%)		1 (10%)
Mesentery	(1)			
Fat, mineralization	1 (100%)			
Fat, necrosis	1 (100%)			
Pancreas	(10)			(10)
Acinus, atrophy	2 (20%)			
Stomach, forestomach	(10)		(1)	(10)
Acanthosis	1 (10%)			1 (10%)
Stomach, glandular	(10)		(2)	(10)
Muscularis, hypoplasia			2 (100%)	
<b>Cardiovascular System</b>				
Heart	(10)			(10)
Thrombosis	1 (10%)			
<b>Endocrine System</b>				
Adrenal cortex	(10)			(10)
Hemorrhage				1 (10%)
Pituitary gland	(10)		(5)	(10)
Cyst			3 (60%)	
Pars distalis, hyperplasia				1 (10%)
Thyroid gland	(10)			(10)
Ultimobranchial cyst				1 (10%)
C-cell, hyperplasia				1 (10%)
<b>General Body System</b>				
None				

**TABLE B4**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation (continued)</b>				
<b>Genital System</b>				
Ovary	(10)			(10)
Cyst				1 (10%)
Uterus	(10)		(10)	(10)
Dilatation			2 (20%)	
Endometrium, hyperplasia				1 (10%)
<b>Hematopoietic System</b>				
Lymph node, mandibular	(10)	(1)		(10)
Hyperplasia, lymphoid	1 (10%)			1 (10%)
Lymph node, mediastinal	(10)	(1)	(1)	(10)
Hemorrhage		1 (100%)		
Spleen	(10)			(10)
Ectopic tissue				1 (10%)
<b>Integumentary System</b>				
None				
<b>Musculoskeletal System</b>				
None				
<b>Nervous System</b>				
None				
<b>Respiratory System</b>				
Larynx	(10)	(9)	(10)	(10)
Foreign body	2 (20%)		3 (30%)	
Hyperplasia	1 (10%)			
Inflammation, chronic		1 (11%)		
Inflammation, suppurative	2 (20%)		2 (20%)	
Metaplasia, squamous	2 (20%)	1 (11%)		
Lung	(10)	(10)	(10)	(10)
Alveolus, hemorrhage	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Alveolus, infiltration cellular, multifocal, histiocyte	2 (20%)	2 (20%)		
Artery, mineralization	1 (10%)	1 (10%)	2 (20%)	1 (10%)
Bronchiole, pigmentation		1 (10%)	6 (60%)	10 (100%)
Peribronchiolar, pigmentation			1 (10%)	8 (80%)
Nose	(10)	(10)	(10)	(10)
Foreign body			2 (20%)	1 (10%)
Hemorrhage	1 (10%)			
Inflammation, suppurative			2 (20%)	2 (20%)
Pigmentation		8 (80%)	10 (100%)	9 (90%)
Nasolacrimal duct, hemorrhage	1 (10%)			2 (20%)
Respiratory epithelium, hyperplasia			2 (20%)	2 (20%)
Respiratory epithelium, metaplasia, squamous			1 (10%)	1 (10%)



**TABLE B4**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation (continued)</b>				
<b>Respiratory System (continued)</b>				
Trachea	(10)	(10)	(10)	(10)
Inflammation, chronic		1 (10%)	1 (10%)	
<b>Special Senses System</b>				
Eye	(1)		(1)	
Cataract	1 (100%)			
<b>Urinary System</b>				
Kidney	(10)	(10)	(10)	(10)
Mineralization	1 (10%)	1 (10%)	2 (20%)	
Nephropathy, chronic	10 (100%)	10 (100%)	10 (100%)	10 (100%)
<b>2-Year Study</b>				
<b>Alimentary System</b>				
Esophagus	(50)	(18)	(19)	(50)
Inflammation, chronic				1 (2%)
Mediastinum, inflammation, granulomatous		1 (6%)		
Liver	(50)	(31)	(32)	(50)
Angiectasis	1 (2%)	1 (3%)	4 (13%)	2 (4%)
Basophilic focus	7 (14%)	2 (6%)	2 (6%)	3 (6%)
Clear cell focus	2 (4%)	3 (10%)	3 (9%)	3 (6%)
Eosinophilic focus		1 (3%)		
Granuloma, multifocal	5 (10%)	1 (3%)	2 (6%)	4 (8%)
Hepatodiaphragmatic nodule	7 (14%)	9 (29%)	8 (25%)	11 (22%)
Pigmentation, hemosiderin	1 (2%)			
Vacuolization cytoplasmic	7 (14%)	5 (16%)	4 (13%)	3 (6%)
Biliary tract, cyst	1 (2%)			
Biliary tract, hyperplasia	1 (2%)			
Hepatocyte, hyperplasia	2 (4%)		2 (6%)	
Mesentery	(9)	(6)	(6)	(3)
Hemorrhage	1 (11%)		2 (33%)	1 (33%)
Inflammation, granulomatous		1 (17%)	2 (33%)	
Thrombosis	1 (11%)			
Fat, necrosis	8 (89%)	6 (100%)	5 (83%)	2 (67%)
Pancreas	(50)	(17)	(19)	(50)
Fibrosis				1 (2%)
Acinus, atrophy	13 (26%)	1 (6%)	3 (16%)	9 (18%)
Artery, inflammation		1 (6%)		
Pharynx	(3)		(1)	
Hyperkeratosis	1 (33%)			
Hyperplasia	2 (67%)			

**TABLE B4**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Alimentary System (continued)</b>				
Stomach, forestomach	(49)	(18)	(21)	(50)
Acanthosis	6 (12%)	8 (44%)	7 (33%)	7 (14%)
Erosion		3 (17%)		3 (6%)
Hyperkeratosis	3 (6%)	6 (33%)	6 (29%)	4 (8%)
Inflammation, suppurative	3 (6%)	2 (11%)	1 (5%)	2 (4%)
Ulcer	3 (6%)	3 (17%)	3 (14%)	1 (2%)
Muscularis, hypoplasia		1 (6%)		
Stomach, glandular	(49)	(17)	(21)	(50)
Erosion	1 (2%)	1 (6%)		2 (4%)
Inflammation, suppurative	3 (6%)	2 (12%)	1 (5%)	2 (4%)
Mineralization		1 (6%)		
Tooth			(1)	(1)
Inflammation, suppurative			1 (100%)	1 (100%)
<b>Cardiovascular System</b>				
Heart	(50)	(17)	(19)	(50)
Cardiomyopathy	4 (8%)		1 (5%)	4 (8%)
Thrombosis	1 (2%)		1 (5%)	
<b>Endocrine System</b>				
Adrenal cortex	(50)	(21)	(19)	(50)
Cytomegaly	8 (16%)	5 (24%)	2 (11%)	7 (14%)
Hemorrhage		1 (5%)		
Hyperplasia				3 (6%)
Necrosis	1 (2%)	1 (5%)		1 (2%)
Adrenal medulla	(47)	(19)	(20)	(50)
Hyperplasia	3 (6%)	3 (16%)	4 (20%)	4 (8%)
Bilateral, hyperplasia			1 (5%)	3 (6%)
Islets, pancreatic	(50)	(18)	(19)	(50)
Hyperplasia	1 (2%)			1 (2%)
Parathyroid gland	(42)	(17)	(19)	(45)
Hyperplasia	1 (2%)	2 (12%)		2 (4%)
Pituitary gland	(50)	(39)	(33)	(50)
Cyst	4 (8%)	9 (23%)	5 (15%)	2 (4%)
Hemorrhage			1 (3%)	
Pars distalis, hyperplasia	4 (8%)	6 (15%)	4 (12%)	3 (6%)
Pars intermedia, hyperplasia		1 (3%)		
Thyroid gland	(50)	(19)	(19)	(50)
Ultimobranchial cyst		2 (11%)		1 (2%)
C-cell, hyperplasia	12 (24%)	3 (16%)	1 (5%)	11 (22%)
<b>General Body System</b>				
None				

**TABLE B4**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Genital System</b>				
Clitoral gland	(49)	(22)	(27)	(50)
Cyst	2 (4%)	3 (14%)	3 (11%)	1 (2%)
Hyperplasia	4 (8%)	1 (5%)	6 (22%)	1 (2%)
Inflammation, suppurative	3 (6%)	2 (9%)	1 (4%)	3 (6%)
Ovary	(50)	(18)	(24)	(49)
Cyst	1 (2%)	1 (6%)	5 (21%)	1 (2%)
Uterus	(50)	(22)	(49)	(50)
Infarct			1 (2%)	
Inflammation, suppurative			1 (2%)	
Cervix, muscularis, hyperplasia				2 (4%)
Endometrium, hyperplasia		1 (5%)	3 (6%)	3 (6%)
<b>Hematopoietic System</b>				
Bone marrow	(50)	(17)	(19)	(50)
Hyperplasia, reticulum cell			1 (5%)	
Myelofibrosis		2 (12%)		
Lymph node		(2)	(1)	(3)
Renal, hyperplasia, lymphoid		1 (50%)		
Renal, pigmentation		1 (50%)		1 (33%)
Lymph node, bronchial	(42)	(17)	(16)	(48)
Hemorrhage			1 (6%)	
Lymph node, mandibular	(48)	(17)	(18)	(49)
Hyperplasia, lymphoid	2 (4%)		1 (6%)	1 (2%)
Inflammation, chronic	1 (2%)		2 (11%)	
Lymph node, mesenteric	(50)	(17)	(18)	(49)
Hemorrhage	1 (2%)		1 (6%)	
Lymph node, mediastinal	(47)	(17)	(17)	(44)
Hemorrhage	1 (2%)		1 (6%)	
Pigmentation			1 (6%)	2 (5%)
Spleen	(50)	(21)	(26)	(50)
Ectopic tissue		1 (5%)	2 (8%)	1 (2%)
Fibrosis	4 (8%)	3 (14%)	5 (19%)	
Hyperplasia, reticulum cell	4 (8%)		1 (4%)	
Necrosis	1 (2%)		2 (8%)	
Pigmentation, hemosiderin	1 (2%)			
Thymus	(47)	(17)	(16)	(45)
Cyst		1 (6%)		
<b>Integumentary System</b>				
Mammary gland	(50)	(33)	(28)	(50)
Inflammation, suppurative				1 (2%)
Skin	(50)	(17)	(19)	(50)
Abscess				1 (2%)
Ulcer		1 (6%)		1 (2%)
<b>Musculoskeletal System</b>				
None				

**TABLE B4**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Nervous System</b>				
Brain	(50)	(18)	(19)	(50)
Compression	11 (22%)	6 (33%)	4 (21%)	16 (32%)
Hemorrhage	3 (6%)	2 (11%)	8 (42%)	6 (12%)
Hydrocephalus	4 (8%)	1 (6%)	3 (16%)	10 (20%)
Necrosis			1 (5%)	
<b>Respiratory System</b>				
Larynx	(50)	(50)	(48)	(50)
Foreign body	1 (2%)	1 (2%)		
Inflammation, chronic	4 (8%)	1 (2%)	4 (8%)	5 (10%)
Inflammation, suppurative	3 (6%)	2 (4%)		4 (8%)
Metaplasia, squamous	9 (18%)	20 (40%)	15 (31%)	24 (48%)
Lung	(50)	(50)	(49)	(50)
Congestion			1 (2%)	3 (6%)
Foreign body	1 (2%)			1 (2%)
Granuloma	3 (6%)		1 (2%)	
Alveolar epithelium, hyperplasia	3 (6%)	3 (6%)	2 (4%)	9 (18%)
Alveolus, hemorrhage	9 (18%)	8 (16%)	12 (24%)	13 (26%)
Alveolus, infiltration cellular, multifocal, histiocyte	3 (6%)	5 (10%)	8 (16%)	10 (20%)
Alveolus, inflammation, suppurative	1 (2%)			3 (6%)
Artery, mineralization		1 (2%)		
Bronchiole, pigmentation		25 (50%)	42 (86%)	50 (100%)
Peribronchiolar, pigmentation	3 (6%)	1 (2%)	4 (8%)	27 (54%)
Pleura, fibrosis			2 (4%)	1 (2%)
Nose	(50)	(50)	(49)	(50)
Foreign body	3 (6%)	1 (2%)	4 (8%)	6 (12%)
Hemorrhage	3 (6%)	1 (2%)	6 (12%)	1 (2%)
Inflammation, suppurative	5 (10%)	5 (10%)	2 (4%)	10 (20%)
Pigmentation		34 (68%)	47 (96%)	48 (96%)
Nasolacrimal duct, hemorrhage	2 (4%)		1 (2%)	
Nasolacrimal duct, inflammation, suppurative	2 (4%)	10 (20%)	9 (18%)	3 (6%)
Respiratory epithelium, hyperplasia	4 (8%)	6 (12%)	2 (4%)	10 (20%)
Respiratory epithelium, metaplasia, squamous	1 (2%)		1 (2%)	2 (4%)
Trachea	(50)	(50)	(49)	(50)
Inflammation, chronic				1 (2%)
Inflammation, suppurative	1 (2%)			
Pigmentation				1 (2%)
<b>Special Senses System</b>				
Eye	(4)	(1)	(5)	(4)
Cataract	2 (50%)	1 (100%)	2 (40%)	4 (100%)
Anterior chamber, inflammation, suppurative	1 (25%)			
Cornea, inflammation	1 (25%)			
Harderian gland	(1)	(1)		
Inflammation, suppurative	1 (100%)			

**TABLE B4**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<i>2-Year Study (continued)</i>				
<b>Urinary System</b>				
Kidney	(50)	(50)	(49)	(50)
Mineralization	12 (24%)	13 (26%)	11 (22%)	14 (28%)
Nephropathy, chronic	47 (94%)	49 (98%)	47 (96%)	50 (100%)
Cortex, renal tubule, cytoplasmic alteration			1 (2%)	
Pelvis, transitional epithelium, hyperplasia	1 (2%)			
Urinary bladder	(50)	(17)	(19)	(49)
Transitional epithelium, hyperplasia	1 (2%)			1 (2%)

<sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

**APPENDIX C**  
**SUMMARY OF LESIONS IN MALE MICE**  
**IN THE 2-YEAR INHALATION STUDY**  
**OF HEXACHLOROCYCLOPENTADIENE**

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**TABLE C1**  
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Disposition Summary</b>				
Animals initially in study	60	60	60	60
<i>15-Month interim evaluation</i>	10	10	10	10
Early deaths				
Accidental deaths	1	2		
Moribund	8	6	3	9
Natural deaths	6	9	5	7
Survivors				
Terminal sacrifice	35	33	42	34
Animals examined microscopically	60	60	60	60
<b>15-Month Interim Evaluation</b>				
<b>Alimentary System</b>				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma	2 (20%)			
Hepatocellular adenoma	3 (30%)	2 (20%)	2 (20%)	1 (10%)
<b>Cardiovascular System</b>				
None				
<b>Endocrine System</b>				
Islets, pancreatic	(10)			(10)
Adenoma	1 (10%)			
<b>General Body System</b>				
None				
<b>Genital System</b>				
None				
<b>Hematopoietic System</b>				
None				
<b>Integumentary System</b>				
None				
<b>Musculoskeletal System</b>				
None				
<b>Nervous System</b>				
None				

TABLE C1

Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene  
(continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation</b> (continued)				
<b>Respiratory System</b>				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)		1 (10%)	
Alveolar/bronchiolar adenoma, multiple				1 (10%)
Alveolar/bronchiolar carcinoma		1 (10%)		1 (10%)
<b>Special Senses System</b>				
None				
<b>Urinary System</b>				
Urinary bladder	(10)		(1)	(10)
<b>Systemic Lesions</b>				
Multiple organs <sup>b</sup>	(10)	(10)	(10)	(10)
Lymphoma malignant histiocytic			1 (10%)	
<b>2-Year Study</b>				
<b>Alimentary System</b>				
Intestine small, duodenum	(50)	(17)	(8)	(49)
Intestine small, jejunum	(50)	(18)	(9)	(50)
Adenocarcinoma	1 (2%)			1 (2%)
Intestine small, ileum	(50)	(19)	(9)	(50)
Liver	(50)	(32)	(37)	(50)
Hemangiosarcoma		1 (3%)		2 (4%)
Hepatocellular carcinoma	7 (14%)	7 (22%)	10 (27%)	9 (18%)
Hepatocellular carcinoma, multiple				1 (2%)
Hepatocellular carcinoma, two				1 (2%)
Hepatocellular adenoma	19 (38%)	13 (41%)	19 (51%)	10 (20%)
Hepatocellular adenoma, multiple		1 (3%)		
Hepatocellular adenoma, two			2 (5%)	1 (2%)
Mesentery	(4)	(5)	(2)	(2)
Pancreas	(49)	(18)	(8)	(50)
Stomach, forestomach	(50)	(19)	(12)	(50)
Squamous cell papilloma		1 (5%)	1 (8%)	1 (2%)
Stomach, glandular	(50)	(16)	(8)	(50)
<b>Cardiovascular System</b>				
Heart	(50)	(17)	(8)	(50)
<b>Endocrine System</b>				
Adrenal cortex	(49)	(17)	(8)	(50)
Adrenal medulla	(49)	(17)	(8)	(50)
Pheochromocytoma NOS				1 (2%)



**TABLE C1**  
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Endocrine System (continued)</b>				
Pituitary gland	(49)	(16)	(8)	(49)
Carcinoma	1 (2%)			
Thyroid gland	(48)	(19)	(12)	(50)
Follicular cell, adenoma	1 (2%)		3 (25%)	2 (4%)
<b>General Body System</b>				
None				
<b>Genital System</b>				
Epididymis	(50)	(17)	(8)	(50)
Fibrosarcoma			1 (13%)	
Testes	(50)	(18)	(9)	(50)
Interstitial cell, adenoma		1 (6%)	1 (11%)	1 (2%)
<b>Hematopoietic System</b>				
Lymph node	(1)	(5)	(3)	(2)
Lymph node, bronchial	(48)	(17)	(6)	(50)
Lymph node, mandibular	(41)	(13)	(3)	(43)
Lymph node, mesenteric	(48)	(21)	(13)	(49)
Lymph node, mediastinal	(46)	(16)	(8)	(50)
Spleen	(50)	(18)	(13)	(50)
Thymus	(47)	(16)	(7)	(50)
<b>Integumentary System</b>				
Skin	(50)	(18)	(10)	(50)
Fibrosarcoma			1 (10%)	
Hemangiosarcoma			1 (10%)	
Papilloma				1 (2%)
<b>Musculoskeletal System</b>				
None				
<b>Nervous System</b>				
None				
<b>Respiratory System</b>				
Lung	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	11 (22%)	7 (14%)	8 (16%)	12 (24%)
Alveolar/bronchiolar adenoma, multiple		3 (6%)	2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma		2 (4%)	4 (8%)	1 (2%)
Hemangiosarcoma, metastatic, liver		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	3 (6%)	1 (2%)		3 (6%)

TABLE C1

Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene  
(continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study</b> (continued)				
<b>Special Senses System</b>				
Harderian gland	(7)	(4)	(7)	(2)
Adenoma	7 (100%)	3 (75%)	5 (71%)	2 (100%)
Adenoma, two			2 (29%)	
<b>Urinary System</b>				
Kidney	(50)	(22)	(12)	(50)
Urinary bladder	(50)	(18)	(16)	(50)
<b>Systemic Lesions</b>				
Multiple organs	(50)	(50)	(50)	(50)
Lymphoma malignant histiocytic				2 (4%)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	2 (4%)	5 (10%)	4 (8%)	2 (4%)
<b>Neoplasm Summary</b>				
Total animals with primary neoplasms <sup>c</sup>				
15-Month interim evaluation	7	3	4	3
2-Year study	35	32	39	33
Total primary neoplasms				
15-Month interim evaluation	7	3	4	3
2-Year study	49	44	64	54
Total animals with benign neoplasms				
15-Month interim evaluation	5	2	3	2
2-Year study	29	23	31	25
Total benign neoplasms				
15-Month interim evaluation	5	2	3	2
2-Year study	38	29	43	33
Total animals with malignant neoplasms				
15-Month interim evaluation	2	1	1	1
2-Year study	11	14	19	17
Total malignant neoplasms				
15-Month interim evaluation	2	1	1	1
2-Year study	11	15	21	20
Total animals with metastatic neoplasms				
2-Year study	3	2		3
Total metastatic neoplasms				
2-Year study	3	2		3
Total animals with uncertain neoplasms				
benign or malignant				
2-Year study				1
Total uncertain neoplasms				
2-Year study				1

<sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

<sup>b</sup> Number of animals with any tissue examined microscopically

<sup>c</sup> Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2

Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:  
0 ppm

Number of Days on Study	0	2	4	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7		
	3	6	6	5	0	2	2	4	4	4	8	8	8	1	1	3	3	3	3	3	3	3	3	3	3		
	7	4	4	4	7	6	7	3	8	9	1	2	9	1	7	3	3	3	3	3	3	3	3	3	3		
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	1	1	1	1	0	0	0	1	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0		
	1	0	5	6	3	5	7	6	1	1	9	3	4	4	6	2	2	3	3	4	4	5	5	5	7		
	3	4	1	5	5	2	1	4	3	4	4	1	2	2	1	1	3	2	4	3	4	1	3	5	3		
<b>Alimentary System</b>																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma																											
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular carcinoma											X	X	X	X													
Hepatocellular adenoma							X	X			X						X	X	X			X	X				
Mesentery							+								+	+											
Pancreas	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>Cardiovascular System</b>																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>Endocrine System</b>																											
Adrenal cortex	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Parathyroid gland	M	+	M	M	+	M	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma																											
Thyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Follicular cell, adenoma																											
<b>General Body System</b>																											
None																											
<b>Genital System</b>																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Penis				+	+			+	+																		
Preputial gland			+					+	+	+			+														
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

+: Tissue examined microscopically  
A: Autolysis precludes examination

M: Missing tissue  
I: Insufficient tissue

X: Lesion present  
Blank: Not examined





**TABLE C2**  
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0 ppm (continued)**

<b>Number of Days on Study</b>	7 7	
	3 3	
	3 3	
<b>Carcass ID Number</b>	0 0	
	0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
	7 7 8 8 9 9 9 0 0 1 2 2 2 2 3 3 4 4 4 6 6 7 7 8 8	Total Tissues/ Tumors
	4 5 3 4 1 2 3 1 3 5 1 3 4 5 2 3 1 3 5 2 3 4 5 1 2	
<b>Hematopoietic System</b>		
Bone marrow	+ +	50
Lymph node		1
Lymph node, bronchial	+ +	48
Lymph node, mandibular	+ + + M + + + + + + + + + + + + + + + M + + + + + + + +	41
Lymph node, mesenteric	+ +	48
Lymph node, mediastinal	+ + + + + + + + + + + + + + + M + + + + + + + M + + + + + +	46
Spleen	+ +	50
Thymus	+ + + + + + + + + + + + + + + M + + + + + + + + + + + + + +	47
<b>Integumentary System</b>		
Mammary gland	M M M M M M + M M M M M M M M M M + M M M M M M M	4
Skin	+ +	50
<b>Musculoskeletal System</b>		
Bone	+ +	50
Skeletal muscle		2
<b>Nervous System</b>		
Brain	+ +	50
Peripheral nerve		1
Spinal cord		1
<b>Respiratory System</b>		
Larynx	+ +	50
Lung	+ +	49
Alveolar/bronchiolar adenoma	X	X X X
Hepatocellular carcinoma, metastatic, liver		X
Nose	+ +	50
Trachea	+ +	50
<b>Special Senses System</b>		
Eye		+
Harderian gland		+ +
Adenoma		X X
		X
		X
<b>Urinary System</b>		
Kidney	+ +	50
Urethra		1
Urinary bladder	+ +	50
<b>Systemic Lesions</b>		
Multiple organs	+ +	50
Lymphoma malignant mixed		2







TABLE C2

Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.01 ppm (continued)

Number of Days on Study	3 4 4 4 5 5 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7
	1 2 4 5 1 5 7 0 1 5 8 8 8 9 1 1 2 3 3 3 3 3 3 3
	9 5 3 1 6 7 0 6 7 5 2 7 9 7 1 4 5 3 3 3 3 3 3 3
Carcass ID Number	0 0
	3 4 3 4 3 3 4 3 3 3 4 3 4 3 3 3 3 3 3 3 3 3 3
	1 1 4 0 2 3 2 6 7 9 2 8 1 9 8 6 4 1 1 1 1 2 2 2 3
	2 5 4 1 1 2 4 5 3 5 1 1 4 3 5 3 5 1 3 4 5 3 4 5 1
<b>Hematopoietic System</b>	
Bone marrow	+ + + + + + + + + + + + + + + + +
Lymph node	+ + + + + + + + + + + + + + + + +
Lymph node, bronchial	+ + + + + + + + + + + + + + + + +
Lymph node, mandibular	+ + + M + M M + + + + + + + + M +
Lymph node, mesenteric	+ M + + + + + + + + + + + + + + + +
Lymph node, mediastinal	+ + + + + M + + + + + + + + + + +
Spleen	+ + + + + + + + + + + + + + + + +
Thymus	+ + + + + M + M + + + + + + + + + +
<b>Integumentary System</b>	
Mammary gland	+ M M + M M M M M + M M M M M
Skin	+ + + + + + + + + + + + + + + + +
<b>Musculoskeletal System</b>	
Bone	M + + + + + + + + + + + + + + + +
Skeletal muscle	+
<b>Nervous System</b>	
Brain	+ + + + + + + + + + + + + + + + +
Peripheral nerve	+
Spinal cord	M + + + + + + + + + + + + + + + +
<b>Respiratory System</b>	
Larynx	+ + + + + + + + + + + + + + + + +
Lung	+ + + + + + + + + + + + + + + + +
Alveolar/bronchiolar adenoma	+ + + + + + + + + + + + + + + + +
Alveolar/bronchiolar adenoma, multiple	+ + + + + + + + + + + + + + + + +
Alveolar/bronchiolar carcinoma	+ + + + + + + + + + + + + + + + +
Hemangiosarcoma, metastatic, liver	+ + + + + + + + + + + + + + + + +
Hepatocellular carcinoma, metastatic, liver	+ + + + + + + + + + + + + + + + +
Nose	+ + + + + + + + + + + + + + + + +
Trachea	+ + + + + + + + + + + + + + + + +
<b>Special Senses System</b>	
Harderian gland	+ + + + + + + + + + + + + + + + +
Adenoma	+ + + + + + + + + + + + + + + + +
<b>Urinary System</b>	
Kidney	+ + + + + + + + + + + + + + + + +
Urinary bladder	+ + + + + + + + + + + + + + + + +
<b>Systemic Lesions</b>	
Multiple organs	+ + + + + + + + + + + + + + + + +
Lymphoma malignant mixed	+ + + + + + + + + + + + + + + + +







**TABLE C2**  
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.05 ppm (continued)**

	5 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
Number of Days on Study	2 0 0 1 2 9 1 1 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3
	9 7 7 8 0 9 5 8 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
Carcass ID Number	0 0
	6 5 6 6 6 6 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5
	0 7 5 0 6 5 4 5 5 5 5 5 6 6 6 7 7 7 7 8 8 8 8 9 9
	3 3 5 5 1 3 2 2 1 3 4 5 1 2 4 1 2 4 5 1 2 3 5 1 2
<b>Hematopoietic System</b>	
Bone marrow	+ + + + + + + +
Lymph node	+ + + + +
Lymph node, bronchial	+ + M + M + + +
Lymph node, mandibular	+ M M + M + M M
Lymph node, mesenteric	+ + + + + + + +
Lymph node, mediastinal	+ + + + + + + +
Spleen	+ + + + + + + + + +
Thymus	+ + + + + + + +
<b>Integumentary System</b>	
Mammary gland	M M M M M M M M M
Skin	+ + + M + + + +
Fibrosarcoma	
Hemangiosarcoma	
<b>Musculoskeletal System</b>	
Bone	+ + + + + + + +
<b>Nervous System</b>	
Brain	+ + + + + + + +
<b>Respiratory System</b>	
Larynx	+ + + + + + + +
Lung	+ +
Alveolar/bronchiolar adenoma	X X X
Alveolar/bronchiolar adenoma, multiple	X X
Alveolar/bronchiolar carcinoma	
Nose	+ +
Trachea	+ +
<b>Special Senses System</b>	
Harderian gland	+ + + +
Adenoma	X X X
Adenoma, two	X
<b>Urinary System</b>	
Kidney	+ + + + + + + +
Urinary bladder	+ + + + + + + + + + +
<b>Systemic Lesions</b>	
Multiple organs	+ +
Lymphoma malignant mixed	X X X













**TABLE C3**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Harderian Gland: Adenoma</b>				
Overall rate <sup>a</sup>	7/50 (14%)	3/50 (6%)	7/50 (14%)	2/50 (4%)
Adjusted rate <sup>b</sup>	19.0%	9.1%	16.7%	5.6%
Terminal rate <sup>c</sup>	6/35 (17%)	3/33 (9%)	7/42 (17%)	1/34 (3%)
First incidence (days)	627	731 (T)	731 (T)	715
Life table test <sup>d</sup>	P=0.130N	P=0.183N	P=0.478N	P=0.090N
Logistic regression test <sup>d</sup>	P=0.130N	P=0.168N	P=0.531N	P=0.086N
Cochran-Armitage test <sup>d</sup>	P=0.126N			
Fisher exact test <sup>d</sup>		P=0.159N	P=0.613N	P=0.080N
<b>Liver: Hepatocellular Adenoma</b>				
Overall rate	19/50 (38%)	14/32 (44%) <sup>e</sup>	21/37 (57%) <sup>e</sup>	10/50 (20%)
Adjusted rate	49.5%			27.0%
Terminal rate	16/35 (46%)			8/34 (24%)
First incidence (days)	626			460
Life table test				P=0.049N
Logistic regression test				P=0.042N
Cochran-Armitage test				
Fisher exact test				P=0.038N
<b>Liver: Hepatocellular Carcinoma</b>				
Overall rate	7/50 (14%)	7/32 (22%) <sup>e</sup>	10/37 (27%) <sup>e</sup>	11/50 (22%)
Adjusted rate	17.6%			25.6%
Terminal rate	3/35 (9%)			3/34 (9%)
First incidence (days)	648			393
Life table test				P=0.228
Logistic regression test				P=0.217
Cochran-Armitage test				
Fisher exact test				P=0.218
<b>Liver: Hepatocellular Adenoma or Carcinoma</b>				
Overall rate	24/50 (48%)	21/32 (66%) <sup>e</sup>	28/37 (76%) <sup>e</sup>	19/50 (38%)
Adjusted rate	56.9%			43.6%
Terminal rate	17/35 (49%)			10/34 (29%)
First incidence (days)	626			393
Life table test				P=0.271N
Logistic regression test				P=0.211N
Cochran-Armitage test				
Fisher exact test				P=0.210N
<b>Lung: Alveolar/bronchiolar Adenoma</b>				
Overall rate	11/49 (22%)	10/50 (20%)	10/50 (20%)	15/50 (30%)
Adjusted rate	31.3%	29.2%	23.1%	37.5%
Terminal rate	10/34 (29%)	9/33 (27%)	9/42 (21%)	10/34 (29%)
First incidence (days)	689	689	618	393
Life table test	P=0.119	P=0.528N	P=0.301N	P=0.253
Logistic regression test	P=0.125	P=0.499N	P=0.367N	P=0.261
Cochran-Armitage test	P=0.138			
Fisher exact test		P=0.479N	P=0.479N	P=0.266

**TABLE C3**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Lung: Alveolar/bronchiolar Carcinoma</b>				
Overall rate	0/49 (0%)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted rate	0.0%	6.1%	9.5%	2.9%
Terminal rate	0/34 (0%)	2/33 (6%)	4/42 (10%)	1/34 (3%)
First incidence (days)	- <sup>f</sup>	731 (T)	731 (T)	731 (T)
Life table test	P=0.585N	P=0.232	P=0.093	P=0.500
Logistic regression test	P=0.585N	P=0.230	P=0.093	P=0.500
Cochran-Armitage test	P=0.572N			
Fisher exact test		P=0.253	P=0.061	P=0.505
<b>Lung: Alveolar/bronchiolar Adenoma or Carcinoma</b>				
Overall rate	11/49 (22%)	11/50 (22%)	14/50 (28%)	16/50 (32%)
Adjusted rate	31.3%	32.1%	32.4%	40.1%
Terminal rate	10/34 (29%)	10/33 (30%)	13/42 (31%)	11/34 (32%)
First incidence (days)	689	689	618	393
Life table test	P=0.118	P=0.569	P=0.549	P=0.190
Logistic regression test	P=0.122	P=0.598N	P=0.473	P=0.195
Cochran-Armitage test	P=0.140			
Fisher exact test		P=0.574N	P=0.343	P=0.200
<b>Thyroid Gland (Follicular Cell): Adenoma</b>				
Overall rate	1/48 (2%)	0/19 (0%) <sup>e</sup>	3/12 (25%) <sup>e</sup>	2/50 (4%)
Adjusted rate	2.9%			5.9%
Terminal rate	1/34 (3%)			2/34 (6%)
First incidence (days)	731 (T)			731 (T)
Life table test				P=0.500
Logistic regression test				P=0.500
Cochran-Armitage test				
Fisher exact test				P=0.515
<b>All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)</b>				
Overall rate	2/50 (4%)	5/50 (10%)	4/50 (8%)	5/50 (10%)
Adjusted rate	4.9%	13.2%	8.6%	12.6%
Terminal rate	0/35 (0%)	2/33 (6%)	1/42 (2%)	2/34 (6%)
First incidence (days)	627	617	607	435
Life table test	P=0.321	P=0.207	P=0.406	P=0.214
Logistic regression test	P=0.331	P=0.216	P=0.302	P=0.209
Cochran-Armitage test	P=0.330			
Fisher exact test		P=0.218	P=0.339	P=0.218
<b>All Organs: Benign Neoplasms</b>				
Overall rate	29/50 (58%)	23/50 (46%)	31/50 (62%)	25/50 (50%)
Adjusted rate	72.2%	63.4%	67.2%	60.5%
Terminal rate	24/35 (69%)	20/33 (61%)	27/42 (64%)	18/34 (53%)
First incidence (days)	626	443	529	393
Life table test	P=0.451N	P=0.228N	P=0.347N	P=0.334N
Logistic regression test	P=0.426N	P=0.181N	P=0.583	P=0.295N
Cochran-Armitage test	P=0.385N			
Fisher exact test		P=0.158N	P=0.419	P=0.274N

**TABLE C3**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>All Organs: Malignant Neoplasms</b>				
Overall rate	11/50 (22%)	14/50 (28%)	19/50 (38%)	17/50 (34%)
Adjusted rate	26.6%	33.0%	39.4%	37.9%
Terminal rate	5/35 (14%)	6/33 (18%)	13/42 (31%)	7/34 (21%)
First incidence (days)	627	443	607	393
Life table test	P=0.194	P=0.303	P=0.177	P=0.153
Logistic regression test	P=0.214	P=0.292	P=0.066	P=0.131
Cochran-Armitage test	P=0.194			
Fisher exact test		P=0.322	P=0.063	P=0.133
<b>All Organs: Benign or Malignant Neoplasms</b>				
Overall rate	35/50 (70%)	32/50 (64%)	39/50 (78%)	33/50 (66%)
Adjusted rate	79.5%	75.8%	78.0%	71.4%
Terminal rate	26/35 (74%)	23/33 (70%)	31/42 (74%)	21/34 (62%)
First incidence (days)	626	443	529	393
Life table test	P=0.520N	P=0.476N	P=0.425N	P=0.491N
Logistic regression test	P=0.447N	P=0.369N	P=0.396	P=0.415N
Cochran-Armitage test	P=0.432N			
Fisher exact test		P=0.335N	P=0.247	P=0.415N

(T) Terminal sacrifice

- <sup>a</sup> Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for bone marrow, brain, epididymis, gallbladder, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
- <sup>b</sup> Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
- <sup>c</sup> Observed incidence at terminal kill
- <sup>d</sup> Beneath the control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
- <sup>e</sup> Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not appropriate.
- <sup>f</sup> Not applicable; no neoplasms in animal group

**TABLE C4**  
**Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Male B6C3F<sub>1</sub> Mice<sup>a</sup>**

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
<b>Historical Incidence at Battelle Pacific Northwest Laboratories</b>			
1,3-Butadiene	18/50	5/50	21/50
Allyl glycidyl ether	7/50	0/50	7/50
2-Chloroacetophenone	7/50	6/50	11/50
Epinephrine hydrochloride	11/50	5/50	15/50
Ethyl chloride	3/50	2/50	5/50
<i>o</i> -Chlorobenzalmalonitrile	7/49	7/49	14/49
<b>Overall Historical Incidence</b>			
Total	102/624 (16.3%)	45/624 (7.2%)	139/624 (22.3%)
Standard deviation	7.8%	5.5%	9.4%
Range	6%-36%	0%-16%	10%-42%

<sup>a</sup> Data as of 20 August 1992.

**TABLE C5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Disposition Summary</b>				
Animals initially in study	60	60	60	60
<b>15-Month interim evaluation</b>				
15-Month interim evaluation	10	10	10	10
<b>Early deaths</b>				
Accidental deaths	1	2		
Moribund	8	6	3	9
Natural deaths	6	9	5	7
<b>Survivors</b>				
Terminal sacrifice	35	33	42	34
Animals examined microscopically	60	60	60	60
<b>15-Month Interim Evaluation</b>				
<b>Alimentary System</b>				
Liver	(10)	(10)	(10)	(10)
Cytoplasmic alteration			1 (10%)	2 (20%)
Inflammation, subacute	1 (10%)			1 (10%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Hyperkeratosis			1 (10%)	2 (20%)
<b>Cardiovascular System</b>				
None				
<b>Endocrine System</b>				
None				
<b>General Body System</b>				
None				
<b>Genital System</b>				
Epididymis	(10)			(10)
Inflammation, chronic				1 (10%)
Testes	(10)			(10)
Atrophy	1 (10%)			
<b>Hematopoietic System</b>				
Lymph node, mesenteric	(10)	(1)		(10)
Hemorrhage		1 (100%)		
<b>Integumentary System</b>				
Skin	(10)		(1)	(10)
Alopecia			1 (100%)	
<b>Musculoskeletal System</b>				
None				

**TABLE C5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation (continued)</b>				
<b>Nervous System</b>				
Brain	(10)			(10)
Mineralization	3 (30%)			5 (50%)
<b>Respiratory System</b>				
Lung	(10)	(10)	(10)	(10)
Hemorrhage			1 (10%)	
Inflammation, subacute		1 (10%)		1 (10%)
Alveolar epithelium, hyperplasia			2 (20%)	1 (10%)
Artery, inflammation, subacute			1 (10%)	
Mucosa, pigmentation			7 (70%)	10 (100%)
Nose	(10)	(10)	(10)	(10)
Inflammation, suppurative			1 (10%)	10 (100%)
Mucosa, pigmentation		7 (70%)	10 (100%)	10 (100%)
Trachea	(10)	(10)	(10)	(10)
Mucosa, pigmentation			10 (100%)	10 (100%)
<b>Special Senses System</b>				
None				
<b>Urinary System</b>				
Kidney	(10)			(10)
Inflammation, suppurative	1 (10%)			
Nephropathy, chronic	1 (10%)			
Urinary bladder	(10)		(1)	(10)
Dilatation	1 (10%)			
<b>2-Year Study</b>				
<b>Alimentary System</b>				
Intestine small, duodenum	(50)	(17)	(8)	(49)
Congestion				1 (2%)
Hyperplasia				1 (2%)
Inflammation, suppurative	1 (2%)			
Peyer's patch, hyperplasia, lymphoid				1 (2%)
Intestine small, jejunum	(50)	(18)	(9)	(50)
Congestion				1 (2%)
Inflammation, chronic				1 (2%)
Epithelium, hyperplasia		1 (6%)		
Peyer's patch, hyperplasia, lymphoid	2 (4%)			3 (6%)
Intestine small, ileum	(50)	(19)	(9)	(50)
Congestion				1 (2%)
Peyer's patch, hyperplasia, lymphoid	1 (2%)		1 (11%)	



**TABLE C5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Alimentary System (continued)</b>				
Liver	(50)	(32)	(37)	(50)
Angiectasis		1 (3%)	1 (3%)	
Basophilic focus	1 (2%)			
Cyst	1 (2%)	1 (3%)	1 (3%)	
Cytoplasmic alteration	1 (2%)		1 (3%)	2 (4%)
Fatty change	1 (2%)			
Fibrosis		1 (3%)		
Focal cellular change	1 (2%)	1 (3%)	1 (3%)	
Hematopoietic cell proliferation			1 (3%)	
Hyperplasia, nodular	1 (2%)		2 (5%)	
Infarct	1 (2%)	1 (3%)		1 (2%)
Inflammation, chronic	1 (2%)	1 (3%)		
Inflammation, necrotizing	1 (2%)			
Inflammation, subacute	2 (4%)	1 (3%)		
Inflammation, suppurative	1 (2%)			
Mineralization				1 (2%)
Necrosis, acute	1 (2%)	1 (3%)		2 (4%)
Mesentery	(4)	(5)	(2)	(2)
Congestion		1 (20%)	1 (50%)	
Inflammation, suppurative		1 (20%)		
Necrosis	1 (25%)	1 (20%)		1 (50%)
Fat, hemorrhage	1 (25%)			
Fat, necrosis	1 (25%)	2 (40%)	1 (50%)	1 (50%)
Pancreas	(49)	(18)	(8)	(50)
Inflammation, subacute	1 (2%)			
Duct, cyst	1 (2%)	1 (6%)		
Stomach, forestomach	(50)	(19)	(12)	(50)
Cyst			1 (8%)	
Hyperkeratosis		2 (11%)		2 (4%)
Hyperplasia			1 (8%)	
Stomach, glandular	(50)	(16)	(8)	(50)
Mineralization	1 (2%)			2 (4%)
Necrosis	3 (6%)	1 (6%)		
Tooth		(2)	(1)	(2)
Developmental malformation		2 (100%)	1 (100%)	2 (100%)
Inflammation, suppurative		1 (50%)		
<b>Cardiovascular System</b>				
Heart	(50)	(17)	(8)	(50)
Inflammation, subacute		1 (6%)		
Arteriole, mineralization				1 (2%)
Atrium, thrombosis	1 (2%)			
<b>Endocrine System</b>				
Adrenal cortex	(49)	(17)	(8)	(50)
Hyperplasia				1 (2%)
Thyroid gland	(48)	(19)	(12)	(50)
Follicular cell, hyperplasia	4 (8%)	2 (11%)	2 (17%)	5 (10%)

**TABLE C5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>General Body System</b>				
None				
<b>Genital System</b>				
Epididymis	(50)	(17)	(8)	(50)
Inflammation, granulomatous	1 (2%)			1 (2%)
Serosa, inflammation, suppurative		1 (6%)		
Penis	(4)	(3)	(1)	(3)
Concretion		2 (67%)		1 (33%)
Hemorrhage, acute		1 (33%)		
Inflammation, suppurative	2 (50%)	1 (33%)	1 (100%)	2 (67%)
Preputial gland	(9)	(5)	(4)	(4)
Inflammation, granulomatous	1 (11%)			
Inflammation, suppurative	2 (22%)	1 (20%)	1 (25%)	
Duct, dilatation	5 (56%)	3 (60%)	3 (75%)	3 (75%)
Prostate	(50)	(17)	(8)	(50)
Inflammation, suppurative	1 (2%)	1 (6%)		
Seminal vesicle	(50)	(18)	(9)	(50)
Dilatation	1 (2%)	1 (6%)	1 (11%)	1 (2%)
Hemorrhage	1 (2%)			
Testes	(50)	(18)	(9)	(50)
Atrophy				1 (2%)
<b>Hematopoietic System</b>				
Bone marrow	(50)	(17)	(8)	(50)
Hyperplasia	1 (2%)			2 (4%)
Lymph node	(1)	(5)	(3)	(2)
Congestion		1 (20%)		
Deep cervical, hematopoietic cell proliferation				1 (50%)
Iliac, hyperplasia, lymphoid			1 (33%)	
Inguinal, hyperplasia, lymphoid		1 (20%)		
Renal, hyperplasia, lymphoid			2 (67%)	
Lymph node, mandibular	(41)	(13)	(3)	(43)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia				1 (2%)
Hyperplasia, lymphoid				5 (12%)
Lymph node, mesenteric	(48)	(21)	(13)	(49)
Congestion	1 (2%)	2 (10%)	3 (23%)	3 (6%)
Hematopoietic cell proliferation			1 (8%)	1 (2%)
Hemorrhage	2 (4%)			2 (4%)
Hyperplasia, lymphoid	4 (8%)	1 (5%)	3 (23%)	7 (14%)
Inflammation, suppurative			1 (8%)	
Spleen	(50)	(18)	(13)	(50)
Hematopoietic cell proliferation	2 (4%)	1 (6%)	3 (23%)	3 (6%)
Hyperplasia, lymphoid			3 (23%)	

**TABLE C5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Integumentary System</b>				
Skin	(50)	(18)	(10)	(50)
Alopecia	2 (4%)	1 (6%)		
Edema				1 (2%)
Hyperkeratosis			1 (10%)	
Inflammation, necrotizing		1 (6%)		
Inflammation, suppurative	4 (8%)	2 (11%)	2 (20%)	
Prepuce, inflammation, suppurative	1 (2%)		1 (10%)	
<b>Musculoskeletal System</b>				
Bone	(50)	(16)	(9)	(50)
Arthrosis			1 (11%)	
<b>Nervous System</b>				
Brain	(50)	(17)	(8)	(50)
Compression	1 (2%)			
Inflammation, subacute				1 (2%)
Inflammation, suppurative				1 (2%)
Mineralization	13 (26%)		1 (13%)	10 (20%)
Cerebellum, infarct		1 (6%)		
Spinal cord	(1)	(1)		
Hemorrhage, acute		1 (100%)		
<b>Respiratory System</b>				
Lung	(49)	(50)	(50)	(50)
Congestion		3 (6%)	1 (2%)	2 (4%)
Hemorrhage, multifocal		1 (2%)		
Infiltration cellular, lymphocyte		1 (2%)		
Infiltration cellular, histiocyte	1 (2%)	1 (2%)		
Inflammation, subacute	1 (2%)		1 (2%)	2 (4%)
Inflammation, suppurative				4 (8%)
Metaplasia, osseous		1 (2%)		
Alveolar epithelium, hyperplasia		1 (2%)	3 (6%)	5 (10%)
Alveolar epithelium, inflammation, subacute			1 (2%)	
Arteriole, inflammation, suppurative		1 (2%)		
Bronchiole, hyperplasia	1 (2%)			1 (2%)
Mucosa, pigmentation		2 (4%)	42 (84%)	45 (90%)
Pleura, inflammation, suppurative	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Hemorrhage, acute	1 (2%)			
Inflammation, suppurative			1 (2%)	36 (72%)
Mucosa, pigmentation		45 (90%)	50 (100%)	44 (88%)
Trachea	(50)	(50)	(50)	(50)
Inflammation, suppurative				2 (4%)
Mucosa, pigmentation		29 (58%)	48 (96%)	48 (96%)

**TABLE C5**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Special Senses System</b>				
None				
<b>Urinary System</b>				
Kidney	(50)	(22)	(12)	(50)
Casts	1 (2%)			
Cyst	1 (2%)	2 (9%)		3 (6%)
Dilatation	3 (6%)			
Hydronephrosis	1 (2%)	1 (5%)		
Hypertrophy	1 (2%)			
Inflammation, chronic	1 (2%)		2 (17%)	1 (2%)
Inflammation, subacute	4 (8%)			2 (4%)
Inflammation, suppurative	2 (4%)	2 (9%)		
Metaplasia, osseous		1 (5%)		1 (2%)
Mineralization		1 (5%)		4 (8%)
Nephropathy, chronic	1 (2%)			1 (2%)
Polycystic kidney	1 (2%)			
Pelvis, dilatation	6 (12%)	4 (18%)	4 (33%)	2 (4%)
Renal tubule, degeneration		2 (9%)		1 (2%)
Urethra	(1)			
Concretion	1 (100%)			
Urinary bladder	(50)	(18)	(16)	(50)
Concretion		1 (6%)		
Dilatation	6 (12%)	5 (28%)	10 (63%)	4 (8%)

<sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

**APPENDIX D**  
**SUMMARY OF LESIONS IN FEMALE MICE**  
**IN THE 2-YEAR INHALATION STUDY**  
**OF HEXACHLOROCYCLOPENTADIENE**

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**TABLE D1**  
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Disposition Summary</b>				
Animals initially in study	60	60	60	60
<i>15-Month interim evaluation</i>	10	10	10	10
Early deaths				
Accidental deaths	1		1	1
Moribund	8	10	11	15
Natural deaths	10	8	8	13
Survivors				
Terminal sacrifice	31	32	30	21
Animals examined microscopically	60	60	60	60
<b>15-Month Interim Evaluation</b>				
<b>Alimentary System</b>				
Liver	(10)	(10)	(10)	(10)
Hepatocellular adenoma	1 (10%)			1 (10%)
<b>Cardiovascular System</b>				
None				
<b>Endocrine System</b>				
None				
<b>General Body System</b>				
None				
<b>Genital System</b>				
None				
<b>Hematopoietic System</b>				
None				
<b>Integumentary System</b>				
None				
<b>Musculoskeletal System</b>				
None				
<b>Nervous System</b>				
None				

TABLE D1

Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene  
(continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation</b> (continued)				
<b>Respiratory System</b>				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma			1 (10%)	1 (10%)
<b>Special Senses System</b>				
Harderian gland				(1)
Adenoma				1 (100%)
<b>Urinary System</b>				
None				
<b>2-Year Study</b>				
<b>Alimentary System</b>				
Intestine large, colon	(49)	(49)	(50)	(50)
Intestine large, cecum	(49)	(50)	(50)	(50)
Intestine small, duodenum	(49)	(50)	(50)	(50)
Intestine small, jejunum	(49)	(50)	(50)	(50)
Adenocarcinoma				1 (2%)
Fibrosarcoma, metastatic, skin		1 (2%)		
Intestine small, ileum	(49)	(50)	(50)	(50)
Liver	(49)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma	4 (8%)	2 (4%)	4 (8%)	1 (2%)
Hepatocellular adenoma	5 (10%)	10 (20%)	6 (12%)	5 (10%)
Hepatocellular adenoma, two			1 (2%)	
Histiocytic sarcoma	1 (2%)	1 (2%)		
Mesentery	(7)	(4)	(6)	(2)
Fibrosarcoma, metastatic, skin		1 (25%)		
Hemangiosarcoma		1 (25%)		
Histiocytic sarcoma	1 (14%)			
Pancreas	(49)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Salivary glands	(49)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Squamous cell papilloma			1 (2%)	2 (4%)
Stomach, glandular	(49)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Tongue	(1)			
Squamous cell papilloma	1 (100%)			
<b>Cardiovascular System</b>				
Heart	(49)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)

**TABLE D1**  
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Endocrine System</b>				
Adrenal cortex	(49)	(50)	(50)	(50)
Carcinoma	1 (2%)			
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Adrenal medulla	(49)	(50)	(50)	(49)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Islets, pancreatic	(49)	(50)	(49)	(50)
Carcinoma		1 (2%)		
Pituitary gland	(49)	(49)	(48)	(50)
Adenoma	8 (16%)	3 (6%)	5 (10%)	3 (6%)
Carcinoma		1 (2%)	1 (2%)	
Thyroid gland	(49)	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)	1 (2%)	6 (12%)	
<b>General Body System</b>				
Tissue NOS		(1)		
Sarcoma, metastatic, skin		1 (100%)		
<b>Genital System</b>				
Ovary	(49)	(50)	(50)	(50)
Adenoma	1 (2%)		2 (4%)	
Cystadenoma		1 (2%)		
Granulosa cell tumor benign	1 (2%)			
Hemangioma		1 (2%)		
Histiocytic sarcoma	2 (4%)			
Teratoma NOS		1 (2%)		
Uterus	(49)	(50)	(49)	(50)
Adenocarcinoma		1 (2%)		
Adenoma	1 (2%)		2 (4%)	
Hemangioma	1 (2%)	1 (2%)		
Hemangioma, mild			1 (2%)	
Histiocytic sarcoma	3 (6%)	1 (2%)		
Endometrium, polyp, moderate		1 (2%)		
Endometrium, polyp stromal, moderate			1 (2%)	
<b>Hematopoietic System</b>				
Bone marrow	(49)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Lymph node	(7)	(8)	(5)	(5)
Lymph node, bronchial	(47)	(50)	(50)	(50)
Lymph node, mandibular	(42)	(44)	(47)	(48)
Lymph node, mesenteric	(49)	(49)	(48)	(50)
Histiocytic sarcoma	1 (2%)			
Lymph node, mediastinal	(49)	(48)	(48)	(50)
Histiocytic sarcoma	1 (2%)			
Spleen	(49)	(50)	(50)	(50)
Hemangiosarcoma		2 (4%)		
Histiocytic sarcoma	1 (2%)			
Thymus	(49)	(48)	(48)	(50)



TABLE D1

Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene  
(continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Integumentary System</b>				
Mammary gland	(48)	(47)	(44)	(43)
Adenocarcinoma	1 (2%)			
Skin	(49)	(49)	(49)	(49)
Fibrosarcoma	1 (2%)	1 (2%)		1 (2%)
Myxosarcoma		1 (2%)		
Subcutaneous tissue, osteosarcoma, metastatic, bone			1 (2%)	
Subcutaneous tissue, sarcoma		1 (2%)		
<b>Musculoskeletal System</b>				
Bone	(49)	(50)	(50)	(50)
Osteosarcoma			1 (2%)	
Skeletal muscle		(1)	(1)	(2)
Fibrosarcoma, metastatic, skin		1 (100%)		
<b>Nervous System</b>				
Brain	(49)	(50)	(50)	(50)
Meninges, fibrosarcoma		1 (2%)		
<b>Respiratory System</b>				
Lung	(48)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	4 (8%)	3 (6%)	3 (6%)	4 (8%)
Alveolar/bronchiolar carcinoma	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)	
Fibrosarcoma, metastatic, skin		1 (2%)		
Hemangiosarcoma, metastatic, liver		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	1 (2%)	1 (2%)		
Histiocytic sarcoma	3 (6%)			
Osteosarcoma, metastatic, bone			1 (2%)	
Nose	(49)	(50)	(50)	(48)
Mucosa, squamous cell carcinoma		1 (2%)		
<b>Special Senses System</b>				
Harderian gland	(7)	(6)	(4)	(1)
Adenocarcinoma	1 (14%)			
Adenoma	4 (57%)	5 (83%)	4 (100%)	1 (100%)
Adenoma, two		1 (17%)		
<b>Urinary System</b>				
Kidney	(49)	(50)	(50)	(50)
Urinary bladder	(48)	(50)	(50)	(48)

**TABLE D1**  
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study</b> (continued)				
<b>Systemic Lesions</b>				
Multiple organs <sup>b</sup>	(50)	(50)	(50)	(50)
Histiocytic sarcoma	4 (8%)	1 (2%)		
Lymphoma malignant histiocytic		2 (4%)		
Lymphoma malignant lymphocytic	1 (2%)			1 (2%)
Lymphoma malignant mixed	12 (24%)	9 (18%)	5 (10%)	8 (16%)
<b>Neoplasm Summary</b>				
Total animals with primary neoplasms <sup>c</sup>				
15-Month interim evaluation	1		1	2
2-Year study	34	37	33	20
Total primary neoplasms				
15-Month interim evaluation	1		1	3
2-Year study	55	56	45	29
Total animals with benign neoplasms				
15-Month interim evaluation	1		1	2
2-Year study	23	22	24	13
Total benign neoplasms				
15-Month interim evaluation	1		1	3
2-Year study	27	27	32	15
Total animals with malignant neoplasms				
2-Year study	21	22	11	12
Total malignant neoplasms				
2-Year study	28	28	13	14
Total animals with metastatic neoplasms				
2-Year study	1	4	1	
Total metastatic neoplasms				
2-Year study	1	13	2	
Total animals with uncertain neoplasms benign or malignant				
2-Year study		1		
Total uncertain neoplasms				
2-Year study		1		

<sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

<sup>b</sup> Number of animals with any tissue examined microscopically

<sup>c</sup> Primary neoplasms: all neoplasms except metastatic neoplasms

**TABLE D2**  
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0 ppm**

<b>Number of Days on Study</b>	2	3	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	
	4	9	8	2	8	8	9	2	2	3	3	5	6	7	8	9	9	1	3	3	3	3	3	3	
	9	6	3	0	4	9	8	0	9	3	4	7	0	2	7	1	3	6	7	7	7	7	7	7	
<b>Carcass ID Number</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	2	2	2	2	2	2	2	3	2	2	1	2	2	1	2	2	2	2	1	1	1	1	2	2	
	5	6	9	1	9	2	4	0	9	0	9	2	6	9	5	6	6	8	9	9	9	0	0	1	
	1	2	5	4	2	4	2	5	3	2	3	2	3	5	4	5	1	3	1	2	4	1	3	1	
<b>Alimentary System</b>																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular carcinoma																									
Hepatocellular adenoma																								X	
Histiocytic sarcoma				X																					
Mesentery			+							+								+						+	
Histiocytic sarcoma			X																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																								X	
Tongue																									
Squamous cell papilloma																									
Tooth																									
<b>Cardiovascular System</b>																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>Endocrine System</b>																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Parathyroid gland	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	M	+	+	+	+	+	+	M	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Follicular cell, adenoma																								X	
<b>General Body System</b>																									
None																									

+: Tissue examined microscopically  
A: Autolysis precludes examination

M: Missing tissue  
I: Insufficient tissue

X: Lesion present  
Blank: Not examined

**TABLE D2**  
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0 ppm (continued)**

Number of Days on Study	7 7
	3 3
	7 7
Carcass ID Number	0 0
	2 3 3 3
	1 1 1 3 3 3 4 4 4 4 5 5 5 6 7 7 7 7 8 8 8 9 0 0 0
	2 3 5 1 3 4 1 3 4 5 2 3 5 4 1 2 3 5 2 4 5 4 1 2 4
	Total Tissues/Tumors
<b>Alimentary System</b>	
Esophagus	+ 49
Gallbladder	+ 48
Intestine large, colon	+ 49
Intestine large, rectum	+ 49
Intestine large, cecum	+ 49
Intestine small, duodenum	+ 49
Intestine small, jejunum	+ 49
Intestine small, ileum	+ 49
Liver	+ 49
Hepatocellular carcinoma	+ 4
Hepatocellular adenoma	+ 5
Histiocytic sarcoma	+ 1
Mesentery	+ 7
Histiocytic sarcoma	+ 1
Pancreas	+ 49
Salivary glands	+ 49
Stomach, forestomach	+ 49
Stomach, glandular	+ 49
Histiocytic sarcoma	+ 1
Tongue	+ 1
Squamous cell papilloma	+ 1
Tooth	
<b>Cardiovascular System</b>	
Heart	+ 49
<b>Endocrine System</b>	
Adrenal cortex	+ 49
Carcinoma	+ 1
Adrenal medulla	+ 49
Islets, pancreatic	+ 49
Parathyroid gland	M M M + M + + M M + + M + + + + M + + + M + + 34
Pituitary gland	+ 49
Adenoma	+ 8
Thyroid gland	+ 49
Follicular cell, adenoma	+ 1
<b>General Body System</b>	
None	







**TABLE D2**  
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0 ppm (continued)**

<b>Number of Days on Study</b>	7 7	
	3 3	
	7 7	
<b>Carcass ID Number</b>	0 0	<b>Total Tissues/ Tumors</b>
	2 3 3 3	
	1 1 1 3 3 3 4 4 4 4 5 5 5 6 7 7 7 7 8 8 8 9 0 0 0	
	2 3 5 1 3 4 1 3 4 5 2 3 5 4 1 2 3 5 2 4 5 4 1 2 4	
<b>Special Senses System</b>		
Eye		1
Harderian gland	+	7
Adenocarcinoma		1
Adenoma	X X	4
<b>Urinary System</b>		
Kidney	+	49
Urinary bladder	+	48
<b>Systemic Lesions</b>		
Multiple organs	+	49
Histiocytic sarcoma		4
Lymphoma malignant lymphocytic		1
Lymphoma malignant mixed	X X X X X	12





**TABLE D2**  
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.01 ppm (continued)**

Number of Days on Study	7 7
Carcass ID Number	3 7 0 4 4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 7 7 7 8 9 9 0 0 1 1 1 1 2 2 2 2 3 3 3 3 4 4 1 1 4 3 4 5 5 3 5 1 5 1 2 3 4 1 3 4 5 1 3 4 5 2 5
Total Tissues/Tumors	
<b>Alimentary System</b>	
Esophagus	+ 50
Gallbladder	+ 48
Intestine large, colon	+ 49
Intestine large, rectum	+ 48
Intestine large, cecum	+ 50
Intestine small, duodenum	+ 50
Intestine small, jejunum	+ 50
Fibrosarcoma, metastatic, skin	
Intestine small, ileum	+ 50
Liver	+ 50
Fibrosarcoma, metastatic, skin	
Hemangiosarcoma	
Hepatocellular carcinoma	
Hepatocellular adenoma	X X X X X X X X
Histiocytic sarcoma	
Mesentery	+ 4
Fibrosarcoma, metastatic, skin	
Hemangiosarcoma	
Pancreas	+ 50
Fibrosarcoma, metastatic, skin	
Salivary glands	+ 50
Stomach, forestomach	+ 50
Fibrosarcoma, metastatic, skin	
Stomach, glandular	+ 50
Fibrosarcoma, metastatic, skin	
<b>Cardiovascular System</b>	
Heart	+ 50
<b>Endocrine System</b>	
Adrenal cortex	+ 50
Hepatocellular carcinoma, metastatic, liver	
Adrenal medulla	+ 50
Hepatocellular carcinoma, metastatic, liver	
Islets, pancreatic	+ 50
Carcinoma	X
Parathyroid gland	M + + + + M + + M + M + M + M + + + + M M + M + + 22
Pituitary gland	+ + + + + + + + + + + + + + + + + M + + + + + + + + + 49
Adenoma	X X
Carcinoma	
Thyroid gland	+ 50
Follicular cell, adenoma	X



**TABLE D2**  
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.01 ppm (continued)**

<b>Number of Days on Study</b>	7 7	
	3 3	
	7 7	
<b>Carcass ID Number</b>	0 0	Total Tissues/ Tumors
	4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5	
	5 6 6 7 7 7 8 9 9 0 0 1 1 1 1 2 2 2 2 3 3 3 3 4 4	
	1 1 4 3 4 5 5 3 5 1 5 1 2 3 4 1 3 4 5 1 3 4 5 2 5	
<b>General Body System</b>		
Tissue NOS		1
Sarcoma, metastatic, skin		1
<b>Genital System</b>		
Ovary	+ +	50
Cystadenoma		1
Hemangioma		1
Teratoma NOS		1
Uterus	+ +	50
Adenocarcinoma		1
Hemangioma		1
Histiocytic sarcoma		1
Endometrium, polyp, moderate		1
<b>Hematopoietic System</b>		
Blood		2
Bone marrow	+ +	50
Hemangiosarcoma		1
Lymph node		8
Lymph node, bronchial	+ +	50
Lymph node, mandibular	+ + M + + + + + + + + + + M + + + + + + + + + + + +	44
Lymph node, mesenteric	+ +	49
Lymph node, mediastinal	+ +	48
Spleen	+ +	50
Hemangiosarcoma		2
Thymus	+ +	48
<b>Integumentary System</b>		
Mammary gland	+ +	47
Skin	+ +	49
Fibrosarcoma		1
Myxosarcoma		1
Subcutaneous tissue, sarcoma		1
<b>Musculoskeletal System</b>		
Bone	+ +	50
Skeletal muscle		1
Fibrosarcoma, metastatic, skin		1
<b>Nervous System</b>		
Brain	+ +	50
Meninges, fibrosarcoma		1
Peripheral nerve		1



**TABLE D2**  
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.01 ppm (continued)**

<b>Number of Days on Study</b>	7 7	
	3 3	
	7 7	
<b>Carcass ID Number</b>	0 0	
	4 4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5	Total
	5 6 6 7 7 7 8 9 9 0 0 1 1 1 1 2 2 2 2 3 3 3 3 4 4	Tissues/
	1 1 4 3 4 5 5 3 5 1 5 1 2 3 4 1 3 4 5 1 3 4 5 2 5	Tumors
<b>Respiratory System</b>		
Larynx	+ +	50
Lung	+ +	50
Alveolar/bronchiolar adenoma		3
Alveolar/bronchiolar carcinoma	X X	1
Fibrosarcoma, metastatic, skin		1
Hemangiosarcoma, metastatic, liver		1
Hepatocellular carcinoma, metastatic, liver		1
Nose	+ +	50
Mucosa, squamous cell carcinoma		1
Trachea	+ +	50
<b>Special Senses System</b>		
Eye		1
Harderian gland	+ +	6
Adenoma	X X X	5
Adenoma, two		1
<b>Urinary System</b>		
Kidney	+ +	50
Urinary bladder	+ +	50
<b>Systemic Lesions</b>		
Multiple organs	+ +	50
Histiocytic sarcoma		1
Lymphoma malignant histiocytic		2
Lymphoma malignant mixed	X X X	9









**TABLE D2**  
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.05 ppm (continued)**

<b>Number of Days on Study</b>	7 7	
	3 3	
	6 6	
<b>Carcass ID Number</b>	0 0	Total Tissues/ Tumors
	6 6 7	
	8 9 0 0 0 1 1 1 2 2 2 4 4 4 4 5 5 6 6 6 7 7 7 8 8	
	3 1 2 4 5 1 3 4 1 2 5 1 3 4 5 2 5 1 3 4 1 3 4 2 3	
<b>Hematopoietic System</b>		
Bone marrow	+ +	50
Lymph node		5
Lymph node, bronchial	+ +	50
Lymph node, mandibular	+ M + +	47
Lymph node, mesenteric	+ + + + + M + + + + + + + + + + + + + + + + +	48
Lymph node, mediastinal	+ +	48
Spleen	+ +	50
Thymus	+ +	48
<b>Integumentary System</b>		
Mammary gland	+ M +	44
Skin	+ +	49
Subcutaneous tissue, osteosarcoma, metastatic, bone		1
<b>Musculoskeletal System</b>		
Bone	+ +	50
Osteosarcoma		1
Skeletal muscle		1
<b>Nervous System</b>		
Brain	+ +	50
Peripheral nerve		1
Spinal cord		1
<b>Respiratory System</b>		
Larynx	+ +	50
Lung	+ +	50
Alveolar/bronchiolar adenoma		3
Alveolar/bronchiolar carcinoma		1
Alveolar/bronchiolar carcinoma, multiple		1
Osteosarcoma, metastatic, bone		1
Nose	+ +	50
Trachea	+ +	48
<b>Special Senses System</b>		
Eye		1
Harderian gland		4
Adenoma		4
<b>Urinary System</b>		
Kidney	+ +	50
Urinary bladder	+ +	50
<b>Systemic Lesions</b>		
Multiple organs	+ +	50
Lymphoma malignant mixed		5





**TABLE D2**  
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene:**  
**0.2 ppm (continued)**

Number of Days on Study	0	4	4	4	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	2	0	1	6	9	9	0	1	1	2	4	5	7	0	1	1	1	1	1	1	2	7	7	9	9						
	2	0	8	6	6	8	0	6	9	8	6	4	0	6	0	0	1	4	8	9	1	3	4	0	5						
Carcass ID Number	1	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	9	9	0	9	9	9	9	9	9	9	0	0	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
	2	1	1	1	2	5	5	4	7	5	2	2	0	2	3	8	3	8	1	6	3	6	1	5	2						
	3	1	2	3	2	1	3	2	2	4	4	5	1	5	1	5	2	1	3	1	3	3	4	2	3						
<b>Hematopoietic System</b>																															
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node			+		+																										
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>Integumentary System</b>																															
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibrosarcoma																															
<b>Musculoskeletal System</b>																															
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle	+	+																													
<b>Nervous System</b>																															
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Peripheral nerve	+																														
Spinal cord	+																														
<b>Respiratory System</b>																															
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																										X	X	X			
Alveolar/bronchiolar carcinoma																															
Nose	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>Special Senses System</b>																															
Harderian gland																															
Adenoma																															
<b>Urinary System</b>																															
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
<b>Systemic Lesions</b>																															
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant lymphocytic																															
Lymphoma malignant mixed		X	X							X																		X			



**TABLE D3**  
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Harderian Gland: Adenoma</b>				
Overall rate <sup>a</sup>	4/50 (8%)	6/50 (12%)	4/50 (8%)	1/50 (2%)
Adjusted rate <sup>b</sup>	12.9%	18.8%	12.1%	4.8%
Terminal rate <sup>c</sup>	4/31 (13%)	6/32 (19%)	2/30 (7%)	1/21 (5%)
First incidence (days)	736 (T)	736 (T)	660	736 (T)
Life table test <sup>d</sup>	P=0.164N	P=0.387	P=0.631	P=0.311N
Logistic regression test <sup>d</sup>	P=0.130N	P=0.387	P=0.634N	P=0.311N
Cochran-Armitage test <sup>d</sup>	P=0.070N			
Fisher exact test <sup>d</sup>		P=0.370	P=0.643N	P=0.181N
<b>Harderian Gland: Adenoma or Carcinoma</b>				
Overall rate	5/50 (10%)	6/50 (12%)	4/50 (8%)	1/50 (2%)
Adjusted rate	15.5%	18.8%	12.1%	4.8%
Terminal rate	4/31 (13%)	6/32 (19%)	2/30 (7%)	1/21 (5%)
First incidence (days)	693	736 (T)	660	736 (T)
Life table test	P=0.126N	P=0.520	P=0.510N	P=0.205N
Logistic regression test	P=0.095N	P=0.521	P=0.486N	P=0.169N
Cochran-Armitage test	P=0.050N			
Fisher exact test		P=0.500	P=0.500N	P=0.102N
<b>Liver: Hepatocellular Adenoma</b>				
Overall rate	5/49 (10%)	10/50 (20%)	7/50 (14%)	5/50 (10%)
Adjusted rate	15.0%	31.3%	22.5%	19.9%
Terminal rate	4/31 (13%)	10/32 (31%)	6/30 (20%)	2/21 (10%)
First incidence (days)	629	736 (T)	718	673
Life table test	P=0.575	P=0.139	P=0.362	P=0.409
Logistic regression test	P=0.499N	P=0.137	P=0.392	P=0.496
Cochran-Armitage test	P=0.269N			
Fisher exact test		P=0.140	P=0.394	P=0.617N
<b>Liver: Hepatocellular Carcinoma</b>				
Overall rate	4/49 (8%)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted rate	11.2%	5.4%	10.8%	4.8%
Terminal rate	2/31 (6%)	0/32 (0%)	1/30 (3%)	1/21 (5%)
First incidence (days)	634	668	625	736 (T)
Life table test	P=0.326N	P=0.328N	P=0.633N	P=0.300N
Logistic regression test	P=0.251N	P=0.329N	P=0.633N	P=0.214N
Cochran-Armitage test	P=0.194N			
Fisher exact test		P=0.329N	P=0.631N	P=0.175N
<b>Liver: Hepatocellular Adenoma or Carcinoma</b>				
Overall rate	9/49 (18%)	12/50 (24%)	10/50 (20%)	6/50 (12%)
Adjusted rate	25.4%	35.0%	29.3%	24.1%
Terminal rate	6/31 (19%)	10/32 (31%)	7/30 (23%)	3/21 (14%)
First incidence (days)	629	668	625	673
Life table test	P=0.408N	P=0.342	P=0.488	P=0.560N
Logistic regression test	P=0.252N	P=0.335	P=0.522	P=0.423N
Cochran-Armitage test	P=0.118N			
Fisher exact test		P=0.331	P=0.520	P=0.274N

**TABLE D3**  
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Lung: Alveolar/bronchiolar Adenoma</b>				
Overall rate	4/48 (8%)	3/50 (6%)	3/50 (6%)	4/49 (8%)
Adjusted rate	12.9%	9.4%	10.0%	14.6%
Terminal rate	4/31 (13%)	3/32 (9%)	3/30 (10%)	1/21 (5%)
First incidence (days)	736 (T)	736 (T)	736 (T)	621
Life table test	P=0.280	P=0.482N	P=0.518N	P=0.452
Logistic regression test	P=0.362	P=0.482N	P=0.518N	P=0.556
Cochran-Armitage test	P=0.506			
Fisher exact test		P=0.477N	P=0.477N	P=0.631N
<b>Lung: Alveolar/bronchiolar Carcinoma</b>				
Overall rate	3/48 (6%)	1/50 (2%)	2/50 (4%)	1/49 (2%)
Adjusted rate	8.3%	3.1%	5.6%	4.8%
Terminal rate	1/31 (3%)	1/32 (3%)	1/30 (3%)	1/21 (5%)
First incidence (days)	620	736 (T)	604	736 (T)
Life table test	P=0.503N	P=0.305N	P=0.504N	P=0.436N
Logistic regression test	P=0.401N	P=0.289N	P=0.481N	P=0.338N
Cochran-Armitage test	P=0.368N			
Fisher exact test		P=0.293N	P=0.480N	P=0.301N
<b>Lung: Alveolar/bronchiolar Adenoma or Carcinoma</b>				
Overall rate	7/48 (15%)	4/50 (8%)	5/50 (10%)	5/49 (10%)
Adjusted rate	20.5%	12.5%	15.3%	18.9%
Terminal rate	5/31 (16%)	4/32 (13%)	4/30 (13%)	2/21 (10%)
First incidence (days)	620	736 (T)	604	621
Life table test	P=0.402	P=0.249N	P=0.396N	P=0.617
Logistic regression test	P=0.538	P=0.236N	P=0.351N	P=0.477N
Cochran-Armitage test	P=0.501N			
Fisher exact test		P=0.239N	P=0.351N	P=0.365N
<b>Pituitary Gland (Pars Distalis): Adenoma</b>				
Overall rate	8/49 (16%)	3/49 (6%)	5/48 (10%)	3/50 (6%)
Adjusted rate	22.0%	8.8%	15.6%	14.3%
Terminal rate	4/31 (13%)	2/31 (6%)	4/30 (13%)	3/21 (14%)
First incidence (days)	589	646	654	736 (T)
Life table test	P=0.399N	P=0.107N	P=0.293N	P=0.242N
Logistic regression test	P=0.277N	P=0.098N	P=0.287N	P=0.152N
Cochran-Armitage test	P=0.189N			
Fisher exact test		P=0.100N	P=0.290N	P=0.094N
<b>Pituitary Gland (Pars Distalis): Adenoma or Carcinoma</b>				
Overall rate	8/49 (16%)	4/49 (8%)	6/48 (13%)	3/50 (6%)
Adjusted rate	22.0%	10.8%	17.5%	14.3%
Terminal rate	4/31 (13%)	2/31 (6%)	4/30 (13%)	3/21 (14%)
First incidence (days)	589	576	592	736 (T)
Life table test	P=0.337N	P=0.186N	P=0.401N	P=0.242N
Logistic regression test	P=0.194N	P=0.177N	P=0.402N	P=0.152N
Cochran-Armitage test	P=0.147N			
Fisher exact test		P=0.178N	P=0.403N	P=0.094N



TABLE D3

**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Thyroid Gland (Follicular Cell): Adenoma</b>				
Overall rate	1/49 (2%)	1/50 (2%)	6/50 (12%)	0/50 (0%)
Adjusted rate	2.6%	3.1%	18.2%	0.0%
Terminal rate	0/31 (0%)	1/32 (3%)	4/30 (13%)	0/21 (0%)
First incidence (days)	657	736 (T)	660	- <sup>e</sup>
Life table test	P=0.409N	P=0.754N	P=0.061	P=0.554N
Logistic regression test	P=0.339N	P=0.757N	P=0.062	P=0.493N
Cochran-Armitage test	P=0.268N			
Fisher exact test		P=0.747N	P=0.059	P=0.495N
<b>All Organs: Hemangioma or Hemangiosarcoma</b>				
Overall rate	1/50 (2%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rate	2.3%	9.9%	3.3%	3.8%
Terminal rate	0/31 (0%)	1/32 (3%)	1/30 (3%)	0/21 (0%)
First incidence (days)	598	503	736 (T)	695
Life table test	P=0.434N	P=0.193	P=0.757	P=0.720
Logistic regression test	P=0.311N	P=0.142	P=0.761	P=0.760N
Cochran-Armitage test	P=0.333N			
Fisher exact test		P=0.181	P=0.753N	P=0.753N
<b>All Organs: Histiocytic Sarcoma</b>				
Overall rate	4/50 (8%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	9.6%	2.9%	0.0%	0.0%
Terminal rate	0/31 (0%)	0/32 (0%)	0/30 (0%)	0/21 (0%)
First incidence (days)	396	688	-	-
Life table test	P=0.105N	P=0.184N	P=0.065N	P=0.083N
Logistic regression test	P=0.063N	P=0.239N	P=0.065N	P=0.045N
Cochran-Armitage test	P=0.088N			
Fisher exact test		P=0.181N	P=0.059N	P=0.059N
<b>All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)</b>				
Overall rate	13/50 (26%)	10/50 (20%)	5/50 (10%)	9/50 (18%)
Adjusted rate	33.8%	26.0%	13.7%	29.2%
Terminal rate	7/31 (23%)	5/32 (16%)	2/30 (7%)	3/21 (14%)
First incidence (days)	520	577	625	400
Life table test	P=0.483	P=0.313N	P=0.045N	P=0.503N
Logistic regression test	P=0.355N	P=0.307N	P=0.033N	P=0.250N
Cochran-Armitage test	P=0.341N			
Fisher exact test		P=0.318N	P=0.033N	P=0.235N
<b>All Organs: Malignant Lymphoma or Histiocytic Sarcoma</b>				
Overall rate	15/50 (30%)	11/50 (22%)	5/50 (10%)	9/50 (18%)
Adjusted rate	36.5%	28.2%	13.7%	29.2%
Terminal rate	7/31 (23%)	5/32 (16%)	2/30 (7%)	3/21 (14%)
First incidence (days)	396	577	625	400
Life table test	P=0.493N	P=0.252N	P=0.019N	P=0.337N
Logistic regression test	P=0.191N	P=0.264N	P=0.013N	P=0.109N
Cochran-Armitage test	P=0.210N			
Fisher exact test		P=0.247N	P=0.011N	P=0.121N

**TABLE D3**  
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene**  
 (continued)

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>All Organs: Benign Neoplasms</b>				
Overall rate	23/50 (46%)	22/50 (44%)	24/50 (48%)	13/50 (26%)
Adjusted rate	58.4%	62.4%	66.4%	47.1%
Terminal rate	15/31 (48%)	19/32 (59%)	18/30 (60%)	7/21 (33%)
First incidence (days)	589	633	654	621
Life table test	P=0.270N	P=0.455N	P=0.469	P=0.275N
Logistic regression test	P=0.093N	P=0.448N	P=0.547	P=0.087N
Cochran-Armitage test	P=0.013N			
Fisher exact test		P=0.500N	P=0.500	P=0.030N
<b>All Organs: Malignant Neoplasms</b>				
Overall rate	21/50 (42%)	22/50 (44%)	11/50 (22%)	12/50 (24%)
Adjusted rate	47.8%	48.7%	27.4%	39.5%
Terminal rate	9/31 (29%)	9/32 (28%)	4/30 (13%)	5/21 (24%)
First incidence (days)	396	503	411	400
Life table test	P=0.219N	P=0.533	P=0.048N	P=0.256N
Logistic regression test	P=0.007N	P=0.583	P=0.019N	P=0.045N
Cochran-Armitage test	P=0.025N			
Fisher exact test		P=0.500	P=0.026N	P=0.044N
<b>All Organs: Benign or Malignant Neoplasms</b>				
Overall rate	34/50 (68%)	37/50 (74%)	33/50 (66%)	20/50 (40%)
Adjusted rate	73.5%	80.3%	78.2%	61.0%
Terminal rate	19/31 (61%)	23/32 (72%)	21/30 (70%)	9/21 (43%)
First incidence (days)	396	340	411	400
Life table test	P=0.137N	P=0.434	P=0.522N	P=0.208N
Logistic regression test	P<0.001N	P=0.347	P=0.475N	P=0.008N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.330	P=0.500N	P=0.004N

(T) Terminal sacrifice

<sup>a</sup> Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for bone marrow, brain, clitoral gland, gallbladder, heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, salivary gland, spleen, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

<sup>b</sup> Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

<sup>c</sup> Observed incidence at terminal kill

<sup>d</sup> Beneath the control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.

<sup>e</sup> Not applicable; no neoplasms in animal group

**TABLE D4**  
**Historical Incidence of Thyroid Gland (Follicular Cell) Neoplasms in Untreated Female B6C3F<sub>1</sub> Mice<sup>a</sup>**

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
<b>Historical Incidence at Battelle Pacific Northwest Laboratories</b>			
1,3-Butadiene	1/50	0/50	1/50
Allyl glycidyl ether	2/50	0/50	2/50
2-Chloroacetophenone	0/49	0/49	0/49
Epinephrine hydrochloride	3/49	0/49	3/49
Ethyl chloride	0/48	0/48	0/48
<i>o</i> -Chlorobenzalmalononitrile	2/49	0/49	2/49
<b>Overall Historical Incidence</b>			
Total	15/602 (2.5%)	2/602 (0.3%)	17/602 (2.8%)
Standard deviation	2.3%	0.8%	2.3%
Range	0%-6%	0%-2%	0%-6%

<sup>a</sup> Data as of 20 August 1992

**TABLE D5**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Disposition Summary</b>				
Animals initially in study	60	60	60	60
<i>15-Month interim evaluation</i>	10	10	10	10
Early deaths				
Accidental deaths	1		1	1
Moribund	8	10	11	15
Natural deaths	10	8	8	13
Survivors				
Terminal sacrifice	31	32	30	21
Animals examined microscopically	60	60	60	60
<b>15-Month Interim Evaluation</b>				
<b>Alimentary System</b>				
Liver	(10)	(10)	(10)	(10)
Congestion				1 (10%)
Infiltration cellular, lymphocyte	1 (10%)			
Inflammation, subacute	1 (10%)	2 (20%)	1 (10%)	4 (40%)
Mesentery				(1)
Fat, necrosis				1 (100%)
<b>Cardiovascular System</b>				
None				
<b>Endocrine System</b>				
None				
<b>General Body System</b>				
None				
<b>Genital System</b>				
Ovary	(10)	(2)	(2)	(10)
Cyst	2 (20%)	2 (100%)	2 (100%)	1 (10%)
Uterus	(10)		(2)	(10)
Endometrium, hyperplasia			2 (100%)	1 (10%)
<b>Hematopoietic System</b>				
Lymph node, mandibular	(8)			(9)
Hyperplasia, lymphoid				1 (11%)
Spleen	(10)			(10)
Hyperplasia, lymphoid	1 (10%)			
<b>Integumentary System</b>				
Skin	(10)	(1)		(10)
Alopecia		1 (100%)		

**TABLE D5**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>15-Month Interim Evaluation (continued)</b>				
<b>Musculoskeletal System</b>				
None				
<b>Nervous System</b>				
Brain	(10)			(10)
Mineralization	3 (30%)			3 (30%)
<b>Respiratory System</b>				
Lung	(10)	(10)	(10)	(10)
Mucosa, pigmentation			4 (40%)	10 (100%)
Nose	(10)	(10)	(10)	(9)
Inflammation, suppurative		1 (10%)		8 (89%)
Mucosa, pigmentation		4 (40%)	10 (100%)	9 (100%)
Trachea	(10)	(10)	(10)	(10)
Inflammation, suppurative				1 (10%)
Mucosa, pigmentation			10 (100%)	10 (100%)
<b>Special Senses System</b>				
Eye				
Cornea, edema			(1) 1 (100%)	
<b>Urinary System</b>				
Kidney	(10)			(10)
Congestion				1 (10%)
Cyst	1 (10%)			
Infiltration cellular, lymphocyte	1 (10%)			
<b>2-Year Study</b>				
<b>Alimentary System</b>				
Gallbladder	(48)	(48)	(50)	(50)
Serosa, inflammation, subacute				1 (2%)
Intestine large, colon	(49)	(49)	(50)	(50)
Inflammation, suppurative				2 (4%)
Arteriole, inflammation, subacute			1 (2%)	
Intestine small, jejunum	(49)	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Peyer's patch, hyperplasia, lymphoid		1 (2%)	2 (4%)	1 (2%)
Intestine small, ileum	(49)	(50)	(50)	(50)
Peyer's patch, hyperplasia, lymphoid	1 (2%)		1 (2%)	

**TABLE D5**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Alimentary System (continued)</b>				
Liver	(49)	(50)	(50)	(50)
Angiectasis	2 (4%)			
Bacterium				1 (2%)
Cytoplasmic alteration	1 (2%)	2 (4%)		
Cytoplasmic alteration, focal				2 (4%)
Focal cellular change		1 (2%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation		3 (6%)	2 (4%)	6 (12%)
Hyperplasia, nodular		2 (4%)	1 (2%)	
Infiltration cellular, lymphocyte	1 (2%)	3 (6%)	1 (2%)	
Inflammation, chronic		1 (2%)		
Inflammation, necrotizing		1 (2%)		
Inflammation, subacute	4 (8%)		1 (2%)	4 (8%)
Inflammation, suppurative	1 (2%)			
Mineralization		1 (2%)		
Necrosis, acute	1 (2%)	2 (4%)	1 (2%)	
Pigmentation	1 (2%)			
Centrilobular, necrosis	1 (2%)			
Serosa, inflammation, suppurative				1 (2%)
Mesentery	(7)	(4)	(6)	(2)
Inflammation, suppurative	1 (14%)		1 (17%)	
Fat, necrosis	4 (57%)	1 (25%)	5 (83%)	2 (100%)
Pancreas	(49)	(50)	(50)	(50)
Amyloid deposition			1 (2%)	
Inflammation, subacute			1 (2%)	
Inflammation, suppurative			2 (4%)	3 (6%)
Acinar cell, hypoplasia				1 (2%)
Stomach, forestomach	(49)	(50)	(50)	(50)
Hyperkeratosis	3 (6%)	1 (2%)		5 (10%)
Hyperplasia, squamous		1 (2%)	1 (2%)	3 (6%)
Serosa, fibrosis				1 (2%)
Serosa, inflammation, suppurative		1 (2%)		
Stomach, glandular	(49)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Hyperplasia	2 (4%)			
Mineralization	1 (2%)		2 (4%)	
Necrosis	2 (4%)	1 (2%)	2 (4%)	2 (4%)
<b>Cardiovascular System</b>				
Heart	(49)	(50)	(50)	(50)
Arteriole, inflammation, subacute			1 (2%)	
Atrium, thrombosis			1 (2%)	

**TABLE D5**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Endocrine System</b>				
Adrenal cortex	(49)	(50)	(50)	(50)
Amyloid deposition				1 (2%)
Hyperplasia	1 (2%)			
Mineralization				1 (2%)
Adrenal medulla	(49)	(50)	(50)	(49)
Amyloid deposition				1 (2%)
Pituitary gland	(49)	(49)	(48)	(50)
Congestion	1 (2%)			
Cyst				1 (2%)
Hyperplasia		5 (10%)	7 (15%)	3 (6%)
Hypertrophy	4 (8%)			
Inflammation, suppurative				1 (2%)
Thyroid gland	(49)	(50)	(50)	(50)
Cyst	1 (2%)			
Inflammation, subacute	1 (2%)			
Follicular cell, hyperplasia	9 (18%)	14 (28%)	16 (32%)	14 (28%)
<b>General Body System</b>				
None				
<b>Genital System</b>				
Ovary	(49)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Cyst	6 (12%)	16 (32%)	11 (22%)	9 (18%)
Hemorrhage		1 (2%)		
Inflammation, subacute	1 (2%)			1 (2%)
Inflammation, suppurative		3 (6%)	6 (12%)	17 (34%)
Mineralization	1 (2%)			
Pigmentation				1 (2%)
Granulosa cell, hyperplasia		1 (2%)		
Uterus	(49)	(50)	(49)	(50)
Angiectasis			1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, suppurative	1 (2%)		2 (4%)	4 (8%)
Endometrium, hyperplasia	10 (20%)	7 (14%)	5 (10%)	4 (8%)
<b>Hematopoietic System</b>				
Bone marrow	(49)	(50)	(50)	(50)
Hyperplasia, neutrophil		1 (2%)		
Lymph node	(7)	(8)	(5)	(5)
Iliac, hyperplasia, lymphoid			1 (20%)	
Renal, congestion		1 (13%)		
Renal, hyperplasia, lymphoid		1 (13%)	1 (20%)	
Renal, inflammation, suppurative				1 (20%)
Lymph node, bronchial	(47)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	2 (4%)	2 (4%)	4 (8%)	2 (4%)
Hyperplasia, plasma cell			1 (2%)	
Inflammation, suppurative		1 (2%)		

**TABLE D5**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Hematopoietic System (continued)</b>				
Lymph node, mandibular	(42)	(44)	(47)	(48)
Hyperplasia, lymphoid	2 (5%)			6 (13%)
Hyperplasia, mast cell				1 (2%)
Lymph node, mesenteric	(49)	(49)	(48)	(50)
Congestion		1 (2%)		
Hyperplasia, lymphoid	6 (12%)	3 (6%)	5 (10%)	2 (4%)
Inflammation, suppurative				1 (2%)
Thrombosis		1 (2%)		
Lymph node, mediastinal	(49)	(48)	(48)	(50)
Hyperplasia, lymphoid		1 (2%)	2 (4%)	4 (8%)
Hyperplasia, plasma cell			1 (2%)	
Inflammation, suppurative		1 (2%)	2 (4%)	3 (6%)
Pigmentation		1 (2%)		
Spleen	(49)	(50)	(50)	(50)
Developmental malformation		1 (2%)		
Hematopoietic cell proliferation	3 (6%)	6 (12%)	7 (14%)	17 (34%)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	5 (10%)	4 (8%)	6 (12%)	
Inflammation, suppurative	1 (2%)			1 (2%)
Capsule, inflammation, subacute				1 (2%)
<b>Integumentary System</b>				
Mammary gland	(48)	(47)	(44)	(43)
Duct, dilatation			1 (2%)	
Skin	(49)	(49)	(49)	(49)
Alopecia	2 (4%)		2 (4%)	
Hemorrhage, acute		1 (2%)		
Inflammation, suppurative	1 (2%)		1 (2%)	
Subcutaneous tissue, mineralization		1 (2%)		
<b>Musculoskeletal System</b>				
Bone	(49)	(50)	(50)	(50)
Developmental malformation			1 (2%)	1 (2%)
Fibrous osteodystrophy	1 (2%)			
Fracture			1 (2%)	
<b>Nervous System</b>				
Brain	(49)	(50)	(50)	(50)
Bacterium				1 (2%)
Compression			1 (2%)	
Inflammation, suppurative				1 (2%)
Mineralization	9 (18%)	8 (16%)	4 (8%)	4 (8%)



**TABLE D5**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>2-Year Study (continued)</b>				
<b>Respiratory System</b>				
Lung	(48)	(50)	(50)	(49)
Bacterium				1 (2%)
Congestion	2 (4%)	1 (2%)		
Hyperplasia, macrophage		1 (2%)		
Infiltration cellular, lymphocyte	1 (2%)	4 (8%)	3 (6%)	1 (2%)
Infiltration cellular, histiocyte				1 (2%)
Inflammation, subacute		1 (2%)	1 (2%)	2 (4%)
Inflammation, suppurative	1 (2%)			2 (4%)
Alveolar epithelium, hyperplasia	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Mucosa, pigmentation			27 (54%)	44 (90%)
Pleura, inflammation, suppurative				2 (4%)
Nose	(49)	(50)	(50)	(48)
Inflammation, subacute			1 (2%)	
Inflammation, suppurative	4 (8%)		3 (6%)	40 (83%)
Mucosa, pigmentation		40 (80%)	48 (96%)	41 (85%)
Trachea	(49)	(50)	(48)	(47)
Inflammation, suppurative				1 (2%)
Mucosa, pigmentation		6 (12%)	43 (90%)	42 (89%)
<b>Special Senses System</b>				
Eye	(1)	(1)	(1)	
Atrophy		1 (100%)		
Cornea, hyperplasia			1 (100%)	
Cornea, inflammation, suppurative	1 (100%)			
Harderian gland	(7)	(6)	(4)	(1)
Cyst	1 (14%)			
Inflammation, suppurative	1 (14%)			1 (100%)
<b>Urinary System</b>				
Kidney	(49)	(50)	(50)	(50)
Amyloid deposition	1 (2%)		1 (2%)	
Bacterium				1 (2%)
Casts	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocyte	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic			1 (2%)	
Inflammation, subacute	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Metaplasia, osseous		1 (2%)	1 (2%)	
Mineralization			1 (2%)	
Nephropathy, chronic	1 (2%)	1 (2%)		2 (4%)
Pelvis, dilatation	2 (4%)			
Renal tubule, degeneration, hyaline		2 (4%)		
Urinary bladder	(48)	(50)	(50)	(48)
Infiltration cellular, lymphocyte		1 (2%)		

<sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

## APPENDIX E

### SUMMARY OF LESIONS IN MALE MICE IN THE STOP-EXPOSURE EVALUATION OF HEXACHLOROCYCLOPENTADIENE

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**TABLE E1**  
**Summary of the Incidence of Neoplasms in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>Disposition Summary</b>						
Animals initially in study	90 <sup>b</sup>	60	80	50	90	70
<i>27-Week interim evaluation<sup>c</sup></i>	10				10	
<i>34-Week interim evaluation<sup>d</sup></i>	10		10		10	
<i>43-Week interim evaluation<sup>e</sup></i>	10		10		10	10
<i>15-Month interim evaluation</i>	10	10	10		10	10
Early deaths						
Accidental deaths	1		1	1		
Moribund	8	9	7	6	5	10
Natural deaths	6	7	7	10	4	7
Survivors						
Terminal sacrifice	35	34	35	33	41	33
Animals examined microscopically	90	60	80	50	90	70
<b>43-Week Interim Evaluation</b>						
<b>Alimentary System</b>						
Liver	(10)		(10)		(10)	(10)
Hepatocellular adenoma	1 (10%)					1 (10%)
<b>Respiratory System</b>						
Lung	(10)		(10)		(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)		1 (10%)			
<b>15-Month Interim Evaluation</b>						
<b>Alimentary System</b>						
Liver	(10)	(10)				
Hepatocellular carcinoma	2 (20%)					
Hepatocellular adenoma	3 (30%)	1 (10%)				
<b>Cardiovascular System</b>						
None						
<b>Endocrine System</b>						
Islets, pancreatic	(10)	(10)				
Adenoma	1 (10%)					
<b>General Body System</b>						
None						
<b>Genital System</b>						
None						

**TABLE E1**  
**Summary of the Incidence of Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene** (continued)

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>15-Month Interim Evaluation</b> (continued)						
<b>Hematopoietic System</b>						
None						
<b>Integumentary System</b>						
None						
<b>Musculoskeletal System</b>						
None						
<b>Nervous System</b>						
None						
<b>Respiratory System</b>						
Lung	(10)	(10)	(8)		(9)	(10)
Alveolar/bronchiolar adenoma	1 (10%)				2 (22%)	
Alveolar/bronchiolar adenoma, multiple		1 (10%)				
Alveolar/bronchiolar carcinoma		1 (10%)				1 (10%)
<b>Special Senses System</b>						
None						
<b>Urinary System</b>						
Urinary bladder		(10)				
<b>Systemic Lesions</b>						
Multiple organs <sup>f</sup>		(10)				
<b>2-Year Study</b>						
<b>Alimentary System</b>						
Intestine small, duodenum	(50)	(49)				
Intestine small, jejunum	(50)	(50)				
Adenocarcinoma	1 (2%)	1 (2%)				
Intestine small, ileum	(50)	(50)				
Liver	(50)	(50)	(1)			
Hemangiosarcoma		2 (4%)				
Hepatocellular carcinoma	7 (14%)	9 (18%)	1 (100%)			
Hepatocellular carcinoma, multiple		1 (2%)				
Hepatocellular carcinoma, two		1 (2%)				
Hepatocellular adenoma	19 (38%)	10 (20%)				
Hepatocellular adenoma, two		1 (2%)				
Mesentery	(4)	(2)				

**TABLE E1**  
**Summary of the Incidence of Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>2-Year Study (continued)</b>						
<b>Alimentary System (continued)</b>						
Stomach, forestomach	(50)	(50)				
Squamous cell papilloma		1 (2%)				
<b>Cardiovascular System</b>						
Heart	(50)	(50)				
<b>Endocrine System</b>						
Adrenal cortex	(49)	(50)				
Adrenal medulla	(49)	(50)				
Pheochromocytoma NOS		1 (2%)				
Pituitary gland	(49)	(49)				
Carcinoma	1 (2%)					
Thyroid gland	(48)	(50)	(47)	(45)	(49)	(40)
Follicular cell, adenoma	1 (2%)	2 (4%)	2 (4%)	2 (4%)	1 (2%)	
<b>General Body System</b>						
None						
<b>Genital System</b>						
Epididymis	(50)	(50)				
Testes	(50)	(50)				
Interstitial cell, adenoma		1 (2%)				
<b>Hematopoietic System</b>						
Bone marrow	(50)	(50)	(39)	(35)		
Mast cell tumor NOS			1 (3%)			
Lymph node	(1)	(2)				
Lymph node, bronchial	(48)	(50)	(50)	(48)	(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)		1 (2%)
Lymph node, mandibular	(41)	(43)				
Lymph node, mesenteric	(48)	(49)				
Lymph node, mediastinal	(46)	(50)	(44)	(44)	(46)	(43)
Alveolar/bronchiolar carcinoma, metastatic, lung						1 (2%)
Spleen	(50)	(50)				
Thymus	(47)	(50)	(48)	(46)		
<b>Integumentary System</b>						
Skin	(50)	(50)	(48)	(46)	(48)	(36)
Papilloma		1 (2%)				

**TABLE E1**  
**Summary of the Incidence of Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>2-Year Study (continued)</b>						
<b>Musculoskeletal System</b>						
None						
<b>Nervous System</b>						
None						
<b>Respiratory System</b>						
Larynx	(50)	(50)	(50)	(49)		
Lung	(49)	(50)	(50)	(49)	(50)	(50)
Alveolar/bronchiolar adenoma	11 (22%)	12 (24%)	9 (18%)	14 (29%)	9 (18%)	10 (20%)
Alveolar/bronchiolar adenoma, multiple		3 (6%)		1 (2%)	1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)	4 (8%)	1 (2%)	5 (10%)	6 (12%)
Alveolar/bronchiolar carcinoma, multiple				1 (2%)		
Hepatocellular carcinoma, metastatic, liver	3 (6%)	3 (6%)	2 (4%)			
Nose	(50)	(50)	(50)	(49)		
Trachea	(50)	(50)	(50)	(49)		
<b>Special Senses System</b>						
Harderian gland	(7)	(2)	(4)	(3)	(4)	(3)
Adenoma	7 (100%)	2 (100%)	4 (100%)	3 (100%)	4 (100%)	1 (33%)
Carcinoma						1 (33%)
<b>Urinary System</b>						
Kidney	(50)	(50)				
Urinary bladder	(50)	(50)				
<b>Systemic Lesions</b>						
Multiple organs	(50)	(50)	(50)	(50)	(50)	(50)
Lymphoma malignant histiocytic		2 (4%)	1 (2%)	1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)				
Lymphoma malignant mixed	2 (4%)	2 (4%)		3 (6%)	1 (2%)	
<b>Neoplasm Summary</b>						
Total animals with primary neoplasms <sup>g</sup>						
43-Week interim evaluation	2		1			1
15-Month interim evaluation	7				2	1
2-Year study	35	33	20	24	18	15
Total primary neoplasms						
43-Week interim evaluation	2		1			1
15-Month interim evaluation	7				2	1
2-Year study	49	54	22	26	22	18

**TABLE E1**  
**Summary of the Incidence of Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>Neoplasm Summary (continued)</b>						
Total animals with benign neoplasms						
43-Week interim evaluation	2		1			1
15-Month interim evaluation	5				2	
2-Year study	29	25	14	18	13	11
Total benign neoplasms						
43-Week interim evaluation	2		1			1
15-Month interim evaluation	5				2	
2-Year study	38	33	15	20	15	11
Total animals with malignant neoplasms						
15-Month interim evaluation	2					1
2-Year study	11	17	6	6	6	7
Total malignant neoplasms						
15-Month interim evaluation	2					1
2-Year study	11	20	6	6	7	7
Total animals with metastatic neoplasms						
2-Year study	3	3	2	1		1
Total metastatic neoplasms						
2-Year study	3	3	2	1		2
Total animals with uncertain neoplasms benign or malignant						
2-Year study		1	1			
Total uncertain neoplasms						
2-Year study		1	1			

- <sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion  
<sup>b</sup> Includes 60 controls from the core study  
<sup>c</sup> No neoplasms were observed at any site in any animal at the 27-week interim evaluation.  
<sup>d</sup> No neoplasms were observed at any site in any animal at the 34-week interim evaluation.  
<sup>e</sup> No neoplasms were observed at any other site in any animal at the 43-week interim evaluation.  
<sup>f</sup> Number of animals with any tissue examined microscopically  
<sup>g</sup> Primary neoplasms: all neoplasms except metastatic neoplasms

**TABLE E2a**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene: 0 ppm versus 0.2 ppm for 33, 66, or 104 Weeks**

	0 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.2 ppm (104 weeks)
<b>Harderian Gland: Adenoma</b>				
Overall rate <sup>a</sup>	7/50 (14%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted rate <sup>b</sup>	19.0%	11.0%	8.5%	5.6%
Terminal rate <sup>c</sup>	6/35 (17%)	3/35 (9%)	2/33 (6%)	1/34 (3%)
First incidence (days)	627	696	654	715
Life table test <sup>d</sup>	P=0.051N	P=0.263N	P=0.187N	P=0.090N
Logistic regression test <sup>d</sup>	P=0.048N	P=0.260N	P=0.178N	P=0.086N
Cochran-Armitage test <sup>d</sup>	P=0.043N			
Fisher exact test <sup>d</sup>		P=0.262N	P=0.159N	P=0.080N
<b>Lung: Alveolar/bronchiolar Adenoma</b>				
Overall rate	11/49 (22%)	9/50 (18%)	15/49 (31%)	15/50 (30%)
Adjusted rate	31.3%	23.1%	43.8%	37.5%
Terminal rate	10/34 (29%)	6/35 (17%)	14/33 (42%)	10/34 (29%)
First incidence (days)	689	626	622	393
Life table test	P=0.103	P=0.379N	P=0.207	P=0.253
Logistic regression test	P=0.104	P=0.376N	P=0.191	P=0.261
Cochran-Armitage test	P=0.119			
Fisher exact test		P=0.382N	P=0.246	P=0.266
<b>Lung: Alveolar/bronchiolar Carcinoma</b>				
Overall rate	0/49 (0%)	4/50 (8%)	2/49 (4%)	1/50 (2%)
Adjusted rate	0.0%	10.5%	5.8%	2.9%
Terminal rate	0/34 (0%)	3/35 (9%)	1/33 (3%)	1/34 (3%)
First incidence (days)	- <sup>e</sup>	542	704	730 (T)
Life table test	P=0.519	P=0.068	P=0.230	P=0.500
Logistic regression test	P=0.529	P=0.065	P=0.229	P=0.500
Cochran-Armitage test	P=0.533			
Fisher exact test		P=0.061	P=0.247	P=0.505
<b>Lung: Alveolar/bronchiolar Adenoma or Carcinoma</b>				
Overall rate	11/49 (22%)	13/50 (26%)	17/49 (35%)	16/50 (32%)
Adjusted rate	31.3%	32.5%	48.3%	40.1%
Terminal rate	10/34 (29%)	9/35 (26%)	15/33 (45%)	11/34 (32%)
First incidence (days)	689	542	622	393
Life table test	P=0.103	P=0.436	P=0.104	P=0.190
Logistic regression test	P=0.104	P=0.439	P=0.091	P=0.195
Cochran-Armitage test	P=0.119			
Fisher exact test		P=0.430	P=0.132	P=0.200
<b>All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)</b>				
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	4.9%	2.9%	9.6%	12.6%
Terminal rate	0/35 (0%)	1/35 (3%)	0/33 (0%)	2/34 (6%)
First incidence (days)	627	730 (T)	526	435
Life table test	P=0.073	P=0.503N	P=0.312	P=0.214
Logistic regression test	P=0.071	P=0.500N	P=0.371	P=0.209
Cochran-Armitage test	P=0.074			
Fisher exact test		P=0.500N	P=0.339	P=0.218



**TABLE E2a**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene: 0 ppm versus 0.2 ppm for 33, 66, or 104 Weeks (continued)**

	0 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.2 ppm (104 weeks)
<b>All Organs: Benign Neoplasms</b>				
Overall rate	29/50 (58%)	14/50 (28%)	18/50 (36%)	25/50 (50%)
Adjusted rate	72.2%	35.4%	51.0%	60.5%
Terminal rate	24/35 (69%)	10/35 (29%)	16/33 (48%)	18/34 (53%)
First incidence (days)	626	626	622	393
Life table test	P=0.442N	P=0.003N	P=0.040N	P=0.334N
Logistic regression test	P=0.426N	P=0.002N	P=0.034N	P=0.295N
Cochran-Armitage test	P=0.367N			
Fisher exact test		P=0.002N	P=0.022N	P=0.274N
<b>All Organs: Malignant Neoplasms</b>				
Overall rate	11/50 (22%)	6/50 (12%)	6/50 (12%)	17/50 (34%)
Adjusted rate	26.6%	15.3%	14.9%	37.9%
Terminal rate	5/35 (14%)	4/35 (11%)	1/33 (3%)	7/34 (21%)
First incidence (days)	627	542	526	393
Life table test	P=0.079	P=0.161N	P=0.201N	P=0.153
Logistic regression test	P=0.074	P=0.141N	P=0.138N	P=0.132
Cochran-Armitage test	P=0.073			
Fisher exact test		P=0.143N	P=0.143N	P=0.133
<b>All Organs: Benign or Malignant Neoplasms</b>				
Overall rate	35/50 (70%)	20/50 (40%)	24/50 (48%)	33/50 (66%)
Adjusted rate	79.5%	48.2%	59.5%	71.4%
Terminal rate	26/35 (74%)	14/35 (40%)	17/33 (52%)	21/34 (62%)
First incidence (days)	626	542	526	393
Life table test	P=0.488	P=0.007N	P=0.076N	P=0.491N
Logistic regression test	P=0.505	P=0.002N	P=0.030N	P=0.415N
Cochran-Armitage test	P=0.523N			
Fisher exact test		P=0.002N	P=0.021N	P=0.415N

(T)Terminal sacrifice

- <sup>a</sup> Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for larynx, lung, nose, and trachea; for other tissues, denominator is number of animals necropsied.
- <sup>b</sup> Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
- <sup>c</sup> Observed incidence at terminal kill
- <sup>d</sup> Beneath the control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
- <sup>e</sup> Not applicable; no neoplasms in animal group

**TABLE E2b**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene: 0 ppm versus 0.5 ppm for 26 or 42 Weeks**

	0 ppm	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>Harderian Gland: Adenoma</b>			
Overall rate <sup>a</sup>	7/50 (14%)	4/50 (8%)	1/50 (2%)
Adjusted rate <sup>b</sup>	19.0%	9.8%	3.0%
Terminal rate <sup>c</sup>	6/35 (17%)	4/41 (10%)	1/33 (3%)
First incidence (days)	627	729 (T)	729 (T)
Life table test <sup>d</sup>	P=0.024N	P=0.185N	P=0.041N
Logistic regression test <sup>d</sup>	P=0.032N	P=0.222N	P=0.048N
Cochran-Armitage test <sup>d</sup>	P=0.025N		
Fisher exact test <sup>d</sup>		P=0.262N	P=0.030N
<b>Harderian Gland: Adenoma or Carcinoma</b>			
Overall rate	7/50 (14%)	4/50 (8%)	2/50 (4%)
Adjusted rate	19.0%	9.8%	6.1%
Terminal rate	6/35 (17%)	4/41 (10%)	2/33 (6%)
First incidence (days)	627	729 (T)	729 (T)
Life table test	P=0.058N	P=0.185N	P=0.099N
Logistic regression test	P=0.073N	P=0.222N	P=0.115N
Cochran-Armitage test	P=0.058N		
Fisher exact test		P=0.262N	P=0.080N
<b>Lung: Alveolar/bronchiolar Adenoma</b>			
Overall rate	11/49 (22%)	10/50 (20%)	10/50 (20%)
Adjusted rate	31.3%	24.4%	29.2%
Terminal rate	10/34 (29%)	10/41 (24%)	9/33 (27%)
First incidence (days)	689	729 (T)	647
Life table test	P=0.453N	P=0.312N	P=0.540N
Logistic regression test	P=0.516N	P=0.333N	P=0.596
Cochran-Armitage test	P=0.433N		
Fisher exact test		P=0.479N	P=0.479N
<b>Lung: Alveolar/bronchiolar Carcinoma</b>			
Overall rate	0/49 (0%)	5/50 (10%)	6/50 (12%)
Adjusted rate	0.0%	11.9%	16.7%
Terminal rate	0/34 (0%)	4/41 (10%)	4/33 (12%)
First incidence (days)	- <sup>e</sup>	725	395
Life table test	P=0.013	P=0.053	P=0.015
Logistic regression test	P=0.012	P=0.050	P=0.016
Cochran-Armitage test	P=0.016		
Fisher exact test		P=0.030	P=0.014
<b>Lung: Alveolar/bronchiolar Adenoma or Carcinoma</b>			
Overall rate	11/49 (22%)	14/50 (28%)	14/50 (28%)
Adjusted rate	31.3%	33.3%	38.5%
Terminal rate	10/34 (29%)	13/41 (32%)	11/33 (33%)
First incidence (days)	689	725	395
Life table test	P=0.263	P=0.529	P=0.275
Logistic regression test	P=0.190	P=0.505	P=0.215
Cochran-Armitage test	P=0.298		
Fisher exact test		P=0.343	P=0.343

**TABLE E2b**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene: 0 ppm versus 0.5 ppm for 26 or 42 Weeks (continued)**

	0 ppm	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>All Organs: Benign Neoplasms</b>			
Overall rate	29/50 (58%)	13/50 (26%)	11/50 (22%)
Adjusted rate	72.2%	31.7%	32.2%
Terminal rate	24/35 (69%)	13/41 (32%)	10/33 (30%)
First incidence (days)	626	729 (T)	647
Life table test	P<0.001N	P<0.001N	P<0.001N
Logistic regression test	P<0.001N	P<0.001N	P=0.001N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.001N	P<0.001N
<b>All Organs: Malignant Neoplasms</b>			
Overall rate	11/50 (22%)	6/50 (12%)	7/50 (14%)
Adjusted rate	26.6%	13.8%	19.6%
Terminal rate	5/35 (14%)	4/41 (10%)	5/33 (15%)
First incidence (days)	627	612	395
Life table test	P=0.183N	P=0.100N	P=0.296N
Logistic regression test	P=0.179N	P=0.130N	P=0.279N
Cochran-Armitage test	P=0.149N		
Fisher exact test		P=0.143N	P=0.218N
<b>All Organs: Benign or Malignant Neoplasms</b>			
Overall rate	35/50 (70%)	18/50 (36%)	15/50 (30%)
Adjusted rate	79.5%	41.8%	41.3%
Terminal rate	26/35 (74%)	16/41 (39%)	12/33 (36%)
First incidence (days)	626	612	395
Life table test	P<0.001N	P<0.001N	P<0.001N
Logistic regression test	P<0.001N	P<0.001N	P<0.001N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P<0.001N	P<0.001N

(T) Terminal sacrifice

- <sup>a</sup> Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for larynx, lung, nose, and trachea; for other tissues, denominator is number of animals necropsied.
- <sup>b</sup> Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
- <sup>c</sup> Observed incidence at terminal kill
- <sup>d</sup> Beneath the control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
- <sup>e</sup> Not applicable; no neoplasms in animal group

**TABLE E2c**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene: 66-Week 0.2 ppm Group versus 26-Week 0.5 ppm Group**

	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)
<b>Harderian Gland: Adenoma</b>		
Overall rate <sup>a</sup>	3/50 (6%)	4/50 (8%)
Adjusted rate <sup>b</sup>	8.5%	9.8%
Terminal rate <sup>c</sup>	2/33 (6%)	4/41 (10%)
First incidence (days)	654	729 (T)
Life table test <sup>d</sup>		P=0.613
Logistic regression test <sup>d</sup>		P=0.559
Fisher exact test <sup>d</sup>		P=0.500
<b>Lung: Alveolar/bronchiolar Adenoma</b>		
Overall rate	15/49 (31%)	10/50 (20%)
Adjusted rate	43.8%	24.4%
Terminal rate	14/33 (42%)	10/41 (24%)
First incidence (days)	622	729 (T)
Life table test		P=0.055N
Logistic regression test		P=0.065N
Fisher exact test		P=0.163N
<b>Lung: Alveolar/bronchiolar Carcinoma</b>		
Overall rate	2/49 (4%)	5/50 (10%)
Adjusted rate	5.8%	11.9%
Terminal rate	1/33 (3%)	4/41 (10%)
First incidence (days)	704	725
Life table test		P=0.314
Logistic regression test		P=0.213
Fisher exact test		P=0.226
<b>Lung: Alveolar/bronchiolar Adenoma or Carcinoma</b>		
Overall rate	17/49 (35%)	14/50 (28%)
Adjusted rate	48.3%	33.3%
Terminal rate	15/33 (45%)	13/41 (32%)
First incidence (days)	622	725
Life table test		P=0.122N
Logistic regression test		P=0.177N
Fisher exact test		P=0.308N
<b>All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)</b>		
Overall rate	4/50 (8%)	2/50 (4%)
Adjusted rate	9.6%	4.6%
Terminal rate	0/33 (0%)	1/41 (2%)
First incidence (days)	526	612
Life table test		P=0.285N
Logistic regression test		P=0.533N
Fisher exact test		P=0.339N

**TABLE E2c**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene: 66-Week 0.2 ppm Group versus 26-Week 0.5 ppm Group (continued)**

	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)
<b>All Organs: Benign Neoplasms</b>		
Overall rate	18/50 (36%)	14/50 (28%)
Adjusted rate	51.0%	34.1%
Terminal rate	16/33 (48%)	14/41 (34%)
First incidence (days)	622	729 (T)
Life table test		P=0.077N
Logistic regression test		P=0.102N
Fisher exact test		P=0.260N
<b>All Organs: Malignant Neoplasms</b>		
Overall rate	6/50 (12%)	6/50 (12%)
Adjusted rate	14.9%	13.8%
Terminal rate	1/33 (3%)	4/41 (10%)
First incidence (days)	526	612
Life table test		P=0.496N
Logistic regression test		P=0.461
Fisher exact test		P=0.620N
<b>All Organs: Benign or Malignant Neoplasms</b>		
Overall rate	24/50 (48%)	19/50 (38%)
Adjusted rate	59.5%	44.1%
Terminal rate	17/33 (52%)	17/41 (41%)
First incidence (days)	526	612
Life table test		P=0.057N
Logistic regression test		P=0.141N
Fisher exact test		P=0.210N

(T)Terminal sacrifice

<sup>a</sup> Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for larynx, lung, nose, and trachea; for other tissues, denominator is number of animals necropsied.

<sup>b</sup> Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

<sup>c</sup> Observed incidence at terminal kill

<sup>d</sup> Beneath the 26-week exposure group incidence are the P values corresponding to pairwise comparison with the 66-week exposure group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in an exposure group is indicated by N.

**TABLE E2d**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene: 104-Week 0.2 ppm Group versus 42-Week 0.5 ppm Group**

	0.2 ppm (104 weeks)	0.5 ppm (42 weeks)
<b>Lung: Alveolar/bronchiolar Adenoma</b>		
Overall rate <sup>a</sup>	15/50 (30%)	10/50 (20%)
Adjusted rate <sup>b</sup>	37.5%	29.2%
Terminal rate <sup>c</sup>	10/34 (29%)	9/33 (27%)
First incidence (days)	393	647
Life table test <sup>d</sup>		P=0.226N
Logistic regression test <sup>d</sup>		P=0.336N
Fisher exact test <sup>d</sup>		P=0.178N
<b>Lung: Alveolar/bronchiolar Carcinoma</b>		
Overall rate	1/50 (2%)	6/50 (12%)
Adjusted rate	2.9%	16.7%
Terminal rate	1/34 (3%)	4/33 (12%)
First incidence (days)	729 (T)	395
Life table test		P=0.051
Logistic regression test		P=0.028
Fisher exact test		P=0.056
<b>Lung: Alveolar/bronchiolar Adenoma or Carcinoma</b>		
Overall rate	16/50 (32%)	14/50 (28%)
Adjusted rate	40.1%	38.5%
Terminal rate	11/34 (32%)	11/33 (33%)
First incidence (days)	393	395
Life table test		P=0.487N
Logistic regression test		P=0.500
Fisher exact test		P=0.414N
<b>All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)</b>		
Overall rate	4/50 (8%)	0/50 (0%)
Adjusted rate	9.8%	0.0%
Terminal rate	1/34 (3%)	0/33 (0%)
First incidence (days)	435	- <sup>e</sup>
Life table test		P=0.080N
Logistic regression test		P=0.143N
Fisher exact test		P=0.059N
<b>All Organs: Benign Neoplasms</b>		
Overall rate	25/50 (50%)	12/50 (24%)
Adjusted rate	62.2%	34.2%
Terminal rate	18/34 (53%)	10/33 (30%)
First incidence (days)	393	647
Life table test		P=0.007N
Logistic regression test		P=0.016N
Fisher exact test		P=0.002N

**TABLE E2d**  
**Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene: 104-Week 0.2 ppm Group versus 42-Week 0.5 ppm Group (continued)**

	0.2 ppm (104 weeks)	0.5 ppm (42 weeks)
<b>All Organs: Malignant Neoplasms</b>		
Overall rate	17/50 (34%)	8/50 (16%)
Adjusted rate	37.9%	22.5%
Terminal rate	7/34 (21%)	6/33 (18%)
First incidence (days)	393	395
Life table test		P=0.071N
Logistic regression test		P=0.162N
Fisher exact test		P=0.032N
<b>All Organs: Benign or Malignant Neoplasms</b>		
Overall rate	34/50 (68%)	17/50 (34%)
Adjusted rate	72.0%	45.8%
Terminal rate	21/34 (62%)	13/33 (39%)
First incidence (days)	393	395
Life table test		P=0.007N
Logistic regression test		P=0.016N
Fisher exact test		P<0.001N

(T)Terminal sacrifice

- <sup>a</sup> Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for larynx, lung, nose, and trachea; for other tissues, denominator is number of animals necropsied.
- <sup>b</sup> Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
- <sup>c</sup> Observed incidence at terminal kill
- <sup>d</sup> Beneath the 42-week exposure group incidence are the P values corresponding to pairwise comparison with the 104-week exposure group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in an exposure group is indicated by N.
- <sup>e</sup> Not applicable; no neoplasms in animal group

**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>Disposition Summary</b>						
Animals initially in study	90 <sup>b</sup>	60	80	50	90	70
<i>27-Week interim evaluation</i>	10				10	
<i>34-Week interim evaluation</i>	10		10		10	
<i>43-Week interim evaluation</i>	10		10		10	10
<i>15-Month interim evaluation</i>	10	10	10		10	10
Early deaths						
Accidental deaths	1		1	1		
Moribund	8	9	7	6	5	10
Natural deaths	6	7	7	10	4	7
Survivors						
Terminal sacrifice	35	34	35	33	41	33
Animals examined microscopically	90	60	80	50	90	70
<b><i>27-Week Interim Evaluation</i></b>						
<b>Alimentary System</b>						
None						
<b>Cardiovascular System</b>						
None						
<b>Endocrine System</b>						
None						
<b>General Body System</b>						
None						
<b>Genital System</b>						
None						
<b>Hematopoietic System</b>						
None						
<b>Integumentary System</b>						
None						
<b>Musculoskeletal System</b>						
None						



**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>27-Week Interim Evaluation (continued)</b>						
<b>Nervous System</b>						
None						
<b>Respiratory System</b>						
Lung	(10)				(10)	
Inflammation, subacute					1 (10%)	
Mucosa, pigmentation					9 (90%)	
Nose	(10)				(10)	
Inflammation, suppurative					10 (100%)	
Mucosa, pigmentation					3 (30%)	
Trachea	(10)				(10)	
Inflammation, suppurative					1 (10%)	
Mucosa, pigmentation					10 (100%)	
<b>Special Senses System</b>						
None						
<b>Urinary System</b>						
Kidney		(1)				
Renal tubule, cytoplasmic alteration		1 (100%)				
<b>34-Week Interim Evaluation</b>						
<b>Alimentary System</b>						
Liver	(10)		(10)		(10)	
Congestion					1 (10%)	
Stomach, forestomach	(10)		(10)		(10)	
Congestion			1 (10%)		1 (10%)	
Stomach, glandular	(9)		(10)		(10)	
Congestion			1 (10%)		1 (10%)	
<b>Cardiovascular System</b>						
None						
<b>Endocrine System</b>						
None						
<b>General Body System</b>						
None						

**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>34-Week Interim Evaluation (continued)</b>						
<b>Genital System</b>						
Testes	(10)		(10)		(10)	
Atrophy	1 (10%)		1 (10%)			
<b>Hematopoietic System</b>						
Lymph node, mandibular	(6)		(9)		(8)	
Congestion	1 (17%)					
Lymph node, mesenteric	(10)		(10)		(10)	
Hyperplasia, lymphoid			1 (10%)			
<b>Integumentary System</b>						
None						
<b>Musculoskeletal System</b>						
None						
<b>Nervous System</b>						
Brain	(10)		(10)		(10)	
Mineralization	1 (10%)					
<b>Respiratory System</b>						
Lung	(10)		(10)		(10)	
Mucosa, pigmentation			10 (100%)		10 (100%)	
Nose	(10)		(10)		(10)	
Inflammation, suppurative			7 (70%)		4 (40%)	
Mucosa, pigmentation			10 (100%)		3 (30%)	
Trachea	(10)		(10)		(10)	
Mucosa, pigmentation			10 (100%)		10 (100%)	
<b>Special Senses System</b>						
None						
<b>Urinary System</b>						
Kidney	(10)		(10)		(10)	
Inflammation, subacute			1 (10%)		1 (10%)	
<b>43-Week Interim Evaluation</b>						
<b>Alimentary System</b>						
Liver	(10)		(10)		(10)	(10)
Cytoplasmic alteration			4 (40%)			
Inflammation, subacute	1 (10%)					

**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>43-Week Interim Evaluation (continued)</b>						
<b>Alimentary System (continued)</b>						
Stomach, glandular Inflammation, subacute	(10)		(10)		(10)	(10) 1 (10%)
<b>Cardiovascular System</b>						
None						
<b>Endocrine System</b>						
Adrenal cortex Hyperplasia	(10) 1 (10%)		(10)		(10)	(10)
<b>General Body System</b>						
None						
<b>Genital System</b>						
Testes Atrophy	(10)		(10)		(10) 1 (10%)	(10)
<b>Hematopoietic System</b>						
Lymph node, bronchial Hyperplasia, lymphoid	(9)		(8)		(8)	(7) 1 (14%)
<b>Integumentary System</b>						
None						
<b>Musculoskeletal System</b>						
None						
<b>Nervous System</b>						
Brain Mineralization	(10)		(10) 2 (20%)		(10) 2 (20%)	(10) 1 (10%)
<b>Respiratory System</b>						
Lung Congestion Inflammation, subacute Inflammation, suppurative Mucosa, pigmentation	(10) 1 (10%)		(10) 3 (30%)		(10) 1 (10%) 5 (50%) 9 (90%)	(10) 1 (10%) 5 (50%) 8 (80%)

**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>43-Week Interim Evaluation (continued)</b>						
<b>Respiratory System (continued)</b>						
Nose	(10)		(10)		(10)	(10)
Inflammation, suppurative			1 (10%)			10 (100%)
Mucosa, pigmentation			10 (100%)		9 (90%)	3 (30%)
Trachea	(10)		(10)		(10)	(10)
Inflammation, suppurative					1 (10%)	6 (60%)
Mucosa, pigmentation			10 (100%)		10 (100%)	6 (60%)
<b>Special Senses System</b>						
None						
<b>Urinary System</b>						
Kidney	(10)		(10)		(10)	(10)
Inflammation, subacute	1 (10%)				2 (20%)	
Renal tubule, cytoplasmic alteration			1 (10%)			
Urinary bladder	(10)		(10)		(10)	(10)
Concretion	1 (10%)					
Dilatation	1 (10%)					
<b>15-Month Interim Evaluation</b>						
<b>Alimentary System</b>						
Liver	(10)	(10)				
Cytoplasmic alteration			2 (20%)			
Inflammation, subacute	1 (10%)		1 (10%)			
Stomach, forestomach	(10)	(10)				
Hyperkeratosis			2 (20%)			
<b>Cardiovascular System</b>						
None						
<b>Endocrine System</b>						
None						
<b>General Body System</b>						
None						
<b>Genital System</b>						
Epididymis	(10)	(10)				
Inflammation, chronic			1 (10%)			
Testes	(10)	(10)				
Atrophy	1 (10%)					

**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>15-Month Interim Evaluation (continued)</b>						
<b>Hematopoietic System</b>						
None						
<b>Integumentary System</b>						
None						
<b>Musculoskeletal System</b>						
None						
<b>Nervous System</b>						
Brain	(10)	(10)				
Mineralization	3 (30%)	5 (50%)				
<b>Respiratory System</b>						
Larynx	(10)		(10)		(10)	(10)
Inflammation, subacute						1 (10%)
Lung	(10)	(10)	(8)		(9)	(10)
Inflammation, subacute		1 (10%)			1 (11%)	3 (30%)
Inflammation, suppurative					1 (11%)	2 (20%)
Alveolar epithelium, hyperplasia		1 (10%)	1 (13%)		1 (11%)	
Mucosa, pigmentation		10 (100%)	8 (100%)		9 (100%)	8 (80%)
Nose	(10)	(10)	(10)		(10)	(10)
Inflammation, suppurative		10 (100%)				5 (50%)
Mucosa, pigmentation		10 (100%)	10 (100%)		10 (100%)	6 (60%)
Trachea	(10)	(10)	(10)		(8)	(10)
Inflammation, subacute						2 (20%)
Mucosa, pigmentation		10 (100%)	10 (100%)		8 (100%)	7 (70%)
<b>Special Senses System</b>						
None						
<b>Urinary System</b>						
Kidney	(10)	(10)				
Inflammation, suppurative	1 (10%)					
Nephropathy, chronic	1 (10%)					
Urinary bladder	(10)	(10)				
Dilatation	1 (10%)					

**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>2-Year Study</b>						
<b>Alimentary System</b>						
Intestine small, duodenum	(50)	(49)				
Congestion		1 (2%)				
Hyperplasia		1 (2%)				
Inflammation, suppurative	1 (2%)					
Peyer's patch, hyperplasia, lymphoid		1 (2%)				
Intestine small, jejunum	(50)	(50)				
Congestion		1 (2%)				
Inflammation, chronic		1 (2%)				
Peyer's patch, hyperplasia, lymphoid	2 (4%)	3 (6%)				
Intestine small, ileum	(50)	(50)				
Congestion		1 (2%)				
Peyer's patch, hyperplasia, lymphoid	1 (2%)					
Liver	(50)	(50)	(1)			
Basophilic focus	1 (2%)					
Cyst	1 (2%)					
Cytoplasmic alteration	1 (2%)	2 (4%)				
Fatty change	1 (2%)					
Focal cellular change	1 (2%)					
Hyperplasia, nodular	1 (2%)					
Infarct	1 (2%)	1 (2%)				
Inflammation, chronic	1 (2%)					
Inflammation, necrotizing	1 (2%)					
Inflammation, subacute	2 (4%)					
Inflammation, suppurative	1 (2%)					
Mineralization		1 (2%)				
Necrosis, acute	1 (2%)	2 (4%)				
Mesentery	(4)	(2)				
Necrosis	1 (25%)	1 (50%)				
Fat, hemorrhage	1 (25%)					
Fat, necrosis	1 (25%)	1 (50%)				
Pancreas	(49)	(50)				
Inflammation, subacute	1 (2%)					
Duct, cyst	1 (2%)					
Stomach, forestomach	(50)	(50)				
Hyperkeratosis		2 (4%)				
Stomach, glandular	(50)	(50)				
Mineralization	1 (2%)	2 (4%)				
Necrosis	3 (6%)					
Tooth		(2)	(1)	(1)	(1)	(3)
Developmental malformation		2 (100%)		1 (100%)	1 (100%)	3 (100%)
Inflammation, suppurative			1 (100%)			
<b>Cardiovascular System</b>						
Heart	(50)	(50)				
Arteriole, mineralization		1 (2%)				
Atrium, thrombosis	1 (2%)					

**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>2-Year Study (continued)</b>						
<b>Endocrine System</b>						
Adrenal cortex	(49)	(50)				
Hyperplasia		1 (2%)				
Thyroid gland	(48)	(50)	(47)	(45)	(49)	(40)
Crystals				1 (2%)		
Cyst			2 (4%)			
Follicular cell, hyperplasia	4 (8%)	5 (10%)	2 (4%)	4 (9%)	7 (14%)	15 (38%)
<b>General Body System</b>						
None						
<b>Genital System</b>						
Epididymis	(50)	(50)				
Inflammation, granulomatous	1 (2%)	1 (2%)				
Penis	(4)	(3)				
Concretion		1 (33%)				
Inflammation, suppurative	2 (50%)	2 (67%)				
Preputial gland	(9)	(4)				
Inflammation, granulomatous	1 (11%)					
Inflammation, suppurative	2 (22%)					
Duct, dilatation	5 (56%)	3 (75%)				
Prostate	(50)	(50)				
Inflammation, suppurative	1 (2%)					
Seminal vesicle	(50)	(50)				
Dilatation	1 (2%)	1 (2%)				
Hemorrhage	1 (2%)					
Testes	(50)	(50)				
Atrophy		1 (2%)				
<b>Hematopoietic System</b>						
Bone marrow	(50)	(50)	(39)	(35)	(47)	(37)
Hyperplasia	1 (2%)	2 (4%)				
Lymph node	(1)	(2)				
Deep cervical, hematopoietic cell proliferation		1 (50%)				
Lymph node, bronchial	(48)				(50)	(49)
Hyperplasia, lymphoid					1 (2%)	6 (12%)
Lymph node, mandibular	(41)	(43)				
Hematopoietic cell proliferation		1 (2%)				
Hyperplasia		1 (2%)				
Hyperplasia, lymphoid		5 (12%)				
Lymph node, mesenteric	(48)	(49)				
Congestion	1 (2%)	3 (6%)				
Hematopoietic cell proliferation		1 (2%)				
Hemorrhage	2 (4%)	2 (4%)				
Hyperplasia, lymphoid	4 (8%)	7 (14%)				

**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>2-Year Study (continued)</b>						
<b>Hematopoietic System (continued)</b>						
Lymph node, mediastinal	(46)				(46)	(43)
Hyperplasia, lymphoid						5 (12%)
Spleen	(50)	(50)				
Hematopoietic cell proliferation	2 (4%)	3 (6%)				
Thymus	(47)				(49)	(40)
Cyst					1 (2%)	
<b>Integumentary System</b>						
Skin	(50)	(50)	(48)	(46)	(48)	(36)
Alopecia	2 (4%)					2 (6%)
Edema		1 (2%)				
Inflammation, suppurative	4 (8%)					
Prepuce, inflammation, suppurative	1 (2%)					
<b>Musculoskeletal System</b>						
None						
<b>Nervous System</b>						
Brain	(50)	(50)				
Compression	1 (2%)					
Inflammation, subacute		1 (2%)				
Inflammation, suppurative		1 (2%)				
Mineralization	13 (26%)	10 (20%)				
<b>Respiratory System</b>						
Larynx	(50)				(50)	(50)
Inflammation, subacute						3 (6%)
Lung	(49)	(50)	(50)	(49)	(50)	(50)
Bronchiectasis						2 (4%)
Congestion		2 (4%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hemorrhage				1 (2%)		
Hyperplasia, macrophage					2 (4%)	
Infiltration cellular, histiocyte	1 (2%)		1 (2%)			
Inflammation, subacute	1 (2%)	2 (4%)	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, suppurative		4 (8%)				16 (32%)
Mineralization						1 (2%)
Pigmentation			1 (2%)			
Alveolar epithelium, hyperplasia		5 (10%)	4 (8%)	2 (4%)	4 (8%)	5 (10%)
Arteriole, bacterium				1 (2%)		
Bronchiole, hyperplasia	1 (2%)	1 (2%)				
Interstitial, inflammation			1 (2%)			
Mucosa, pigmentation		45 (90%)	46 (92%)	45 (92%)	48 (96%)	33 (66%)
Pleura, inflammation, suppurative	1 (2%)					



**TABLE E3**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.2 ppm	0.2 ppm (33 weeks)	0.2 ppm (66 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
<b>2-Year Study (continued)</b>						
<b>Respiratory System (continued)</b>						
Nose	(50)	(50)	(50)	(49)	(50)	(50)
Hemorrhage, acute	1 (2%)					
Inflammation, subacute			1 (2%)	1 (2%)		
Inflammation, suppurative		36 (72%)	2 (4%)	17 (35%)	7 (14%)	24 (48%)
Mucosa, pigmentation		44 (88%)	50 (100%)	46 (94%)	35 (70%)	29 (58%)
Trachea	(50)	(50)	(50)	(49)	(49)	(50)
Inflammation, subacute						5 (10%)
Inflammation, suppurative		2 (4%)				8 (16%)
Mucosa, pigmentation		48 (96%)	50 (100%)	48 (98%)	48 (98%)	27 (54%)
<b>Special Senses System</b>						
None						
<b>Urinary System</b>						
Kidney	(50)	(50)				
Casts	1 (2%)					
Cyst		3 (6%)				
Dilatation	3 (6%)					
Hydronephrosis	1 (2%)					
Hypertrophy	1 (2%)					
Inflammation, chronic	1 (2%)	1 (2%)				
Inflammation, subacute	4 (8%)	2 (4%)				
Inflammation, suppurative	2 (4%)					
Metaplasia, osseous		1 (2%)				
Mineralization		4 (8%)				
Nephropathy, chronic	1 (2%)	1 (2%)				
Polycystic kidney	1 (2%)					
Pelvis, dilatation	6 (12%)	2 (4%)				
Renal tubule, degeneration		1 (2%)				
Urethra	(1)					
Concretion	1 (100%)					
Urinary bladder	(50)	(50)				
Dilatation	6 (12%)	4 (8%)				

<sup>a</sup> Number of animals examined microscopically at site and number of animals with lesion

<sup>b</sup> Includes 60 controls from the core study

## APPENDIX F

### GENETIC TOXICOLOGY

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## GENETIC TOXICOLOGY

### ***SALMONELLA TYPHIMURIUM* MUTAGENICITY TEST PROTOCOL**

Testing was performed as reported by Haworth *et al.* (1983). Hexachlorocyclopentadiene was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of hexachlorocyclopentadiene. High dose was limited to 100 µg/plate. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose-related, not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

### **CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS**

Testing was performed as reported by Galloway *et al.* (1987). Hexachlorocyclopentadiene was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of hexachlorocyclopentadiene. A single flask per dose was used.

**Sister Chromatid Exchange Test:** In the SCE test without S9, CHO cells were incubated for 26 hours with hexachlorocyclopentadiene in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 24 hours, the medium containing hexachlorocyclopentadiene was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with hexachlorocyclopentadiene, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no hexachlorocyclopentadiene, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level; high dose was limited to 5 µg/mL.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence

of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ( $P < 0.05$ ) in the absence of any responses reaching 20% above background led to a call of equivocal.

**Chromosomal Aberrations Test:** In the Abs test without S9, cells were incubated in McCoy's 5A medium with hexachlorocyclopentadiene for 10 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with hexachlorocyclopentadiene and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: no cell cycle delay was anticipated. High dose was limited by toxicity.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype ( $21 \pm 2$  chromosomes). All slides were scored blind and those from a single test were read by the same person. Where possible, 200 first-division metaphase cells were scored per dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ( $P \leq 0.05$ ) difference for one dose point and a significant trend ( $P \leq 0.015$ ) are considered weak evidence for a positive response; significant differences for two or more doses indicate the trial is positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

### ***DROSOPHILA MELANOGASTER* TEST PROTOCOL**

The assays for induction of sex-linked recessive lethal (SLRL) mutations were performed with adult flies as described by Zimmering *et al.* (1985). Hexachlorocyclopentadiene was supplied as a coded aliquot from Radian Corporation. It was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no positive response was obtained, hexachlorocyclopentadiene was retested by injection into adult males.

To administer a chemical by injection, a glass Pasteur pipette is drawn out in a flame to a microfine filament, and the tip is broken off to allow delivery of the test solution. Injection is performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3  $\mu\text{L}$ ) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector that automatically delivers a calibrated volume. Flies are anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, is performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of hexachlorocyclopentadiene at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males to feed for 72 hours on a solution of hexachlorocyclopentadiene in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were treated with a solution of hexachlorocyclopentadiene dissolved in saline and allowed to recover for 24 hours. In the adult exposures, treated males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier postmeiotic

F<sub>1</sub> daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male results from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls, using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result is considered positive if the P value is less than 0.01 and the mutation frequency in the tested group is greater than 0.10%, or if the P value is less than 0.05 and the frequency in the treatment group is greater than 0.15%. A test is considered to be inconclusive if (a) the P value is between 0.05 and 0.01 but the frequency in the treatment group is between 0.10% and 0.15% or (b) the P value is between 0.10 and 0.05 but the frequency in the treatment groups is greater than 0.10%. A test is considered negative if the P value is greater than 0.10 or if the frequency in the treatment group is less than 0.10%.

### MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female B6C3F<sub>1</sub> mice at the end of the 13-week inhalation toxicity study. Smears were immediately prepared and fixed in absolute methanol. They were later stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 polychromatic erythrocytes (PCEs) and 10,000 normochromatic erythrocytes (NCEs) in 10 animals per dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 510 nm UV illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell. In addition, the percentage of PCEs among the total erythrocyte population was determined.

Log transformation of the NCE data, and testing for normality by the Shapiro-Wilk test, and for heterogeneity of variance by Cochran's test, were performed before statistical analyses. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent solvent control using Student's *t*-test. The frequency of micronucleated cells among PCEs was analyzed by the Cochran-Armitage trend test, and individual dose groups were compared to the concurrent solvent control by Kastenbaum-Bowman's binomial test. The percentage of PCEs among total erythrocytes was analyzed by an analysis of variance on ranks (classed by sex), and individual dose groups were compared with the concurrent solvent control using a *t*-test on ranks.

### RESULTS

Hexachlorocyclopentadiene (0.03 to 100  $\mu$ g/plate) was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested by a preincubation protocol, with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table F1; Haworth *et al.*, 1983). In cytogenic assays with cultured CHO cells, hexachlorocyclopentadiene induced both SCEs and Abs with and without S9 (Tables F2 and F3; Galloway *et al.*, 1987). Although no cell cycle delay was evident in either of these CHO cell studies, toxicity was a problem in the Abs test where fewer than the desired number of 200 cells per dose level were available for scoring at the highest doses tested, with and without S9. In the SCE test, no clear dose-response relationship was evident.

*In vivo*, no genetic effects were observed. No induction of sex-linked recessive lethal mutations was noted in germ cells of male *D. melanogaster* treated with hexachlorocyclopentadiene by feeding or injection

(Table F4; Zimmering *et al.*, 1985; Mason *et al.*, 1992). No increase in the frequency of micronucleated erythrocytes was observed in peripheral blood samples obtained from male and female B6C3F<sub>1</sub> mice exposed to hexachlorocyclopentadiene by inhalation for 13 weeks (Table F5).

**TABLE F1**  
**Mutagenicity of Hexachlorocyclopentadiene in *Salmonella typhimurium*<sup>a</sup>**

Strain	Dose ( $\mu\text{g}/\text{plate}$ )	Revertants/plate <sup>b</sup>		
		-S9	+10% hamster S9	+10% rat S9
<b>TA100</b>				
	0.00	79 $\pm$ 6.4	154 $\pm$ 13.1	114 $\pm$ 4.2
	0.03	102 $\pm$ 7.5		
	0.10	94 $\pm$ 2.6		
	0.30	98 $\pm$ 2.6		
	1.00	108 $\pm$ 11.5	143 $\pm$ 9.6	113 $\pm$ 5.5
	3.30	96 $\pm$ 5.2	138 $\pm$ 14.5	121 $\pm$ 13.0
	10.00		118 $\pm$ 12.0	108 $\pm$ 7.1
	33.30		121 $\pm$ 2.3	119 $\pm$ 5.3
	100.00		112 $\pm$ 12.8	124 $\pm$ 4.0
Trial summary		Negative	Negative	Negative
Positive control <sup>c</sup>		404 $\pm$ 11.8	908 $\pm$ 11.0	305 $\pm$ 7.0
<b>TA1535</b>				
	0.00	15 $\pm$ 0.3	11 $\pm$ 0.9	13 $\pm$ 3.1
	0.03	12 $\pm$ 0.3		
	0.10	18 $\pm$ 3.2		
	0.30	17 $\pm$ 2.3		
	1.00	19 $\pm$ 3.2	15 $\pm$ 3.0	10 $\pm$ 2.1
	3.30	17 $\pm$ 1.2	10 $\pm$ 2.1	10 $\pm$ 3.1
	10.00		15 $\pm$ 1.0	13 $\pm$ 2.6
	33.30		15 $\pm$ 1.7	10 $\pm$ 2.1
	100.00		9 $\pm$ 1.9	6 $\pm$ 0.9
Trial summary		Negative	Negative	Negative
Positive control		312 $\pm$ 4.4	360 $\pm$ 4.5	228 $\pm$ 3.8
<b>TA1537</b>				
	0.00	6 $\pm$ 0.3	12 $\pm$ 1.5	10 $\pm$ 1.2
	0.03	5 $\pm$ 0.7		
	0.10	5 $\pm$ 0.3		
	0.30	6 $\pm$ 1.8		
	1.00	4 $\pm$ 0.3	16 $\pm$ 1.9	9 $\pm$ 2.3
	3.30	6 $\pm$ 0.9	14 $\pm$ 1.2	9 $\pm$ 2.0
	10.00		12 $\pm$ 1.8	13 $\pm$ 0.6
	33.30		15 $\pm$ 0.7	12 $\pm$ 2.1
	100.00		11 $\pm$ 1.7	7 $\pm$ 3.5
Trial summary		Negative	Negative	Negative
Positive control		152 $\pm$ 13.7	397 $\pm$ 12.0	154 $\pm$ 5.1

**TABLE FI**  
**Mutagenicity of Hexachlorocyclopentadiene in *Salmonella typhimurium* (continued)**

Strain	Dose ( $\mu\text{g}/\text{plate}$ )	Revertants/plate		
		-S9	+10% hamster S9	+10% rat S9
<b>TA98</b>				
	0.00	17 $\pm$ 2.6	32 $\pm$ 7.0	22 $\pm$ 2.1
	0.03	17 $\pm$ 1.5		
	0.10	13 $\pm$ 0.7		
	0.30	14 $\pm$ 2.1		
	1.00	16 $\pm$ 1.9	28 $\pm$ 1.2	19 $\pm$ 2.9
	3.30	14 $\pm$ 1.8	30 $\pm$ 4.9	25 $\pm$ 4.9
	10.00		27 $\pm$ 1.5	24 $\pm$ 3.7
	33.30		37 $\pm$ 6.4	32 $\pm$ 3.5
	100.00		32 $\pm$ 3.7	26 $\pm$ 4.3
Trial summary		Negative	Negative	Negative
Positive control		675 $\pm$ 61.2	426 $\pm$ 10.5	115 $\pm$ 8.2

<sup>a</sup> Study performed at SRI, International. The detailed protocol and these data are presented in Haworth *et al.* (1983).

<sup>b</sup> Revertants are presented as mean  $\pm$  standard error from three plates. All trials were repeated. Because the data are published elsewhere, only one trial per experimental condition is presented here.

<sup>c</sup> 2-Aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.



TABLE F2  
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Hexachlorocyclopentadiene<sup>a</sup>

Compound	Dose μg/mL	Total Cells	No. of Chromo- somes	No. of SCEs	SCEs/ Chromo- some	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%) <sup>b</sup>
<b>-S9</b>								
<b>Trial 1</b>								
Summary: Weakly positive								
Dimethylsulfoxide		50	1,028	369	0.35	7.4	26.0	
Mitomycin-C	0.0005	50	1,022	519	0.50	10.4	26.0	41.48
	0.0050	10	206	263	1.27	26.3	26.0	255.68
Hexachlorocyclopentadiene	0.016	50	1,030	405	0.39	8.1	26.0	9.54
	0.050	50	1,037	413	0.39	8.3	26.0	10.95
	0.160	50	1,024	469	0.45	9.4	26.0	27.60*
	0.500	50	1,025	432	0.42	8.6	26.0	17.42
								P=0.001 <sup>c</sup>
<b>Trial 2</b>								
Summary: Positive								
Dimethylsulfoxide		50	1,046	383	0.36	7.7	26.0	
Mitomycin-C	0.0008	50	1,047	501	0.47	10.0	26.0	30.69
	0.0050	10	210	317	1.50	31.7	26.0	312.27
Hexachlorocyclopentadiene	0.05	50	1,039	514	0.49	10.3	26.0	35.11 <sup>u</sup>
	0.10	50	1,041	468	0.44	9.4	26.0	22.78 <sup>u</sup>
	0.16	50	1,041	436	0.41	8.7	26.0	14.38
	0.50	50	1,046	538	0.51	10.8	26.0	40.47 <sup>u</sup>
								P<0.001
<b>+S9</b>								
<b>Trial 1</b>								
Summary: Weakly Positive								
Dimethylsulfoxide		50	1,044	408	0.39	8.2	26.0	
Cyclophosphamide	0.15	50	1,039	509	0.48	10.2	26.0	25.36
	0.60	10	206	191	0.92	19.1	26.0	137.25
Hexachlorocyclopentadiene	0.16	50	1,041	379	0.36	7.6	26.0	-6.84
	0.50	50	1,032	439	0.42	8.8	26.0	8.85
	1.60	50	1,036	511	0.49	10.2	26.0	26.21*
	5.00	50	1,045	441	0.42	8.8	26.0	7.98
								P=0.001

\* Positive ( $P \leq 0.01$ )

<sup>a</sup> Study performed at Environmental Health Research and Testing, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the protocol is presented by Galloway *et al.* (1987).

<sup>b</sup> SCEs/chromosome of culture exposed to hexachlorocyclopentadiene relative to those of culture exposed to solvent

<sup>c</sup> Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

**TABLE F3**  
**Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Hexachlorocyclopentadiene<sup>a</sup>**

-S9					+S9				
Dose ( $\mu\text{g/mL}$ )	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose ( $\mu\text{g/mL}$ )	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
<b>Trial 1 - Harvest time: 12.0 hours</b> Summary: Weakly Positive					<b>Trial 1 - Harvest time: 13.0 hours</b> Summary: Weakly Positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	1	0.01	0.5		200	1	0.01	0.5
Mitomycin-C					Cyclophosphamide				
0.125	200	48	0.24	21.5	5.0	200	29	0.15	14.0
0.250	50	16	0.32	28.0	7.5	50	18	0.36	32.0
Hexachlorocyclopentadiene					Hexachlorocyclopentadiene				
0.5	200	2	0.01	1.0	1.6	200	1	0.04	4.0
1.0	200	3	0.02	1.5	3.0	200	1	0.01	1.0
1.6	200	10	0.05	4.0	5.0	200	2	0.03	3.0
3.0	19 <sup>b</sup>	0	0.00	0.0	10.0	136 <sup>b</sup>	43	0.32	21.3*
P=0.011 <sup>c</sup>					P<0.001				
					<b>Trial 2 - Harvest time 13.0 hours</b> Summary: Positive				
					Dimethylsulfoxide				
						200	0	0.00	0.0
					Cyclophosphamide				
					5.0	200	34	0.17	15.5
					7.5	50	27	1.54	50.0
					Hexachlorocyclopentadiene				
					3.0	200	4	0.02	2.0
					5.0	200	6	0.03	3.0*
					7.5	200	28	0.14	9.5*
					P<0.001				

\* Positive ( $P \leq 0.05$ )

<sup>a</sup> Study performed at Environmental Health Research and Testing, Inc. Abs = aberrations. A detailed presentation of the protocol is presented in Galloway *et al.* (1987).

<sup>b</sup> Due to severe chemical-induced toxicity, fewer than 200 cells could be scored for aberrations.

<sup>c</sup> Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

**TABLE F4**  
**Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster***  
**by Hexachlorocyclopentadiene<sup>a</sup>**

Route of Exposure	Dose (ppm)	Incidence of Deaths (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			Total <sup>b</sup>
				Mating 1	Mating 2	Mating 3	
<b>Study 1</b>							
Feeding	10	5	3	0/898	2/856	2/868	4/2,622 (0.15%)
	0			0/321	1/299	0/227	1/847 (0.12%)
Feeding	13	1	46	0/427	1/1,108	1/1,314	2/2,849 (0.07%)
	0			1/2,196	1/2,075	1/1,790	3/6,061 (0.05%)
Injection	900	14	29	2/2,002	3/1,559	1/1,471	6/5,032 (0.12%)
	0			3/2,211	0/1,892	4/1,087	7/5,190 (0.13%)
<b>Study 2</b>							
Feeding	40	16	1	0/2,614	2/2,855	0/2,687	2/8,156 (0.02%)
	0			2/3,373	3/3,248	1/3,279	6/9,900 (0.06%)
Injection	2,000	3	2	2/2,257	3/2,145	1/2,043	6/6,445 (0.09%)
	0			0/2,327	0/2,346	2/2,272	2/6,945 (0.03%)
Injection	3,000	13	11	0/902	2/741	0/591	2/2,234 (0.09%)
	0			1/1,052	0/1,044	0/1,043	0/3,139 (0.00%)

<sup>a</sup> Studies performed at the University of Wisconsin, Madison, WI. A detailed description of the protocol and the data from study 2 are presented in Zimmering *et al.* (1985). The data from study 1 are presented in Mason *et al.* (1992). Results were not significant at the 5% level (Margolin *et al.*, 1983).

<sup>b</sup> Combined total number of lethal mutations/number of X chromosomes tested for three mating trials

**TABLE F5**  
**Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Inhalation Treatment with Hexachlorocyclopentadiene for 13 Weeks<sup>a</sup>**

Dose (ppm)	Micronucleated Cells/1,000 Cells		PCE (%) <sup>b</sup>
	PCE	NCE	
<b>Male</b>			
0.00	2.12 ± 0.73	1.70 ± 0.11	1.57 ± 0.16
0.01	1.71 ± 0.41	1.88 ± 0.14	1.33 ± 0.23
0.05	2.28 ± 0.73	2.07 ± 0.30	1.84 ± 0.28
0.20	2.02 ± 0.51	1.73 ± 0.14	1.18 ± 0.18
Trend test <sup>c</sup> ANOVA <sup>d</sup>	P=0.467	P=0.848	P=0.146
<b>Female</b>			
0.00	1.55 ± 0.39	1.20 ± 0.09	2.10 ± 0.27
0.01	1.96 ± 0.60	1.44 ± 0.35	1.49 ± 0.24
0.05	1.36 ± 0.30	1.09 ± 0.04	1.91 ± 0.23
0.20	0.87 ± 0.23	1.09 ± 0.10	1.81 ± 0.28
Trend test ANOVA	P=0.968	P=0.312	P=0.191

<sup>a</sup> PCE = polychromatic erythrocyte, NCE = normochromatic erythrocyte. Ten animals per dose group; 2,000 PCEs scored/animal, 10,000 NCEs scored/animal; data presented as mean ± standard error of the mean. A detailed presentation of the protocol is presented in MacGregor *et al.* (1990).

<sup>b</sup> Percent PCEs among total erythrocyte population

<sup>c</sup> Exposed groups do not differ from the control by Student's *t*-test (NCE data) or by Kastenbaum-Bowman's binomial test (PCE data).

<sup>d</sup> Exposed groups do not differ from the control by *t*-test on ranks.

## APPENDIX G

### ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

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**TABLE G1**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
<b>Male</b>				
n	10	10	10	10
Necropsy body wt	344 ± 5	330 ± 8	329 ± 9	319 ± 7*
<b>Adrenal Gland</b>				
Absolute	0.042 ± 0.002	0.041 ± 0.005 <sup>b</sup>	0.038 ± 0.003	0.045 ± 0.003
Relative	0.12 ± 0.00	0.13 ± 0.01 <sup>b</sup>	0.12 ± 0.01	0.14 ± 0.01
<b>Brain</b>				
Absolute	1.943 ± 0.030	1.905 ± 0.021	1.925 ± 0.015	1.896 ± 0.025
Relative	5.65 ± 0.09	5.80 ± 0.14	5.88 ± 0.14	5.95 ± 0.07
<b>Heart</b>				
Absolute	0.860 ± 0.016	0.825 ± 0.023	0.821 ± 0.021	0.841 ± 0.016
Relative	2.50 ± 0.05	2.50 ± 0.02	2.50 ± 0.02	2.64 ± 0.03**
<b>R. Kidney</b>				
Absolute	1.107 ± 0.013	1.043 ± 0.024	1.036 ± 0.030	1.066 ± 0.028
Relative	3.22 ± 0.03	3.17 ± 0.04	3.15 ± 0.02	3.34 ± 0.04*
<b>Liver</b>				
Absolute	11.808 ± 0.269	11.214 ± 0.360	11.326 ± 0.309	11.233 ± 0.236
Relative	34.26 ± 0.35	33.94 ± 0.40	34.42 ± 0.39	35.20 ± 0.40
<b>Lungs</b>				
Absolute	1.597 ± 0.051	1.515 ± 0.054	1.561 ± 0.044	1.759 ± 0.044*
Relative	4.64 ± 0.15	4.59 ± 0.13	4.77 ± 0.18	5.52 ± 0.13**
<b>R. Testis</b>				
Absolute	1.430 ± 0.024	1.416 ± 0.026	1.414 ± 0.022	1.419 ± 0.022
Relative	4.15 ± 0.05	4.30 ± 0.07	4.31 ± 0.08	4.46 ± 0.09**
<b>Thymus</b>				
Absolute	0.363 ± 0.027	0.368 ± 0.023	0.303 ± 0.024	0.320 ± 0.020
Relative	1.05 ± 0.08	1.12 ± 0.06	0.92 ± 0.07	1.01 ± 0.07

**TABLE G1**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Inhalation Study of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
<b>Female</b>				
n	10	10	10	10
Necropsy body wt	195 ± 6	191 ± 4	198 ± 3	190 ± 3
<b>Adrenal Gland</b>				
Absolute	0.046 ± 0.002	0.049 ± 0.002	0.046 ± 0.003	0.047 ± 0.001
Relative	0.24 ± 0.01	0.26 ± 0.01	0.23 ± 0.01	0.25 ± 0.01
<b>Brain</b>				
Absolute	1.786 ± 0.022	1.770 ± 0.022	1.778 ± 0.016	1.762 ± 0.026
Relative	9.24 ± 0.29	9.28 ± 0.15	9.01 ± 0.14	9.31 ± 0.15
<b>Heart</b>				
Absolute	0.558 ± 0.011	0.552 ± 0.018	0.566 ± 0.009	0.556 ± 0.010
Relative	2.87 ± 0.05	2.88 ± 0.06	2.86 ± 0.04	2.94 ± 0.03
<b>R. Kidney</b>				
Absolute	0.675 ± 0.017	0.660 ± 0.011	0.672 ± 0.011	0.665 ± 0.011
Relative	3.47 ± 0.07	3.46 ± 0.05	3.40 ± 0.03	3.51 ± 0.04
<b>Liver</b>				
Absolute	6.553 ± 0.224	5.991 ± 0.182	6.555 ± 0.142	6.184 ± 0.131
Relative	33.62 ± 0.51	31.33 ± 0.63*	33.14 ± 0.48	32.64 ± 0.57
<b>Lungs</b>				
Absolute	1.138 ± 0.073	1.107 ± 0.031	1.123 ± 0.028	1.198 ± 0.019
Relative	5.85 ± 0.35	5.80 ± 0.15	5.68 ± 0.14	6.33 ± 0.13
<b>Thymus</b>				
Absolute	0.298 ± 0.007	0.246 ± 0.015*	0.251 ± 0.016	0.329 ± 0.018
Relative	1.54 ± 0.06	1.29 ± 0.08*	1.27 ± 0.08*	1.73 ± 0.07

\* Significantly different ( $P \leq 0.05$ ) from the control group by Williams' or Dunnett's test

\*\*  $P \leq 0.01$

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data were collected for 1 and 2 ppm males and females due to 100% mortality.

<sup>b</sup> n=9

**TABLE G2**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Male</b>				
n	10	10	10	10
Necropsy body wt	485 ± 6	481 ± 7	462 ± 8	481 ± 6
<b>Brain</b>				
Absolute	2.028 ± 0.009	2.039 ± 0.021	1.988 ± 0.018	2.012 ± 0.011
Relative	4.18 ± 0.05	4.24 ± 0.06	4.31 ± 0.08	4.19 ± 0.05
<b>R. Kidney</b>				
Absolute	1.433 ± 0.043	1.576 ± 0.052	1.482 ± 0.041	1.522 ± 0.027
Relative	2.95 ± 0.08	3.27 ± 0.09*	3.21 ± 0.09	3.17 ± 0.07
<b>Liver</b>				
Absolute	15.525 ± 0.316	15.733 ± 0.445	14.720 ± 0.286	15.577 ± 0.243
Relative	31.99 ± 0.55	32.65 ± 0.64	31.89 ± 0.59	32.42 ± 0.42
<b>Lungs</b>				
Absolute	1.775 ± 0.039	1.686 ± 0.037	1.609 ± 0.032**	1.653 ± 0.032**
Relative	3.66 ± 0.09	3.50 ± 0.05	3.48 ± 0.05	3.44 ± 0.07*
<b>Female</b>				
n	10	10	10	10
Necropsy body wt	310 ± 10	324 ± 9	324 ± 8	312 ± 6
<b>Brain</b>				
Absolute	1.823 ± 0.019	1.834 ± 0.015	1.830 ± 0.010	1.830 ± 0.016
Relative	5.94 ± 0.21	5.69 ± 0.14	5.68 ± 0.14	5.88 ± 0.08
<b>R. Kidney</b>				
Absolute	0.960 ± 0.035	0.990 ± 0.022	0.943 ± 0.030	1.013 ± 0.027
Relative	3.10 ± 0.08	3.06 ± 0.04	2.91 ± 0.06	3.25 ± 0.08
<b>Liver</b>				
Absolute	9.595 ± 0.314	9.379 ± 0.270	9.102 ± 0.228	9.710 ± 0.294
Relative	30.97 ± 0.37	28.94 ± 0.20**	28.12 ± 0.29**	31.13 ± 0.72
<b>Lungs</b>				
Absolute	1.128 ± 0.033	1.249 ± 0.033*	1.201 ± 0.024	1.222 ± 0.035
Relative	3.65 ± 0.06	3.87 ± 0.10	3.72 ± 0.06	3.92 ± 0.09

\* Significantly different ( $P \leq 0.05$ ) from the control group by Williams' or Dunnett's test

\*\*  $P \leq 0.01$

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).



**TABLE G3**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
<b>Male</b>				
n	10	5	10	5
Necropsy body wt	31.4 ± 0.5	31.1 ± 0.8	29.3 ± 0.5**	29.1 ± 0.5*
<b>Adrenal Gland</b>				
Absolute	0.002 ± 0.000 <sup>b</sup>	0.003 ± 0.000* <sup>c</sup>	0.003 ± 0.000*	0.003 ± 0.000
Relative	0.07 ± 0.01 <sup>b</sup>	0.10 ± 0.01* <sup>c</sup>	0.10 ± 0.01*	0.10 ± 0.02*
<b>Brain</b>				
Absolute	0.459 ± 0.004	0.465 ± 0.004	0.455 ± 0.005	0.446 ± 0.005
Relative	14.66 ± 0.26	14.78 ± 0.44	15.57 ± 0.25*	15.35 ± 0.25
<b>Heart</b>				
Absolute	0.141 ± 0.005	0.143 ± 0.007	0.145 ± 0.006 <sup>b</sup>	0.144 ± 0.009
Relative	4.50 ± 0.15	4.47 ± 0.20	4.92 ± 0.22 <sup>b</sup>	4.96 ± 0.26
<b>R. Kidney</b>				
Absolute	0.247 ± 0.006	0.262 ± 0.010	0.252 ± 0.008	0.246 ± 0.016
Relative	7.88 ± 0.20	8.67 ± 0.34	8.61 ± 0.25	8.43 ± 0.47
<b>Liver</b>				
Absolute	1.518 ± 0.036	1.545 ± 0.032	1.488 ± 0.034	1.544 ± 0.035
Relative	48.43 ± 0.93	49.08 ± 0.74	50.84 ± 1.27	53.07 ± 0.43*
<b>Lungs</b>				
Absolute	0.211 ± 0.006	0.223 ± 0.010	0.211 ± 0.006	0.227 ± 0.005
Relative	6.75 ± 0.20	6.89 ± 0.21	7.21 ± 0.21	7.83 ± 0.25**
<b>R. Testis</b>				
Absolute	0.118 ± 0.002 <sup>b</sup>	0.130 ± 0.009	0.113 ± 0.003	0.117 ± 0.003
Relative	3.80 ± 0.08 <sup>b</sup>	4.20 ± 0.38	3.85 ± 0.10	4.02 ± 0.04
<b>Thymus</b>				
Absolute	0.049 ± 0.004	0.054 ± 0.003	0.044 ± 0.003	0.047 ± 0.005
Relative	1.56 ± 0.10	1.62 ± 0.11	1.49 ± 0.12	1.61 ± 0.15

**TABLE G3**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
<b>Female</b>				
n	4	9	9	8
Necropsy body wt	25.3 ± 1.3	25.0 ± 0.8	24.3 ± 0.3	23.5 ± 0.5
<b>Adrenal Gland</b>				
Absolute	0.007 ± 0.000	0.007 ± 0.000	0.008 ± 0.000	0.007 ± 0.000
Relative	0.29 ± 0.02	0.30 ± 0.02	0.31 ± 0.02	0.29 ± 0.01
<b>Brain</b>				
Absolute	0.477 ± 0.007	0.485 ± 0.013	0.469 ± 0.005	0.459 ± 0.007
Relative	19.03 ± 0.88	19.47 ± 0.59	19.33 ± 0.25	19.62 ± 0.55
<b>Heart</b>				
Absolute	0.118 ± 0.005	0.139 ± 0.014	0.119 ± 0.003	0.114 ± 0.004
Relative	4.66 ± 0.12	5.49 ± 0.36	4.92 ± 0.13	4.87 ± 0.10
<b>R. Kidney</b>				
Absolute	0.201 ± 0.011	0.185 ± 0.007	0.170 ± 0.005*	0.179 ± 0.007*
Relative	7.99 ± 0.47	7.38 ± 0.18	6.99 ± 0.20*	7.62 ± 0.19
<b>Liver</b>				
Absolute	1.345 ± 0.067	1.301 ± 0.045	1.304 ± 0.043	1.258 ± 0.047
Relative	53.39 ± 2.08	52.01 ± 0.79	53.66 ± 1.45	53.51 ± 1.12
<b>Lungs</b>				
Absolute	0.204 ± 0.004	0.200 ± 0.008	0.207 ± 0.014	0.208 ± 0.006
Relative	8.17 ± 0.59	8.08 ± 0.47	8.52 ± 0.56	8.90 ± 0.36
<b>Thymus</b>				
Absolute	0.082 ± 0.033	0.049 ± 0.003	0.048 ± 0.002	0.046 ± 0.004
Relative	3.19 ± 1.23	1.98 ± 0.11	1.98 ± 0.07	1.96 ± 0.18

\* Significantly different ( $P \leq 0.05$ ) from the control group by Williams' or Dunnett's test

\*\*  $P \leq 0.01$

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data were collected for 1 and 2 ppm males and females due to 100% mortality.

<sup>b</sup> n=9

<sup>c</sup> n=4

**TABLE G4**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Mice**  
**at the 27-Week Stop-Exposure Evaluation of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.5 ppm (26 weeks)
n	10	10
Necropsy body wt	34.7 ± 1.2	32.4 ± 0.8
Brain		
Absolute	0.465 ± 0.003	0.445 ± 0.007*
Relative	13.53 ± 0.43	13.80 ± 0.33
R. Kidney		
Absolute	0.336 ± 0.012	0.309 ± 0.011
Relative	9.70 ± 0.23	9.52 ± 0.16
Liver		
Absolute	1.592 ± 0.049	1.542 ± 0.046
Relative	46.01 ± 0.83	47.57 ± 0.39
Lungs		
Absolute	0.262 ± 0.016	0.273 ± 0.011
Relative	7.55 ± 0.41	8.47 ± 0.38

\* Significantly different ( $P \leq 0.05$ ) from the control group by Williams' or Dunnett's test

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

**TABLE G5**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Mice**  
**at the 34-Week Stop-Exposure Evaluation of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.2 ppm (33 weeks)	0.5 ppm (26 weeks)
n	10	10	10
Necropsy body wt	41.0 ± 1.5	39.3 ± 1.1	35.2 ± 0.7**
Brain			
Absolute	0.468 ± 0.004	0.464 ± 0.006	0.456 ± 0.006
Relative	11.53 ± 0.34	11.88 ± 0.34	13.00 ± 0.22**
R. Kidney			
Absolute	0.363 ± 0.010	0.351 ± 0.008	0.322 ± 0.008**
Relative	8.90 ± 0.20	8.95 ± 0.17	9.16 ± 0.13
Liver			
Absolute	1.792 ± 0.056	1.767 ± 0.047	1.659 ± 0.042
Relative	43.82 ± 0.55	45.02 ± 0.70	47.18 ± 0.70**
Lungs			
Absolute	0.333 ± 0.011	0.312 ± 0.007	0.274 ± 0.007**
Relative	8.16 ± 0.21	7.96 ± 0.14	7.80 ± 0.19

\*\* Significantly different ( $P \leq 0.01$ ) from the control group by Williams' or Dunnett's test

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

**TABLE G6**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Mice**  
**at the 43-Week Stop-Exposure Evaluation of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.2 ppm (33 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
n	10	10	10	10
Necropsy body wt	42.4 ± 0.7	45.3 ± 1.6	36.6 ± 1.3*	30.8 ± 1.6**
Brain				
Absolute	0.476 ± 0.005	0.476 ± 0.003	0.458 ± 0.006*	0.453 ± 0.005**
Relative	11.25 ± 0.17	10.61 ± 0.35	12.65 ± 0.43	15.12 ± 0.90**
R. Kidney				
Absolute	0.402 ± 0.010	0.387 ± 0.010	0.340 ± 0.010**	0.318 ± 0.016**
Relative	9.49 ± 0.20	8.57 ± 0.14*	9.40 ± 0.42	10.36 ± 0.21
Liver				
Absolute	1.800 ± 0.036	1.904 ± 0.084	1.658 ± 0.039	1.514 ± 0.080**
Relative	42.54 ± 1.00	41.90 ± 0.50	45.60 ± 1.14	49.27 ± 1.00**
Lungs				
Absolute	0.248 ± 0.010	0.246 ± 0.010	0.206 ± 0.006	0.357 ± 0.061
Relative	5.87 ± 0.27	5.45 ± 0.19	5.70 ± 0.26	12.91 ± 3.14**

\* Significantly different ( $P \leq 0.05$ ) from the control group by Williams' or Dunnett's test

\*\*  $P \leq 0.01$

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

**TABLE G7**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Mice**  
**at the 15-Month Stop-Exposure Evaluation of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.2 ppm (33 weeks)	0.5 ppm (26 weeks)	0.5 ppm (42 weeks)
n	10	10	10	10
Necropsy body wt	42.5 ± 1.3	44.7 ± 1.5	40.1 ± 1.2	38.8 ± 2.3
Brain				
Absolute	0.463 ± 0.002	0.471 ± 0.007	0.472 ± 0.003	0.462 ± 0.005
Relative	10.99 ± 0.36	10.67 ± 0.43	11.88 ± 0.42	12.34 ± 0.82
R. Kidney				
Absolute	0.358 ± 0.011	0.359 ± 0.009	0.375 ± 0.018	0.331 ± 0.012
Relative	8.46 ± 0.24	8.13 ± 0.39	9.36 ± 0.34	8.68 ± 0.31
Liver				
Absolute	2.054 ± 0.084 <sup>b</sup>	1.888 ± 0.064	1.684 ± 0.058*	1.668 ± 0.120**
Relative	49.08 ± 3.03 <sup>b</sup>	42.49 ± 1.33*	42.02 ± 0.72*	43.03 ± 1.66
Lungs				
Absolute	0.229 ± 0.009	0.216 ± 0.006	0.243 ± 0.005	0.235 ± 0.009
Relative	5.42 ± 0.23	4.87 ± 0.15	6.12 ± 0.24	6.27 ± 0.48

\* Significantly different ( $P \leq 0.05$ ) from the control group by Williams' or Dunnett's test

\*\*  $P \leq 0.01$

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

<sup>b</sup> n=9

**TABLE G8**  
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice**  
**at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Male</b>				
n	10	10	10	10
Necropsy body wt	42.5 ± 1.3	40.7 ± 1.4	42.7 ± 1.4	40.8 ± 1.7
<b>Brain</b>				
Absolute	0.463 ± 0.002	0.465 ± 0.005	0.468 ± 0.005	0.457 ± 0.005
Relative	10.99 ± 0.36	11.51 ± 0.33	11.04 ± 0.33	11.36 ± 0.43
<b>R. Kidney</b>				
Absolute	0.358 ± 0.011	0.358 ± 0.007	0.365 ± 0.010	0.359 ± 0.015
Relative	8.46 ± 0.24	8.85 ± 0.23	8.59 ± 0.27	8.85 ± 0.27
<b>Liver</b>				
Absolute	2.054 ± 0.084 <sup>b</sup>	1.774 ± 0.101	1.907 ± 0.082	1.739 ± 0.055*
Relative	49.08 ± 3.03 <sup>b</sup>	43.59 ± 2.11	44.95 ± 2.40	42.87 ± 0.71
<b>Lungs</b>				
Absolute	0.229 ± 0.009	0.267 ± 0.045	0.211 ± 0.004	0.224 ± 0.003
Relative	5.42 ± 0.23	6.74 ± 1.28	4.98 ± 0.17	5.59 ± 0.27
<b>Female</b>				
n	10	10	10	10
Necropsy body wt	45.1 ± 1.5	39.4 ± 1.5*	41.0 ± 1.7*	37.9 ± 1.6**
<b>Brain</b>				
Absolute	0.492 ± 0.005	0.494 ± 0.005	0.490 ± 0.004	0.480 ± 0.006
Relative	10.99 ± 0.33	12.69 ± 0.43*	12.15 ± 0.52*	12.86 ± 0.55**
<b>R. Kidney</b>				
Absolute	0.259 ± 0.013	0.244 ± 0.005	0.247 ± 0.008	0.228 ± 0.007*
Relative	5.78 ± 0.34	6.25 ± 0.18	6.07 ± 0.18	6.08 ± 0.23
<b>Liver</b>				
Absolute	1.933 ± 0.087	1.682 ± 0.044*	1.792 ± 0.040*	1.601 ± 0.031**
Relative	42.86 ± 1.48	42.96 ± 0.95	44.20 ± 1.47	42.71 ± 1.40
<b>Lungs</b>				
Absolute	0.223 ± 0.010	0.230 ± 0.016	0.221 ± 0.005	0.224 ± 0.003
Relative	4.98 ± 0.25	5.93 ± 0.49	5.46 ± 0.21	5.99 ± 0.22*

\* Significantly different ( $P \leq 0.05$ ) from the control group by Williams' or Dunnett's test

\*\*  $P \leq 0.01$

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

<sup>b</sup> n=9

## APPENDIX H

### HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

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**TABLE H1**  
**Hematology and Clinical Chemistry Data for Rats in the 13-Week Inhalation Study**  
**of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
<b>Male</b>				
n	10	10	10	10
<b>Hematology</b>				
Packed cell volume (%)	40.4 ± 0.6	41.0 ± 0.5	40.2 ± 0.3	42.4 ± 0.5*
Hemoglobin (g/dL)	15.4 ± 0.3	15.9 ± 0.3	15.3 ± 0.1	16.3 ± 0.2**
Erythrocytes (10 <sup>6</sup> /μL)	8.40 ± 0.13	8.60 ± 0.10	8.35 ± 0.06	8.80 ± 0.08*
Mean cell volume (fL)	48.6 ± 0.2	48.1 ± 0.1	48.4 ± 0.2	48.8 ± 0.2
Mean cell hemoglobin (pg)	18.4 ± 0.1	18.3 ± 0.1	18.4 ± 0.1	18.6 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	38.2 ± 0.2	38.3 ± 0.2	38.3 ± 0.2	38.5 ± 0.1
Reticulocytes (10 <sup>6</sup> /μL)	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.1 ± 0.0
Leukocytes (10 <sup>3</sup> /μL)	3.79 ± 0.11	3.29 ± 0.17	3.72 ± 0.29	3.59 ± 0.25
Segmented neutrophils (10 <sup>3</sup> /μL)	1.12 ± 0.15	0.95 ± 0.08	1.17 ± 0.18	0.94 ± 0.08
Lymphocytes (10 <sup>3</sup> /μL)	2.55 ± 0.12	2.27 ± 0.16	2.47 ± 0.17	2.51 ± 0.19
Monocytes (10 <sup>3</sup> /μL)	0.07 ± 0.01	0.03 ± 0.01**	0.03 ± 0.01** <sup>b</sup>	0.08 ± 0.02
Eosinophils (10 <sup>3</sup> /μL)	0.04 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.05 ± 0.01
<b>Clinical Chemistry</b>				
Urea nitrogen (mg/dL)	23.7 ± 0.8	19.7 ± 0.5**	20.6 ± 0.7	22.6 ± 0.4
Creatinine (mg/dL)	0.96 ± 0.02	0.86 ± 0.02*	0.88 ± 0.03	0.89 ± 0.02
Glucose (mg/dL)	180 ± 8	195 ± 6	196 ± 3	184 ± 7
Albumin (g/dL)	4.2 ± 0.0	4.1 ± 0.1	4.0 ± 0.0*	4.1 ± 0.1
Alanine aminotransferase (IU/L)	54 ± 4	39 ± 2**	41 ± 2**	46 ± 2
Aspartate aminotransferase (IU/L)	111 ± 4 <sup>b</sup>	84 ± 3**	88 ± 2**	92 ± 3**
Lactate dehydrogenase (IU/L)	941 ± 136	711 ± 68	717 ± 36	670 ± 70
<b>Female</b>				
n	10	10	10	10
<b>Hematology</b>				
Packed cell volume (%)	41.5 ± 0.3	40.8 ± 0.5	39.4 ± 0.5*	40.9 ± 0.6
Hemoglobin (g/dL)	15.9 ± 0.2	15.6 ± 0.2	14.9 ± 0.2*	15.6 ± 0.3
Erythrocytes (10 <sup>6</sup> /μL)	8.11 ± 0.09	8.01 ± 0.08	7.51 ± 0.17*	7.82 ± 0.11*
Mean cell volume (fL)	51.5 ± 0.2	51.2 ± 0.2	52.9 ± 0.9	52.7 ± 0.2**
Mean cell hemoglobin (pg)	19.7 ± 0.1	19.5 ± 0.1	20.0 ± 0.2	20.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	38.4 ± 0.2	38.4 ± 0.2	37.9 ± 0.2	38.2 ± 0.2
Reticulocytes (10 <sup>6</sup> /μL)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0 <sup>b</sup>	0.1 ± 0.0
Leukocytes (10 <sup>3</sup> /μL)	3.52 ± 0.24	3.20 ± 0.18	3.47 ± 0.26	3.20 ± 0.19
Segmented neutrophils (10 <sup>3</sup> /μL)	0.87 ± 0.09	0.73 ± 0.05	0.70 ± 0.06 <sup>b</sup>	0.69 ± 0.10
Lymphocytes (10 <sup>3</sup> /μL)	2.58 ± 0.19	2.42 ± 0.16	2.54 ± 0.19	2.44 ± 0.15
Monocytes (10 <sup>3</sup> /μL)	0.04 ± 0.01	0.04 ± 0.00	0.03 ± 0.01	0.02 ± 0.01
Eosinophils (10 <sup>3</sup> /μL)	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.01



**TABLE H1**  
**Hematology and Clinical Chemistry Data for Rats in the 13-Week Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
<b>Female (continued)</b>				
n	10	10	10	10
<b>Clinical Chemistry</b>				
Urea nitrogen (mg/dL)	20.5 ± 0.9	19.7 ± 0.5	18.9 ± 0.7	19.4 ± 0.7
Creatinine (mg/dL)	0.87 ± 0.03	0.90 ± 0.04	0.89 ± 0.03	0.87 ± 0.05
Glucose (mg/dL)	179 ± 5	177 ± 7	183 ± 5	190 ± 10
Albumin (g/dL)	4.5 ± 0.1	4.4 ± 0.1	4.3 ± 0.0	4.3 ± 0.1
Alanine aminotransferase (IU/L)	42 ± 4	46 ± 4	45 ± 7	38 ± 3
Aspartate aminotransferase (IU/L)	91 ± 4	95 ± 5	94 ± 11	85 ± 2
Lactate dehydrogenase (IU/L)	738 ± 116	632 ± 49	737 ± 56	679 ± 84

\* Significantly different ( $P \leq 0.05$ ) from the control group by Dunn's or Shirley's test

\*\*  $P \leq 0.01$

<sup>a</sup> Mean ± standard error. No data were collected for 1 and 2 ppm males and females due to 100% mortality.

<sup>b</sup> n=9

**TABLE H2**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Male</b>				
<b>Hematology</b>				
n	4	4	5	
Packed cell volume (%)				
Week 13	42.2 ± 0.9	41.3 ± 0.9	42.5 ± 1.2	
Hemoglobin (g/dL)				
Week 13	16.3 ± 0.4	15.8 ± 0.4	16.1 ± 0.5	
Erythrocytes (10 <sup>6</sup> /μL)				
Week 13	8.91 ± 0.17	8.68 ± 0.20	8.78 ± 0.24	
Mean cell volume (fL)				
Week 13	48.0 ± 0.4	48.3 ± 0.3	49.2 ± 0.2*	
Mean cell hemoglobin (pg)				
Week 13	18.3 ± 0.1	18.2 ± 0.2	18.4 ± 0.1	
Mean cell hemoglobin concentration (g/dL)				
Week 13	38.6 ± 0.1	38.0 ± 0.3	37.9 ± 0.2	
Reticulocytes (10 <sup>6</sup> /μL)				
Week 13	0.2 ± 0.0	0.2 ± 0.1	0.1 ± 0.0	
Leukocytes (10 <sup>3</sup> /μL)				
Week 13	4.35 ± 0.31	4.58 ± 0.44	4.16 ± 0.41	
Segmented neutrophils (10 <sup>3</sup> /μL)				
Week 13	1.08 ± 0.19	1.23 ± 0.11	1.02 ± 0.15	
Lymphocytes (10 <sup>3</sup> /μL)				
Week 13	3.16 ± 0.34	3.20 ± 0.39	3.04 ± 0.36	
Monocytes (10 <sup>3</sup> /μL)				
Week 13	0.04 ± 0.02	0.08 ± 0.04	0.05 ± 0.02	
Eosinophils (10 <sup>3</sup> /μL)				
Week 13	0.07 ± 0.03	0.07 ± 0.01	0.05 ± 0.01	
<b>Clinical Chemistry</b>				
n	5	5	5	5
Urea nitrogen (mg/dL)				
Day 4	17.8 ± 0.9	19.0 ± 1.2	17.4 ± 1.0	32.8 ± 7.8
Day 16	17.0 ± 1.2 <sup>b</sup>	19.0 ± 0.9	19.6 ± 1.5	98.5 ± 28.5* <sup>c</sup>
Day 46	21.0 ± 1.2	18.8 ± 0.9	24.6 ± 1.9	- <sup>d</sup>
Week 13	18.8 ± 0.7	19.6 ± 0.9	19.6 ± 0.8	-
Creatinine (mg/dL)				
Day 4	0.54 ± 0.07	0.62 ± 0.05	0.69 ± 0.02	0.98 ± 0.15* <sup>b</sup>
Day 16	0.80 ± 0.06 <sup>b</sup>	0.73 ± 0.04	0.73 ± 0.01	0.72 ± 0.06 <sup>c</sup>
Day 46	0.79 ± 0.04	0.80 ± 0.04	0.86 ± 0.04	-
Week 13	0.84 ± 0.03	0.86 ± 0.04	0.91 ± 0.10	-
Glucose (mg/dL)				
Day 4	186 ± 6	180 ± 5	200 ± 7	176 ± 55
Day 16	191 ± 7 <sup>b</sup>	218 ± 26	201 ± 7	52 ± 19 <sup>c</sup>
Day 46	228 ± 9	226 ± 3	232 ± 7	-
Week 13	186 ± 7	198 ± 12	255 ± 46	-

**TABLE H2**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Male (continued)</b>				
<b>Clinical Chemistry (continued)</b>				
n	5	5	5	5
<b>Albumin (g/dL)</b>				
Day 4	3.7 ± 0.2	4.0 ± 0.1	3.9 ± 0.1	4.0 ± 0.1
Day 16	4.0 ± 0.0 <sup>b</sup>	4.0 ± 0.2	4.0 ± 0.1	3.3 ± 0.2 <sup>c</sup>
Day 46	4.4 ± 0.1	4.6 ± 0.1	4.6 ± 0.2	–
Week 13	4.7 ± 0.1	4.4 ± 0.1	4.5 ± 0.2	–
<b>Alanine aminotransferase (IU/L)</b>				
Day 4	37 ± 3	38 ± 5	33 ± 3	485 ± 301 <sup>b</sup>
Day 16	33 ± 3 <sup>b</sup>	35 ± 2	31 ± 1	290 ± 186 <sup>c</sup>
Day 46	36 ± 4	31 ± 1	39 ± 2	–
Week 13	44 ± 2	41 ± 3	39 ± 3	–
<b>Aspartate aminotransferase (IU/L)</b>				
Day 4	93 ± 10	100 ± 16	96 ± 8	711 ± 444 <sup>a,b</sup>
Day 16	80 ± 2 <sup>b</sup>	85 ± 5	85 ± 2	304 ± 151 <sup>a,c</sup>
Day 46	94 ± 7	83 ± 5	94 ± 4	–
Week 13	122 ± 5	109 ± 9	98 ± 10 <sup>*</sup>	–
<b>Lactate dehydrogenase (IU/L)</b>				
Day 4	737 ± 202	972 ± 361	625 ± 109	2,246 ± 1,095 <sup>b</sup>
Day 16	765 ± 83 <sup>b</sup>	706 ± 166	757 ± 68	832 ± 82 <sup>c</sup>
Day 46	871 ± 122	773 ± 114	753 ± 127	–
Week 13	1,275 ± 182	1,110 ± 89	579 ± 81 <sup>**</sup>	–
<b>Urinalysis</b>				
n	5	5	5	5
<b>Osmolality (mOsm/kg)</b>				
Day 4	1,569 ± 191	1,614 ± 193	1,538 ± 180	1,972 ± 126
Day 16	1,697 ± 159	1,637 ± 158	1,814 ± 52	2,716 <sup>e</sup>
Day 46	1,821 ± 75	1,458 ± 167	1,771 ± 89	–
Week 13	1,227 ± 65	959 ± 90	1,425 ± 37	–
<b>Creatinine (mg/dL)</b>				
Day 4	56.74 ± 6.44	57.48 ± 8.41	60.58 ± 7.20	61.34 ± 9.02
Day 16	74.54 ± 8.06	71.00 ± 10.02	70.84 ± 3.67	75.90 <sup>e</sup>
Day 46	98.56 ± 4.27	83.90 ± 3.28 <sup>*</sup>	85.26 ± 3.36 <sup>*</sup>	–
Week 13	104.26 ± 8.65	99.62 ± 9.11	110.58 ± 7.79	–
<b>Creatinine (mg/100 g/16 hr)</b>				
Day 4	3.14 ± 0.27	3.04 ± 0.20	1.77 ± 0.35 <sup>*</sup>	0.88 ± 0.13 <sup>**</sup>
Day 16	2.66 ± 0.25	2.36 ± 0.13	2.73 ± 0.20	0.29 <sup>e</sup>
Day 46	2.47 ± 0.11	2.17 ± 0.24	2.57 ± 0.12	–
Week 13	3.39 ± 1.12	1.92 ± 0.20	2.26 ± 0.37	–

**TABLE H2**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the Special 13-Week Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Male (continued)</b>				
<b>Urinalysis (continued)</b>				
n	5	5	5	5
<b>Glucose (mg/dL)</b>				
Day 4	40 ± 5	40 ± 6	48 ± 9	46 ± 5 <sup>b</sup>
Day 16	72 ± 4 <sup>b</sup>	46 ± 11	53 ± 4	106 <sup>e</sup>
Day 46	64 ± 4	59 ± 5	55 ± 7	—
Week 13	23 ± 4	18 ± 3	37 ± 4	—
<b>Glucose (mg/100 g/16 hr)</b>				
Day 4	2.2 ± 0.3	2.1 ± 0.2	1.2 ± 0.2*	0.5 ± 0.1** <sup>b</sup>
Day 16	2.5 ± 0.2 <sup>b</sup>	1.5 ± 0.2*	1.8 ± 0.2*	0.4 <sup>e</sup>
Day 46	1.6 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	—
Week 13	0.6 ± 0.2	0.3 ± 0.1	1.0 ± 0.3	—
<b>Protein (mg/dL)</b>				
Day 4	48 ± 10	40 ± 9	34 ± 13	97 ± 45 <sup>b</sup>
Day 16	145 ± 8	118 ± 36	135 ± 4 <sup>b</sup>	240 <sup>e</sup>
Day 46	163 ± 11	145 ± 8	188 ± 24	—
Week 13	129 ± 10	110 ± 20	224 ± 46	—
<b>Protein (mg/100 g/16 hr)</b>				
Day 4	3 ± 1	2 ± 0	1 ± 0*	1 ± 1 <sup>b</sup>
Day 16	5 ± 1	4 ± 1	4 ± 1	1 <sup>e</sup>
Day 46	4 ± 0	4 ± 0	6 ± 0	—
Week 13	4 ± 2	2 ± 0	4 ± 0	—
<b>Volume (mL/16 hr)</b>				
Day 4	7.9 ± 1.4	7.1 ± 1.4	4.0 ± 1.4	1.0 ± 0.1** <sup>b</sup>
Day 16	7.0 ± 0.9	6.3 ± 0.6	5.7 ± 0.5	0.2 ± 0.1 <sup>c</sup>
Day 46	6.8 ± 0.5	7.2 ± 0.8	7.8 ± 0.8	—
Week 13	8.0 ± 1.5	6.5 ± 1.0	6.4 ± 1.3	—
<b>Female</b>				
<b>Hematology</b>				
n	5	5	5	
<b>Packed cell volume (%)</b>				
Week 13	37.3 ± 1.4	41.1 ± 1.0	41.9 ± 0.7**	
<b>Hemoglobin (g/dL)</b>				
Week 13	14.1 ± 0.6	15.6 ± 0.4	15.8 ± 0.3*	
<b>Erythrocytes (10<sup>6</sup>/μL)</b>				
Week 13	7.35 ± 0.32	8.08 ± 0.20	8.16 ± 0.17*	
<b>Mean cell volume (fL)</b>				
Week 13	51.2 ± 0.2	51.0 ± 0.0	52.2 ± 0.4*	
<b>Mean cell hemoglobin (pg)</b>				
Week 13	19.3 ± 0.1	19.3 ± 0.1	19.4 ± 0.1	

**TABLE H2**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Female (continued)</b>				
<b>Hematology (continued)</b>				
n	5	5	5	
Mean cell hemoglobin concentration (g/dL)				
Week 13	38.0 ± 0.2	37.9 ± 0.2	37.7 ± 0.1	
Reticulocytes (10 <sup>6</sup> /μL)				
Week 13	0.15 ± 0.02	0.14 ± 0.01	0.09 ± 0.02*	
Leukocytes (10 <sup>3</sup> /μL)				
Week 13	2.54 ± 0.24	3.14 ± 0.22	3.38 ± 0.45	
Segmented neutrophils (10 <sup>3</sup> /μL)				
Week 13	0.63 ± 0.07	0.75 ± 0.07	0.63 ± 0.15	
Lymphocytes (10 <sup>3</sup> /μL)				
Week 13	1.87 ± 0.21	2.30 ± 0.26	2.68 ± 0.33	
Monocytes (10 <sup>3</sup> /μL)				
Week 13	0.02 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	
Eosinophils (10 <sup>3</sup> /μL)				
Week 13	0.01 ± 0.00 <sup>b</sup>	0.04 ± 0.01	0.03 ± 0.01	
<b>Clinical Chemistry</b>				
n	5	5	5	3
Urea nitrogen (mg/dL)				
Day 4	21.6 ± 1.2	17.8 ± 1.1	16.0 ± 0.9**	18.7 ± 0.9*
Day 16	14.2 ± 1.2	17.8 ± 1.2	18.4 ± 0.5*	-
Day 46	20.0 ± 2.2 <sup>b</sup>	19.2 ± 1.0	24.0 ± 4.4	-
Week 13	19.4 ± 0.8	25.4 ± 5.8	22.6 ± 1.4	-
Creatinine (mg/dL)				
Day 4	0.69 ± 0.04	0.64 ± 0.02	0.74 ± 0.04	0.84 ± 0.08
Day 16	0.70 ± 0.04	0.66 ± 0.01	0.73 ± 0.02	-
Day 46	0.88 ± 0.07 <sup>b</sup>	0.77 ± 0.02	0.76 ± 0.04 <sup>b</sup>	-
Week 13	0.79 ± 0.03 <sup>b</sup>	0.89 ± 0.18 <sup>b</sup>	0.70 ± 0.03 <sup>f</sup>	-
Glucose (mg/dL)				
Day 4	194 ± 12	182 ± 8	191 ± 8	210 ± 12
Day 16	174 ± 5	184 ± 7	195 ± 8*	-
Day 46	213 ± 14 <sup>b</sup>	234 ± 14	242 ± 11	-
Week 13	240 ± 20	212 ± 8	220 ± 17	-
Albumin (g/dL)				
Day 4	4.1 ± 0.1	3.7 ± 0.1*	3.8 ± 0.0	3.9 ± 0.1
Day 16	3.9 ± 0.1	3.9 ± 0.1	4.2 ± 0.1	-
Day 46	4.7 ± 0.2 <sup>b</sup>	4.5 ± 0.1	4.4 ± 0.1	-
Week 13	4.5 ± 0.1	4.7 ± 0.1	4.5 ± 0.1	-
Alanine aminotransferase (IU/L)				
Day 4	35 ± 2	34 ± 4	27 ± 2	77 ± 29
Day 16	26 ± 2	25 ± 2	25 ± 1	-
Day 46	28 ± 1 <sup>b</sup>	34 ± 2	33 ± 1*	-
Week 13	47 ± 8	44 ± 4	38 ± 3	-

**TABLE H2**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the Special 13-Week Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Female (continued)</b>				
<b>Clinical Chemistry (continued)</b>				
n	5	5	5	3
<b>Aspartate aminotransferase (IU/L)</b>				
Day 4	86 ± 5	91 ± 6	99 ± 6	153 ± 37*
Day 16	86 ± 7	79 ± 4	76 ± 2	-
Day 46	90 ± 3 <sup>b</sup>	90 ± 5	94 ± 7	-
Week 13	107 ± 15	100 ± 13	89 ± 6	-
<b>Lactate dehydrogenase (IU/L)</b>				
Day 4	563 ± 111	798 ± 102	884 ± 82	825 ± 168
Day 16	925 ± 194	767 ± 142	469 ± 52*	-
Day 46	1,009 ± 148 <sup>b</sup>	785 ± 205	807 ± 119	-
Week 13	858 ± 187	629 ± 101	584 ± 128	-
<b>Urinalysis</b>				
n	5	5	5	3
<b>Osmolality (mOsm/kg)</b>				
Day 4	1,796 ± 102	1,780 ± 168	1,557 ± 90	2,264 ± 365
Day 16	1,261 ± 64	1,816 ± 195	1,966 ± 148 <sup>a,b</sup>	-
Day 46	2,089 ± 148 <sup>b</sup>	1,450 ± 158 <sup>a,b</sup>	1,533 ± 175*	-
Week 13	1,516 ± 163	1,582 ± 205	1,552 ± 154	-
<b>Creatinine (mg/dL)</b>				
Day 4	54.94 ± 3.72	57.90 ± 5.83	58.18 ± 2.26	69.23 ± 18.34
Day 16	52.20 ± 2.57	62.76 ± 7.23	78.45 ± 7.65 <sup>a,b</sup>	-
Day 46	108.35 ± 5.20 <sup>b</sup>	67.40 ± 10.00 <sup>a,b</sup>	67.38 ± 5.49*	-
Week 13	71.02 ± 7.45	76.26 ± 11.57	72.36 ± 7.98	-
<b>Creatinine (mg/100 g/16 hr)</b>				
Day 4	3.37 ± 0.29	2.96 ± 0.36	2.09 ± 0.33*	0.60 ± 0.10**
Day 16	3.09 ± 0.15	2.31 ± 0.21*	2.47 ± 0.18 <sup>a,b</sup>	-
Day 46	2.45 ± 0.14 <sup>b</sup>	2.26 ± 0.46 <sup>b</sup>	2.69 ± 0.34	-
Week 13	3.04 ± 0.17	2.47 ± 0.27	2.41 ± 0.27	-
<b>Glucose (mg/dL)</b>				
Day 4	26 ± 5	35 ± 3	38 ± 6	70 ± 0 <sup>a,c</sup>
Day 16	25 ± 3	37 ± 5	47 ± 5 <sup>a,b</sup>	-
Day 46	55 ± 7 <sup>b</sup>	48 ± 17 <sup>b</sup>	30 ± 3*	-
Week 13	26 ± 4	30 ± 8	28 ± 4	-
<b>Glucose (mg/100 g/16 hr)</b>				
Day 4	1.5 ± 0.1	1.8 ± 0.2	1.3 ± 0.1	5.8 ± 5.2
Day 16	1.4 ± 0.1	1.4 ± 0.2	1.5 ± 0.1 <sup>b</sup>	-
Day 46	1.2 ± 0.1 <sup>b</sup>	1.5 ± 0.4 <sup>b</sup>	1.2 ± 0.2	-
Week 13	1.1 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	-

**TABLE H2**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Female (continued)</b>				
<b>Urinalysis (continued)</b>				
n	5	5	5	3
<b>Protein (mg/dL)</b>				
Day 4	15 ± 3	17 ± 3	33 ± 16	20
Day 16	6 ± 1 <sup>b</sup>	22 ± 9 <sup>*</sup>	13 ± 3 <sup>f</sup>	—
Day 46	19 ± 8 <sup>b</sup>	33 ± 7 <sup>f</sup>	23 ± 3	—
Week 13	13 ± 3 <sup>b</sup>	22 ± 10	27 ± 7	—
<b>Protein (mg/100 g/16 hr)</b>				
Day 4	1 ± 0	1 ± 0	1 ± 0	0
Day 16	1 ± 0	1 ± 0	0 ± 0 <sup>f</sup>	—
Day 46	0 ± 0 <sup>b</sup>	3 ± 2 <sup>*b</sup>	1 ± 0	—
Week 13	1 ± 0 <sup>b</sup>	1 ± 0	1 ± 0	—
<b>Volume (mL/16 hr)</b>				
Day 4	6.6 ± 1.0	6.0 ± 1.1	3.6 ± 0.7	0.8 ± 0.2 <sup>**</sup>
Day 16	8.1 ± 0.8	5.2 ± 0.6 <sup>*</sup>	4.3 ± 0.7 <sup>**</sup>	—
Day 46	3.5 ± 0.3 <sup>b</sup>	6.2 ± 2.1 <sup>b</sup>	6.6 ± 1.2	—
Week 13	9.1 ± 1.6	6.9 ± 1.0	6.5 ± 1.4	—

\* Significantly different ( $P \leq 0.05$ ) from the control group by Dunn's or Shirley's test

\*\*  $P \leq 0.01$

<sup>a</sup> Mean ± standard error. No hematology data were collected for 2 ppm males and females.

<sup>b</sup> n=4

<sup>c</sup> n=2

<sup>d</sup> No data collected due to 100% mortality in 2 ppm males after week 2 and 2 ppm females after week 1.

<sup>e</sup> No standard error was calculated due to high mortality.

<sup>f</sup> n=3

**TABLE H3**  
**Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study**  
**of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Male</b>				
n	10	10	10	10
Urinalysis				
Volume (mL/16 hr)	8.8 ± 1.0	6.5 ± 0.7	6.4 ± 0.5	6.6 ± 0.7
Specific gravity	1.029 ± 0.002	1.037 ± 0.003*	1.036 ± 0.002*	1.037 ± 0.003*
<b>Female</b>				
n	10	10	10	9
Urinalysis				
Volume (mL/16 hr)	7.9 ± 0.8	6.8 ± 0.5	5.9 ± 0.5	5.5 ± 0.6*
Specific gravity	1.022 ± 0.002	1.025 ± 0.001	1.029 ± 0.002*	1.029 ± 0.003*

\* Significantly different ( $P \leq 0.05$ ) from the control group by Dunn's or Shirley's test

<sup>a</sup> Mean ± standard error



**TABLE H4**  
**Hematology and Clinical Chemistry Data for Mice in the 13-Week Inhalation Study**  
**of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
<b>Male</b>				
<b>Hematology</b>				
n	10	8	10	5
Packed cell volume (%)	39.2 ± 0.7	40.8 ± 0.8	40.2 ± 0.6	40.7 ± 0.4
Hemoglobin (g/dL)	15.2 ± 0.3	15.5 ± 0.3	15.6 ± 0.2	15.7 ± 0.2
Erythrocytes (10 <sup>6</sup> /μL)	8.68 ± 0.17	8.93 ± 0.18	8.89 ± 0.12	8.94 ± 0.09
Mean cell volume (fL)	45.7 ± 0.2	46.4 ± 0.2	45.8 ± 0.3	46.2 ± 0.2
Mean cell hemoglobin (pg)	17.6 ± 0.1	17.4 ± 0.1	17.6 ± 0.1	17.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)	38.7 ± 0.2	38.0 ± 0.2*	38.7 ± 0.2	38.6 ± 0.0
Reticulocytes (10 <sup>6</sup> /μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10 <sup>3</sup> /μL)	3.89 ± 0.42	3.99 ± 0.59	4.48 ± 0.39	3.80 ± 0.17
Segmented neutrophils (10 <sup>3</sup> /μL)	0.56 ± 0.09	0.77 ± 0.25	0.70 ± 0.09 <sup>b</sup>	0.67 ± 0.12
Lymphocytes (10 <sup>3</sup> /μL)	3.24 ± 0.35	3.16 ± 0.39	3.39 ± 0.29	3.01 ± 0.09
Monocytes (10 <sup>3</sup> /μL)	0.02 ± 0.01	0.02 ± 0.01	0.05 ± 0.01	0.01 ± 0.01
Eosinophils (10 <sup>3</sup> /μL)	0.06 ± 0.02	0.04 ± 0.01	0.05 ± 0.01	0.11 ± 0.02
<b>Clinical Chemistry</b>				
n	9	7	10	4
Urea nitrogen (mg/dL)	29.2 ± 1.7	30.3 ± 1.3 <sup>c</sup>	30.8 ± 1.5	29.6 ± 1.7 <sup>d</sup>
Creatinine (mg/dL)	0.67 ± 0.05 <sup>c</sup>	0.74 ± 0.06	0.69 ± 0.04	0.46 ± 0.09
Glucose (mg/dL)	168 ± 9	180 ± 5	169 ± 8	161 ± 18
Albumin (g/dL)	3.5 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	3.8 ± 0.2
Alanine aminotransferase (IU/L)	93 ± 25 <sup>d</sup>	138 ± 33	70 ± 10 <sup>e</sup>	145 ± 40
Aspartate aminotransferase (IU/L)	119 ± 19 <sup>c</sup>	113 ± 11	148 ± 49 <sup>c</sup>	194 ± 73
<b>Female</b>				
<b>Hematology</b>				
n	4	9	9	8
Packed cell volume (%)	41.2 ± 0.8	41.8 ± 0.9	41.2 ± 0.7	39.6 ± 0.5
Hemoglobin (g/dL)	15.6 ± 0.1	15.8 ± 0.3	15.7 ± 0.2	15.5 ± 0.2
Erythrocytes (10 <sup>6</sup> /μL)	8.82 ± 0.13	9.04 ± 0.18	8.95 ± 0.12	8.76 ± 0.11
Mean cell volume (fL)	47.3 ± 0.5	46.9 ± 0.2	46.3 ± 0.3	45.8 ± 0.4*
Mean cell hemoglobin (pg)	17.7 ± 0.2	17.6 ± 0.1	17.6 ± 0.1	17.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	37.9 ± 0.6	37.8 ± 0.2	38.2 ± 0.2	39.3 ± 0.2
Reticulocytes (10 <sup>6</sup> /μL)	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10 <sup>3</sup> /μL)	3.65 ± 0.47	5.73 ± 0.26**	4.93 ± 0.33	4.44 ± 0.38
Segmented neutrophils (10 <sup>3</sup> /μL)	1.05 ± 0.19	0.97 ± 0.07	0.75 ± 0.18	0.84 ± 0.11
Lymphocytes (10 <sup>3</sup> /μL)	2.59 ± 0.28	4.65 ± 0.29**	4.11 ± 0.30	3.49 ± 0.34
Monocytes (10 <sup>3</sup> /μL)	0.01 ± 0.01	0.05 ± 0.02	0.03 ± 0.01	0.04 ± 0.01
Eosinophils (10 <sup>3</sup> /μL)	0.01 ± 0.01	0.06 ± 0.01	0.04 ± 0.01	0.05 ± 0.02

**TABLE H4**  
**Hematology and Clinical Chemistry Data for Mice in the 13-Week Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
<b>Female (continued)</b>				
<b>Clinical Chemistry</b>				
<b>n</b>	4	7	9	7
Urea nitrogen (mg/dL)	19.8 ± 0.6	17.9 ± 0.6 <sup>b</sup>	18.7 ± 0.8	19.8 ± 1.0 <sup>c</sup>
Creatinine (mg/dL)	0.58 ± 0.06	0.74 ± 0.04 <sup>b</sup>	0.70 ± 0.04	0.59 ± 0.06 <sup>c</sup>
Glucose (mg/dL)	156 ± 14	153 ± 8	150 ± 9	134 ± 2
Albumin (g/dL)	3.7 ± 0.1	4.0 ± 0.1 <sup>a</sup>	3.8 ± 0.1	3.6 ± 0.0
Alanine aminotransferase (IU/L)	97 ± 27	120 ± 21 <sup>f</sup>	149 ± 29	148 ± 29
Aspartate aminotransferase (IU/L)	160 ± 6	218 ± 50 <sup>g</sup>	217 ± 31	273 ± 39

\* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Mean ± standard error. No data were collected for 1 and 2 ppm males and females due to 100% mortality.

<sup>b</sup> n=9

<sup>c</sup> n=8

<sup>d</sup> n=5

<sup>e</sup> n=7

<sup>f</sup> n=4

<sup>g</sup> n=6

**TABLE H5**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Male</b>				
<b>Hematology</b>				
n	5	5	4	
Packed cell volume (%)				
Week 13	42.0 ± 1.7	43.2 ± 0.9	41.3 ± 0.7	
Hemoglobin (g/dL)				
Week 13	15.8 ± 0.6	16.4 ± 0.2	16.0 ± 0.2	
Erythrocytes (10 <sup>6</sup> /μL)				
Week 13	9.21 ± 0.42	9.44 ± 0.13	9.25 ± 0.15	
Mean cell volume (fL)				
Week 13	46.0 ± 0.6	46.4 ± 0.4	44.5 ± 0.3	
Mean cell hemoglobin (pg)				
Week 13	17.2 ± 0.2	17.5 ± 0.1	17.3 ± 0.1	
Mean cell hemoglobin concentration (g/dL)				
Week 13	37.5 ± 0.3	38.1 ± 0.5	38.8 ± 0.1*	
Reticulocytes (10 <sup>6</sup> /μL)				
Week 13	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	
Leukocytes (10 <sup>3</sup> /μL)				
Week 13	6.82 ± 0.65	6.12 ± 0.74	7.93 ± 0.77	
Segmented neutrophils (10 <sup>3</sup> /μL)				
Week 13	1.54 ± 0.37	0.66 ± 0.03 <sup>b</sup>	1.61 ± 0.28	
Lymphocytes (10 <sup>3</sup> /μL)				
Week 13	5.14 ± 0.38	5.13 ± 0.72	6.08 ± 0.74	
Monocytes (10 <sup>3</sup> /μL)				
Week 13	0.08 ± 0.03	0.08 ± 0.04	0.06 ± 0.03	
Eosinophils (10 <sup>3</sup> /μL)				
Week 13	0.05 ± 0.02	0.05 ± 0.01	0.18 ± 0.04*	
<b>Clinical Chemistry</b>				
n	5	5	5	
Urea nitrogen (mg/dL)				
Day 4	18.6 ± 0.8	17.4 ± 0.4	22.6 ± 0.5*	
Day 16	24.4 ± 1.3	22.0 ± 2.3	21.2 ± 1.0	
Day 46	30.4 ± 2.3	25.8 ± 1.8	28.6 ± 2.0	
Week 13	28.2 ± 2.2	29.8 ± 2.4 <sup>b</sup>	26.2 ± 0.9	
Creatinine (mg/dL)				
Day 4	0.42 ± 0.07	0.43 ± 0.01	0.36 ± 0.05	
Day 16	0.53 ± 0.06	0.47 ± 0.07	0.40 ± 0.05	
Day 46	0.66 ± 0.07	0.69 ± 0.09	0.81 ± 0.07 <sup>b</sup>	
Week 13	0.34 ± 0.10	0.31 ± 0.10 <sup>b</sup>	0.30 ± 0.12	
Glucose (mg/dL)				
Day 4	143 ± 14	169 ± 9	131 ± 3	
Day 16	133 ± 13	137 ± 6	123 ± 8	
Day 46	160 ± 2	177 ± 10	152 ± 8	
Week 13	146 ± 10	138 ± 14 <sup>b</sup>	111 ± 3*	

**TABLE H5**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the Special 13-Week Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Male (continued)</b>				
<b>Clinical Chemistry (continued)</b>				
n	5	5	5	
<b>Albumin (g/dL)</b>				
Day 4	3.2 ± 0.2	3.1 ± 0.1	3.1 ± 0.1	
Day 16	3.4 ± 0.1	3.2 ± 0.1	3.4 ± 0.2	
Day 46	3.4 ± 0.1	3.3 ± 0.1	3.6 ± 0.0	
Week 13	3.4 ± 0.1 <sup>c</sup>	3.5 ± 0.0 <sup>b</sup>	3.4 ± 0.1	
<b>Alanine aminotransferase (IU/L)</b>				
Day 4	23 ± 5	114 ± 46*	89 ± 31*	
Day 16	50 ± 11 <sup>b</sup>	225 ± 95	116 ± 59	
Day 46	72 ± 9	33 ± 4*	38 ± 3*	
Week 13	441 ± 52	338 ± 92 <sup>b</sup>	267 ± 88	
<b>Aspartate aminotransferase (IU/L)</b>				
Day 4	91 ± 25	75 ± 15	99 ± 21	
Day 16	79 ± 20	99 ± 19	103 ± 16	
Day 46	75 ± 8	63 ± 9	67 ± 5	
Week 13	468 ± 84	288 ± 135 <sup>b</sup>	190 ± 47*	
<b>Lactate dehydrogenase (IU/L)</b>				
Day 4	404 ± 21 <sup>b</sup>	472 ± 141	745 ± 116	
Day 16	661 ± 226	989 ± 223	998 ± 253	
Day 46	696 ± 107	427 ± 79	410 ± 55	
<b>Urinalysis</b>				
n	5	5	5	
<b>Osmolality (mOsm/kg)</b>				
Day 4	2,528 ± 293 <sup>b</sup>	2,203 ± 118	2,517 ± 95	
Day 16	2,276 ± 270 <sup>b</sup>	1,752 ± 276	2,748 ± 142	
Day 46	2,880 ± 97	2,953 ± 163	3,065 ± 168	
Week 13	3,142 ± 338	3,205 ± 101	3,047 ± 387	
<b>Creatinine (mg/dL)</b>				
Day 4	53.15 ± 3.86 <sup>b</sup>	47.30 ± 2.39	49.88 ± 1.04	
Day 16	53.00 ± 4.47 <sup>b</sup>	40.50 ± 5.70	62.24 ± 1.72	
Day 46	52.38 ± 1.74	52.72 ± 3.39	54.98 ± 2.85	
Week 13	69.10 ± 8.00	67.84 ± 2.26	64.86 ± 6.26	
<b>Creatinine (mg/100 g/16 hr)</b>				
Day 4	2.07 ± 0.48 <sup>b</sup>	1.34 ± 0.15 <sup>b</sup>	3.97 ± 0.52	
Day 16	2.52 ± 0.53 <sup>b</sup>	2.79 ± 0.23	2.98 ± 0.41	
Day 46	2.38 ± 0.60	2.12 ± 0.49	2.74 ± 0.11	
Week 13	1.80 ± 0.52	2.85 ± 0.44	2.46 ± 0.23	

**TABLE H5**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Male (continued)</b>				
<b>Urinalysis (continued)</b>				
n	5	5	5	
<b>Glucose (mg/dL)</b>				
Day 4	160 ± 49 <sup>b</sup>	169 ± 40	44 ± 3 <sup>*b</sup>	
Day 16	107 ± 40 <sup>b</sup>	47 ± 8	50 ± 4	
Day 46	46 ± 5	74 ± 25	89 ± 15 <sup>*</sup>	
Week 13	54 ± 3 <sup>b</sup>	66 ± 12	95 ± 31	
<b>Glucose (mg/100 g/16 hr)</b>				
Day 4	6 ± 2 <sup>b</sup>	10 ± 4	4 ± 1	
Day 16	5 ± 2 <sup>b</sup>	3 ± 1	2 ± 0	
Day 46	2 ± 0	3 ± 1	4 ± 1 <sup>*</sup>	
Week 13	2 ± 0	3 ± 0	3 ± 1	
<b>Protein (mg/dL)</b>				
Day 4	295 ± 42 <sup>c</sup>	151 ± 41 <sup>*c</sup>	115 ± 31 <sup>*</sup>	
Day 16	143 ± 30 <sup>b</sup>	148 ± 19	148 ± 37	
Day 46	200 ± 54	250 ± 70	103 ± 18	
Week 13	159 ± 30 <sup>b</sup>	159 ± 31	114 ± 21	
<b>Protein (mg/100 g/16 hr)</b>				
Day 4	13 ± 2 <sup>c</sup>	7 ± 1 <sup>c</sup>	8 ± 1	
Day 16	6 ± 1 <sup>b</sup>	10 ± 1	7 ± 1	
Day 46	7 ± 1	10 ± 3	5 ± 1	
Week 13	5 ± 1 <sup>b</sup>	6 ± 1	5 ± 1	
<b>Volume (mL/16 hr)</b>				
Day 4	0.9 ± 0.2 <sup>b</sup>	0.6 ± 0.1 <sup>b</sup>	1.8 ± 0.3	
Day 16	1.1 ± 0.2 <sup>b</sup>	1.8 ± 0.2	1.1 ± 0.2	
Day 46	1.3 ± 0.3	1.2 ± 0.3	1.4 ± 0.1	
Week 13	0.9 ± 0.3	1.5 ± 0.2	1.2 ± 0.1	
<b>Female</b>				
<b>Hematology</b>				
n	2	5	5	
<b>Packed cell volume (%)</b>				
Week 13	42.6 ± 0.4	42.2 ± 1.2	41.6 ± 0.6	
<b>Hemoglobin (g/dL)</b>				
Week 13	15.5 ± 0.3	16.0 ± 0.5	15.9 ± 0.1	
<b>Erythrocytes (10<sup>6</sup>/μL)</b>				
Week 13	8.93 ± 0.13	9.04 ± 0.24	9.02 ± 0.08	
<b>Mean cell volume (fL)</b>				
Week 13	48.5 ± 0.5	47.2 ± 0.2	46.6 ± 0.2 <sup>*</sup>	
<b>Mean cell hemoglobin (pg)</b>				
Week 13	17.5 ± 0.1	17.8 ± 0.1	17.7 ± 0.1	

**TABLE H5**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the Special 13-Week Inhalation Study**  
**of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Female (continued)</b>				
<b>Hematology (continued)</b>				
n	2	5	5	
Mean cell hemoglobin concentration (g/dL)				
Week 13	36.6 ± 0.5	37.9 ± 0.1*	38.3 ± 0.4*	
Reticulocytes (10 <sup>6</sup> /μL)				
Week 13	0.1 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	
Leukocytes (10 <sup>3</sup> /μL)				
Week 13	6.55 ± 0.65	5.82 ± 0.80	6.64 ± 0.60	
Segmented neutrophils (10 <sup>3</sup> /μL)				
Week 13	1.81 ± 0.31	0.93 ± 0.14	1.22 ± 0.21	
Lymphocytes (10 <sup>3</sup> /μL)				
Week 13	4.53 ± 0.34	4.79 ± 0.65	5.32 ± 0.55	
Monocytes (10 <sup>3</sup> /μL)				
Week 13	0.13 ± 0.01	0.03 ± 0.01	0.06 ± 0.03	
Eosinophils (10 <sup>3</sup> /μL)				
Week 13	0.08 ± 0.01	0.04 ± 0.02	0.04 ± 0.02	
<b>Clinical Chemistry</b>				
n	5	5	5	1
Urea nitrogen (mg/dL)				
Day 4	16.2 ± 1.2	16.6 ± 1.3	24.6 ± 2.1**	31.0 <sup>d</sup>
Day 16	18.6 ± 0.8	21.0 ± 1.5	19.6 ± 1.1	- <sup>e</sup>
Day 46	21.5 ± 2.1 <sup>b</sup>	20.8 ± 1.8	23.0 ± 1.8	-
Week 13	23.6 ± 2.2	25.6 ± 2.8	24.2 ± 1.5	-
Creatinine (mg/dL)				
Day 4	0.32 ± 0.06	0.50 ± 0.03* <sup>b</sup>	0.37 ± 0.00 <sup>c</sup>	0.24
Day 16	0.39 ± 0.02	0.39 ± 0.04	0.35 ± 0.08	-
Day 46	0.54 ± 0.07 <sup>b</sup>	0.60 ± 0.07 <sup>c</sup>	0.66 ± 0.05	-
Week 13	0.38 ± 0.14	0.28 ± 0.09	0.31 ± 0.06	-
Glucose (mg/dL)				
Day 4	107 ± 23	143 ± 3	118 ± 5	146
Day 16	114 ± 2	129 ± 5*	143 ± 7**	-
Day 46	133 ± 6 <sup>b</sup>	148 ± 10	136 ± 5	-
Week 13	107 ± 6	111 ± 6	114 ± 6	-
Albumin (g/dL)				
Day 4	3.3 ± 0.1	3.2 ± 0.0	3.3 ± 0.2	2.9
Day 16	3.3 ± 0.1	3.2 ± 0.0	3.2 ± 0.1	-
Day 46	3.5 ± 0.1 <sup>b</sup>	3.5 ± 0.1	3.6 ± 0.0 <sup>b</sup>	-
Week 13	3.5 ± 0.1	3.5 ± 0.0 <sup>b</sup>	3.6 ± 0.0	-
Alanine aminotransferase (IU/L)				
Day 4	102 ± 36	79 ± 25	63 ± 20	216
Day 16	37 ± 10 <sup>b</sup>	45 ± 7	51 ± 15	-
Day 46	43 ± 7 <sup>b</sup>	35 ± 10	38 ± 8	-
Week 13	249 ± 99	241 ± 76	217 ± 87	-

**TABLE H5**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Female (continued)</b>				
<b>Clinical Chemistry (continued)</b>				
n	5	5	5	1
<b>Aspartate aminotransferase (IU/L)</b>				
Day 4	121 ± 35	85 ± 3 <sup>b</sup>	94 ± 11	192
Day 16	90 ± 13	99 ± 15	95 ± 20	—
Day 46	160 ± 57 <sup>b</sup>	116 ± 24	86 ± 23	—
Week 13	271 ± 35	327 ± 99	263 ± 58	—
<b>Lactate dehydrogenase (IU/L)</b>				
Day 4	802 ± 202	517 ± 42 <sup>b</sup>	768 ± 158	796
Day 16	613 ± 176	602 ± 115	609 ± 97	—
Day 46	604 ± 151 <sup>b</sup>	458 ± 96	404 ± 57	—
<b>Urinalysis</b>				
n	5	5	5	
<b>Osmolality (mOsm/kg)</b>				
Day 4	2,897 ± 309	2,125 ± 322	3,308 ± 360	
Day 16	2,442 ± 274	2,798 ± 184 <sup>b</sup>	2,868 ± 180	
Day 46	2,844 ± 280 <sup>b</sup>	2,426 ± 264	2,860 ± 151	
Week 13	2,296 ± 394	2,791 ± 186	2,439 ± 243	
<b>Creatinine (mg/dL)</b>				
Day 4	49.84 ± 4.73	41.78 ± 5.40	58.43 ± 5.25 <sup>b</sup>	
Day 16	55.22 ± 5.72	61.93 ± 4.56 <sup>b</sup>	59.12 ± 3.53	
Day 46	57.23 ± 4.09 <sup>b</sup>	46.44 ± 4.32	51.38 ± 2.64	
Week 13	57.36 ± 7.63	65.28 ± 2.56	53.68 ± 5.81	
<b>Creatinine (mg/100 g/16 hr)</b>				
Day 4	4.28 ± 0.28	2.67 ± 0.62	2.32 ± 0.48 <sup>b</sup>	
Day 16	3.90 ± 0.26	3.29 ± 0.61 <sup>b</sup>	3.43 ± 0.36	
Day 46	3.15 ± 0.10 <sup>c</sup>	2.62 ± 0.34	3.23 ± 0.47	
Week 13	3.89 ± 0.57	3.34 ± 0.27	4.32 ± 0.51	
<b>Glucose (mg/dL)</b>				
Day 4	170 ± 60	290 ± 98	121 ± 36 <sup>b</sup>	
Day 16	116 ± 31	194 ± 63 <sup>b</sup>	87 ± 16	
Day 46	80 ± 20 <sup>b</sup>	120 ± 39	55 ± 5	
Week 13	78 ± 30	98 ± 31	47 ± 9	
<b>Glucose (mg/100 g/16 hr)</b>				
Day 4	10 ± 5	16 ± 3	5 ± 1 <sup>b</sup>	
Day 16	8 ± 2	6 ± 1 <sup>b</sup>	5 ± 1	
Day 46	5 ± 1 <sup>c</sup>	7 ± 3	3 ± 0	
Week 13	5 ± 2	5 ± 2	4 ± 1	

**TABLE H5**  
**Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene (continued)**

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
<b>Female (continued)</b>				
<b>Urinalysis (continued)</b>				
n	5	5	5	
<b>Protein (mg/dL)</b>				
Day 4	85 ± 13	76 ± 15 <sup>b</sup>	73 ± 17 <sup>c</sup>	
Day 16	86 ± 16	104 ± 19 <sup>b</sup>	83 ± 24	
Day 46	74 ± 17 <sup>b</sup>	90 ± 16	45 ± 3	
Week 13	56 ± 13	98 ± 7 <sup>a</sup>	46 ± 8	
<b>Protein (mg/100 g/16 hr)</b>				
Day 4	7 ± 1	6 ± 2 <sup>b</sup>	3 ± 0 <sup>*c</sup>	
Day 16	6 ± 0	5 ± 1 <sup>b</sup>	4 ± 1	
Day 46	5 ± 1 <sup>c</sup>	5 ± 1	3 ± 0	
Week 13	4 ± 1	5 ± 0	4 ± 1	
<b>Volume (mL/16 hr)</b>				
Day 4	1.6 ± 0.2	1.2 ± 0.2	0.6 ± 0.2 <sup>*</sup>	
Day 16	1.5 ± 0.2	1.1 ± 0.2 <sup>b</sup>	1.2 ± 0.2	
Day 46	1.5 ± 0.2 <sup>b</sup>	1.6 ± 0.4	1.5 ± 0.2	
Week 13	1.9 ± 0.4	1.5 ± 0.1	2.4 ± 0.5	

\* Significantly different ( $P \leq 0.05$ ) from the control group by Dunn's or Shirley's test

\*\*  $P \leq 0.01$

<sup>a</sup> Mean ± standard error. No data were collected for 2 ppm males due to 100% mortality; no hematology or urinalysis data were collected for 2 ppm females.

<sup>b</sup> n=4

<sup>c</sup> n=3

<sup>d</sup> No standard error was calculated due to high mortality in this group.

<sup>e</sup> No data collected due to 100% mortality in 2 ppm females after week 1.



**TABLE H6**  
**Urinalysis Data for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Hexachlorocyclopentadiene<sup>a</sup>**

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
<b>Male</b>				
n	7	10	8	10
<b>Urinalysis</b>				
Volume (mL/16 hr)	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.1	0.7 ± 0.1
Specific gravity	1.033 ± 0.001	1.035 ± 0.002	1.045 ± 0.004*	1.045 ± 0.004*
<b>Female</b>				
n	10	10	10	10
<b>Urinalysis</b>				
Volume (mL/16 hr)	1.6 ± 0.1	1.3 ± 0.1	1.5 ± 0.2	0.9 ± 0.1** <sup>b</sup>
Specific gravity	1.026 ± 0.001	1.025 ± 0.002	1.029 ± 0.001	1.030 ± 0.004

\* Significantly different ( $P \leq 0.05$ ) from the control group by Shirley's test

\*\*  $P \leq 0.01$

<sup>a</sup> Mean ± standard error

<sup>b</sup> n=9

# APPENDIX I

## CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS

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# CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS

## PROCUREMENT AND CHARACTERIZATION OF HEXACHLOROCYCLOPENTADIENE

Hexachlorocyclopentadiene was obtained from Velsicol Chemical Corporation (Chicago, IL) in one lot (lot 2291-1), which was used throughout the 13-week and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and confirmed by the study laboratory. Reports on the analyses performed in support of the hexachlorocyclopentadiene studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a viscous, pale yellow liquid, was identified as hexachlorocyclopentadiene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy (Figures I1 and I2). All spectra were consistent with those expected for the structure and with the literature spectra of hexachlorocyclopentadiene (*Sadtler Standard Spectra*).

The purity was determined by elemental analysis, free acid titration, thin-layer chromatography (TLC), and gas chromatography. Free acid titration was performed in deionized water with 0.05N sodium hydroxide as the titrant and with a phenolphthalein indicator solution. TLC was performed with two systems: A) silica gel 60, F254 plates (0.25 mm layer) with a solvent of 100% hexanes and B) silanized silica gel 60, F-254 plates (0.25 mm layer) with a solvent of methanol:saturated aqueous sodium chloride (80:20). Visualization was achieved with ultraviolet light (254 nm) and a spray reagent (N,N-dimethyl-*p*-phenylenediammonium dichloride in sodium alkoxide). Gas chromatography was performed using a chromatograph equipped with a flame ionization detector and a nitrogen carrier gas at 70 mL/minute with two systems: A) 10% Carbowax 20M-TPA on 80/100 mesh Chromosorb W(AW), with an oven temperature program of 60° C for 5 minutes then 60° to 200° C at 10° C per minute, using 100% hexachlorocyclopentadiene and solutions of 10%, 1.0%, or 0.5% hexachlorocyclopentadiene in hexanes; and B) 20% SP-2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, with an oven temperature of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute.

Elemental analyses of carbon and chlorine agreed with the theoretical values for hexachlorocyclopentadiene. Back-titrating aqueous extracts of hexachlorocyclopentadiene with sodium hydroxide gave an acid content expressed as hydrochloric acid of  $224 \pm 16(s)$  ppm. One trace impurity was observed in TLC system A and one trace and two slight trace impurities were observed in TLC system B. Both gas chromatography systems gave two impurity peaks with areas greater than 0.1% relative to the major peak. In system A, the impurity peak areas were 0.64% and 1.3% relative to the major peak; impurity peak areas in system B were 0.14% and 0.28% relative to the major peak. Results of these analyses indicated an overall purity of approximately 98% for the bulk chemical.

The largest impurity peak observed using gas chromatography system A was identified by the analytical chemistry laboratory as hexachloro-1,3-butadiene using a gas chromatograph/mass spectrometer; a J&W fused silica, DB-5 stationary phase column; helium carrier gas at a flow rate of 1 mL/minute; and an oven temperature program of 30° C for 2 minutes, then 30° to 300° C at 10° C per minute. Quantitation of the impurity was performed using an authentic standard with gas chromatography system A with an oven temperature program of 50° C for 1 minute, then 50° to 245° C at 10° C per minute. Its concentration was determined to be 0.44%. The study laboratory determined the concentration of the known impurity, hexachloro-3-cyclopentadiene-1-one (hex-ketone), in the bulk chemical. Gas chromatography was performed with a system consisting of an electron capture detector and a SILAR 5CP column. The carrier gas was argon/methane (90/10) and the oven temperature was 200° C. The concentration of hex-ketone was found to be 1.46%.

Bulk chemical stability studies were conducted using gas chromatography system B but with an isothermal oven temperature of 200° C, and with 2-methoxynaphthalene as an internal standard. Hexachlorocyclopentadiene was determined to be stable as a bulk chemical when stored in sealed containers with a nitrogen headspace and protected from light for as long as 2 weeks at temperatures up to 60° C. The study laboratory stored the bulk chemical at room temperature in the original shipping containers.

During the 13-week and 2-year studies, the study laboratory monitored the stability of the bulk chemical using gas chromatography and free acid titration. The gas chromatography system consisted of a packed column of 3% SP-2100 on 100/120 mesh Supelcoport and an isothermal oven temperature of 135° C with an internal standard solution of *n*-dodecane. No degradation of the bulk chemical occurred during the 13-week and 2-year studies.

## GENERATION AND MONITORING OF CHAMBER CONCENTRATIONS

*Vapor Generation System.* Liquid hexachlorocyclopentadiene was contained in a flask under a nitrogen gas headspace. Liquid was pumped from the reservoir to a vaporizer that consisted of a stainless steel cylinder heated to approximately 100° C (13-week studies) or 81° C (2-year studies) and covered with a glass fiber wick (Figure I3a). Vapor was generated by drawing filtered, fresh air across the vaporizer and into the vapor distribution manifold where the vapor was drawn through impulse-principle air amplifiers, diluted to the appropriate concentrations, and distributed to the individual exposure chambers (Figure I3b). A Gardner Type "CN" condensation nuclei detector was used prior to study start to ensure that the system produced a hexachlorocyclopentadiene vapor and not an aerosol. The study laboratory designed the inhalation exposure chamber (Hazleton 2000, Lab Products, Inc., Aberdeen, MD) (Figure I4) so that uniform vapor concentrations could be maintained throughout the chamber when the catch pans are in place. The total active mixing volume of each chamber was 1.7 m<sup>3</sup>. A diagram of the exposure suite is shown in Figure I5.

*Vapor Concentration Monitoring.* A single on-line gas chromatograph equipped with an electron capture detector was used to monitor chamber concentrations. The system was a 3% OV-225 coating on a 100/120 mesh Gas Chrom Q column and an argon/methane (90:10) carrier gas at a flow rate of 30 mL/minute. The column was maintained isothermally at 125° C. The monitor was coupled with the inhalation chambers using an automated, multiplexed, 8-port (13-week studies) or 12-port (2-year studies) sampling valve. Each chamber was sampled every 37 minutes (13-week studies) or 40 minutes (2-year studies). Calibration was confirmed and corrected by periodic analysis of grab samples from the chambers, which were obtained using bubblers filled with isooctane. Samples were drawn through the bubblers using a vacuum pump at a constant flow rate ensured by a calibrated critical orifice. Bubbler contents were analyzed using an off-line gas chromatograph maintained under similar conditions, which was calibrated using gravimetrically prepared standards of hexachlorocyclopentadiene. Drift of the on-line gas chromatograph was monitored using an on-line standard of tetrachlorobenzene.

*Chamber Concentration Characterization.* Buildup and decay rates for chamber concentrations were determined with and without animals present in the chambers. The time to achieve 90% of target concentration after the start of vapor generation ( $T_{90}$ ) without animals was 25 minutes for the 13-week studies.  $T_{90}$  in empty chambers was determined to be 15 minutes in the 2-year studies. The time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated ( $T_{10}$ ) ranged from 11 to 19 minutes. Additional tests with animals present were conducted during the first 2 weeks of the 2-year study and a  $T_{90}$  of 20 minutes was adopted.

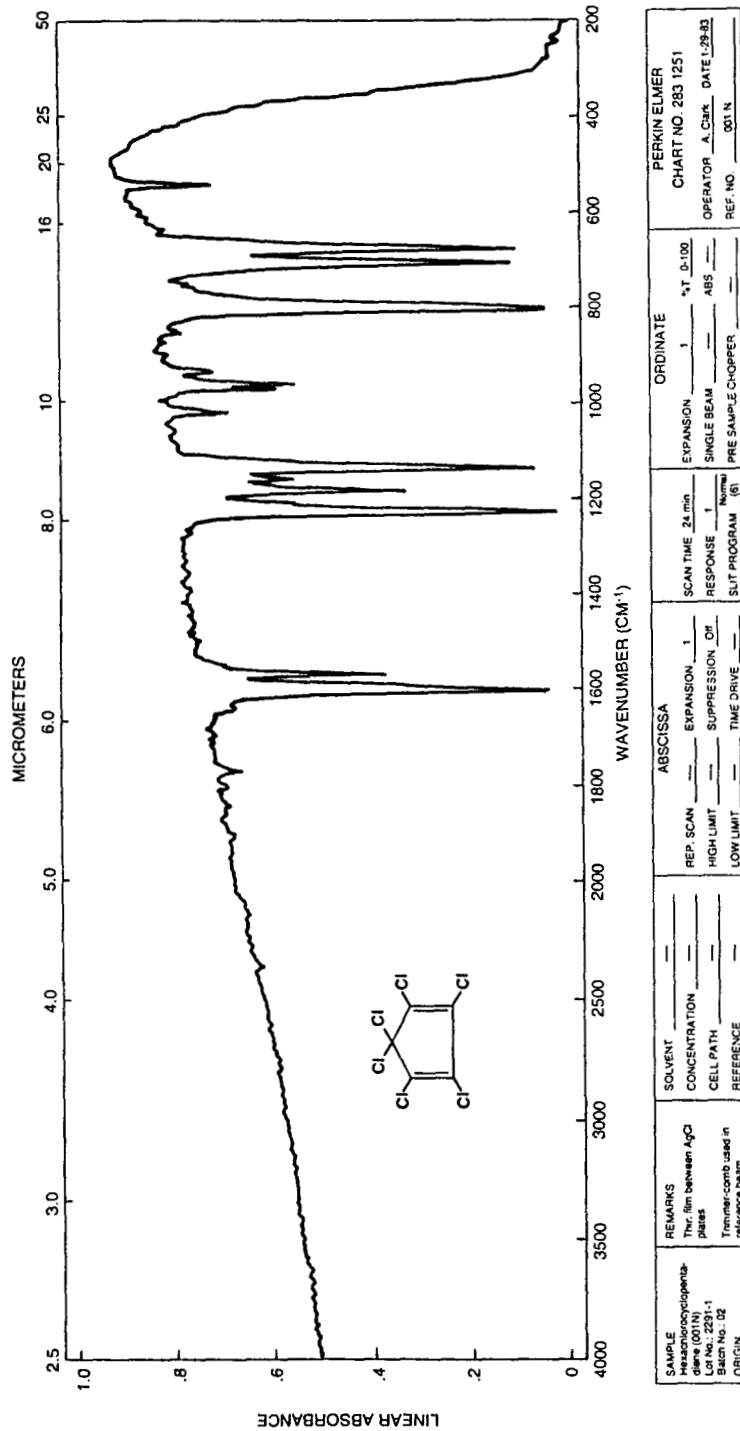
Uniformity of vapor concentration in the inhalation exposure chambers was evaluated prior to the start of the 13-week studies, once during the 13-week studies, prior to the start of the 2-year studies, and every 90 days during the 2-year studies. Vapor concentration was determined using the on-line gas

chromatograph with the multiport sample valve disabled to allow continuous monitoring from a single line. Chamber atmosphere uniformity was maintained throughout the 13-week and 2-year studies.

In order to determine the persistence of hexachlorocyclopentadiene in the chamber following exposure, the concentration was monitored overnight. During the 13-week studies, chamber concentrations dropped to 10% in approximately 30 minutes. The 1% level was reached in 30 to 40 minutes in the 0.04 and 0.15 ppm chambers but was not reached until 8 hours in the 2 ppm chamber. To determine the amount of hexachlorocyclopentadiene retained in the animal pelts and released during nonexposure periods, the pelt of a moribund animal was removed and cut in half after necropsy. One of the halves was immediately extracted with isooctane. The other half was placed under a fume hood to simulate normal overnight loss of hexachlorocyclopentadiene from the pelt and was extracted in the morning. The difference in the amount of hexachlorocyclopentadiene retained in the pelt between the two extractions was approximately 61  $\mu\text{g}$ . It was concluded that the hexachlorocyclopentadiene retained by animal pelts contributed to the overnight persistence of hexachlorocyclopentadiene in the chambers. During the 2-year studies, after 129 minutes in the 0.2 ppm rat chamber, 4.3% of the initial concentration of hexachlorocyclopentadiene vapor was still present. Concentration in the 0.5 ppm mouse chamber was below 1% of the target value in less than 3 hours. A trace of hexachlorocyclopentadiene was detectable in each chamber the following morning.

*Hexachlorocyclopentadiene Degradation.* Studies of hexachlorocyclopentadiene degradation in the chambers were conducted during the 13-week and 2-year studies. Isooctane bubblers were used to collect samples that were compared with a reference sample of bulk hexachlorocyclopentadiene using a gas chromatograph equipped with an electron capture detector. No significant degradation of the bulk chemical was observed during the 13-week or 2-year studies. A second degradation study was conducted during the 13-week studies to determine the quantity of the impurity, hex-ketone present in the chamber. A 5-hour bubbler sample was taken from the 0.5 ppm chamber for comparison with a reference standard provided by the analytical chemistry laboratory. The amount of hex-ketone collected in the exposure chamber (0.77%) was approximately half that in the bulk chemical (1.46%).

Summaries of the chamber concentrations for the 13-week and 2-year studies are in Tables I1 and I2. Table I3 shows the distribution of mean monthly concentrations in the 2-year studies. The monthly mean exposure concentrations for the 2-year study chambers, including the stop-exposure chamber, are presented in Figures I6 through I12.



**FIGURE II**  
**Infrared Absorption Spectrum of Hexachlorocyclopentadiene**

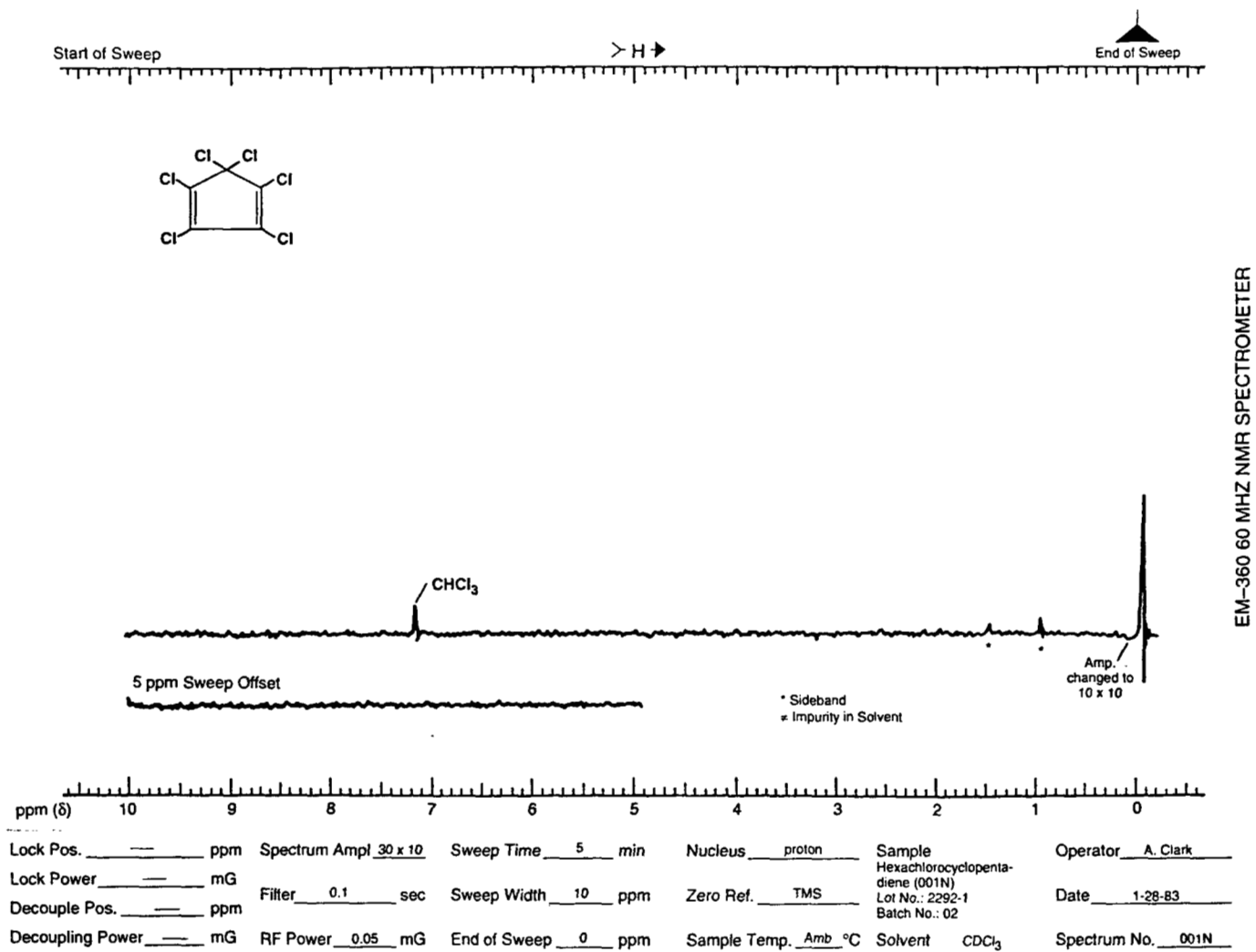
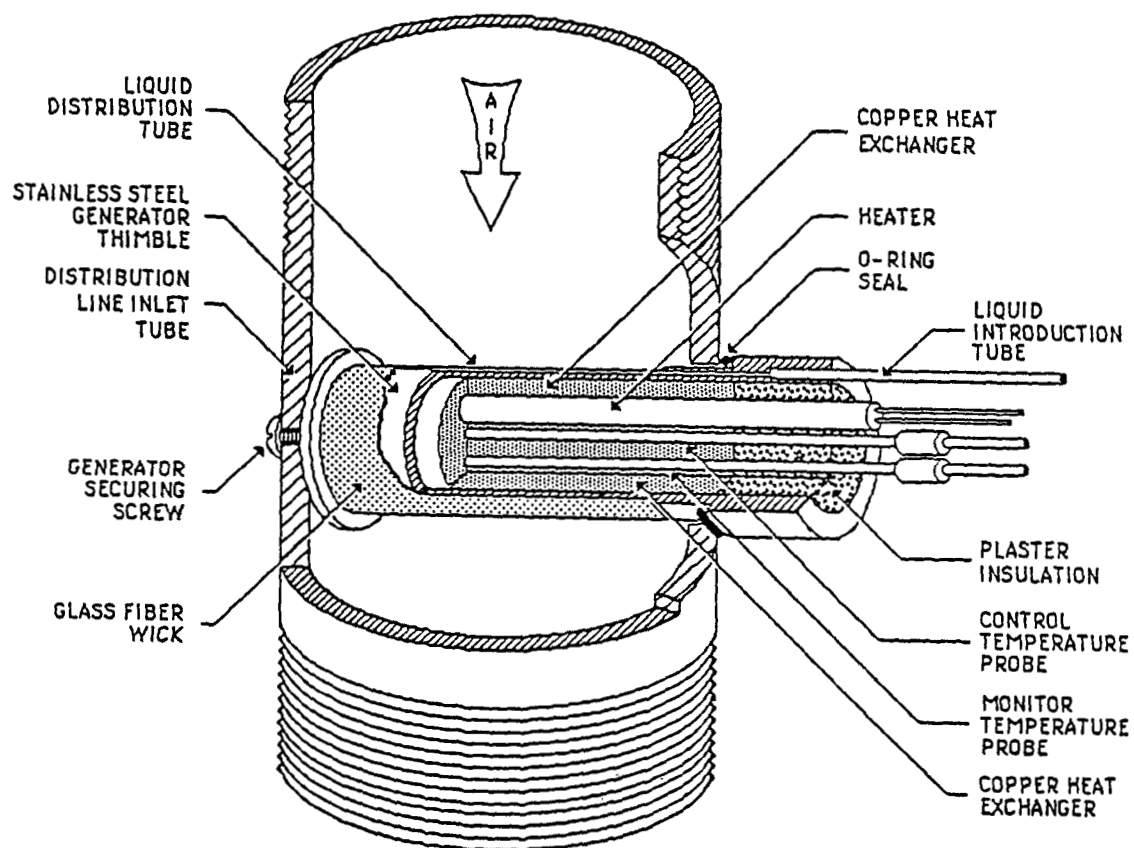


FIGURE 12  
Nuclear Magnetic Resonance Spectrum of Hexachlorocyclopentadiene



**FIGURE I3a**  
Hexachlorocyclopentadiene Liquid Vapor Generator



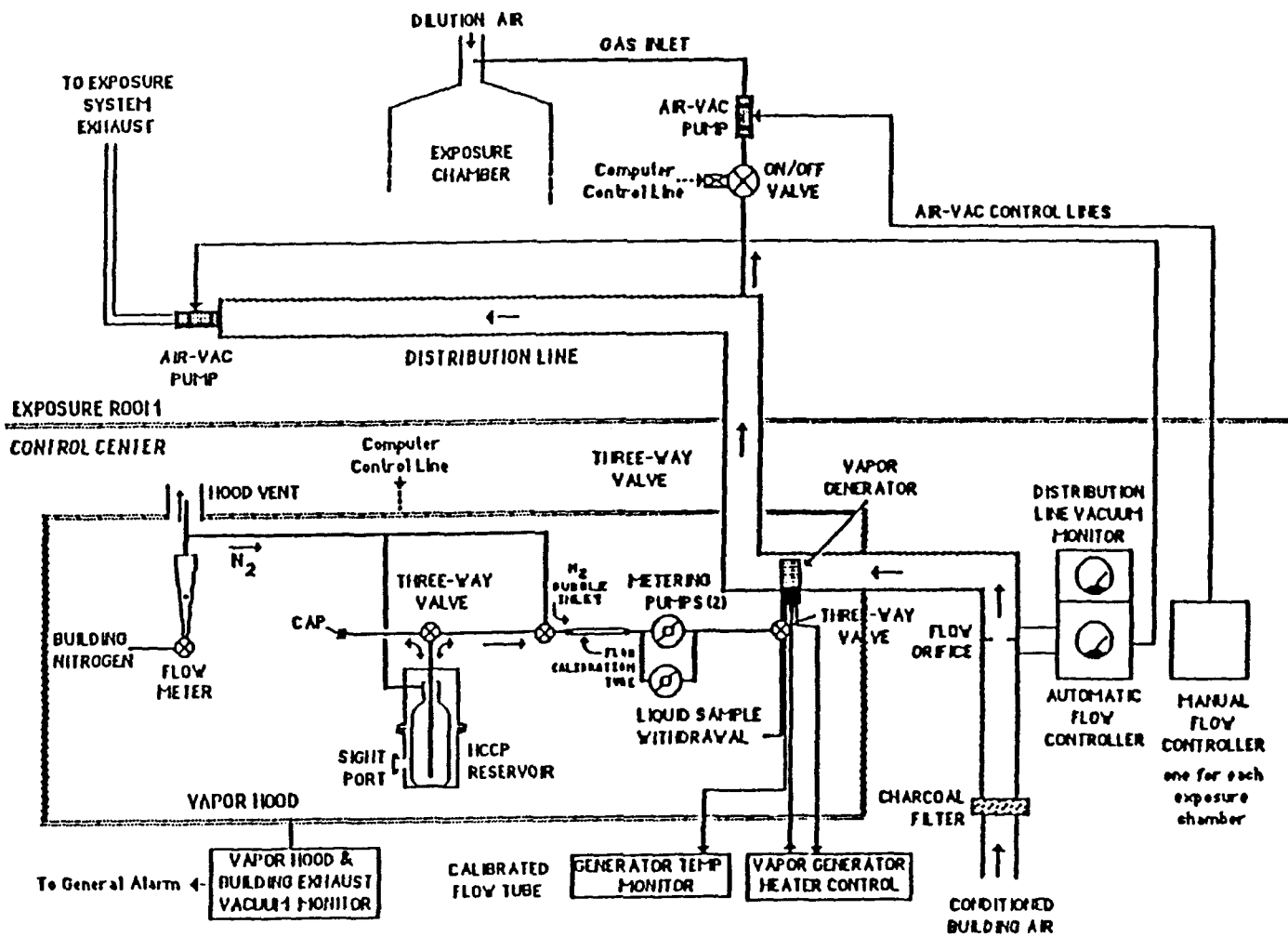
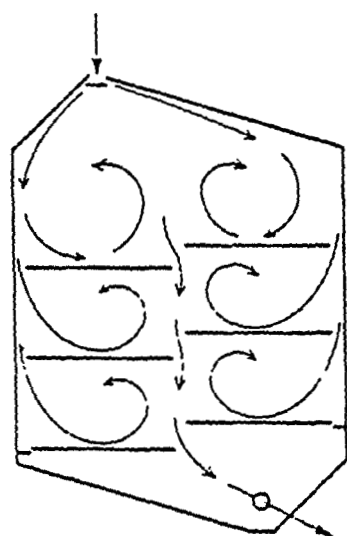
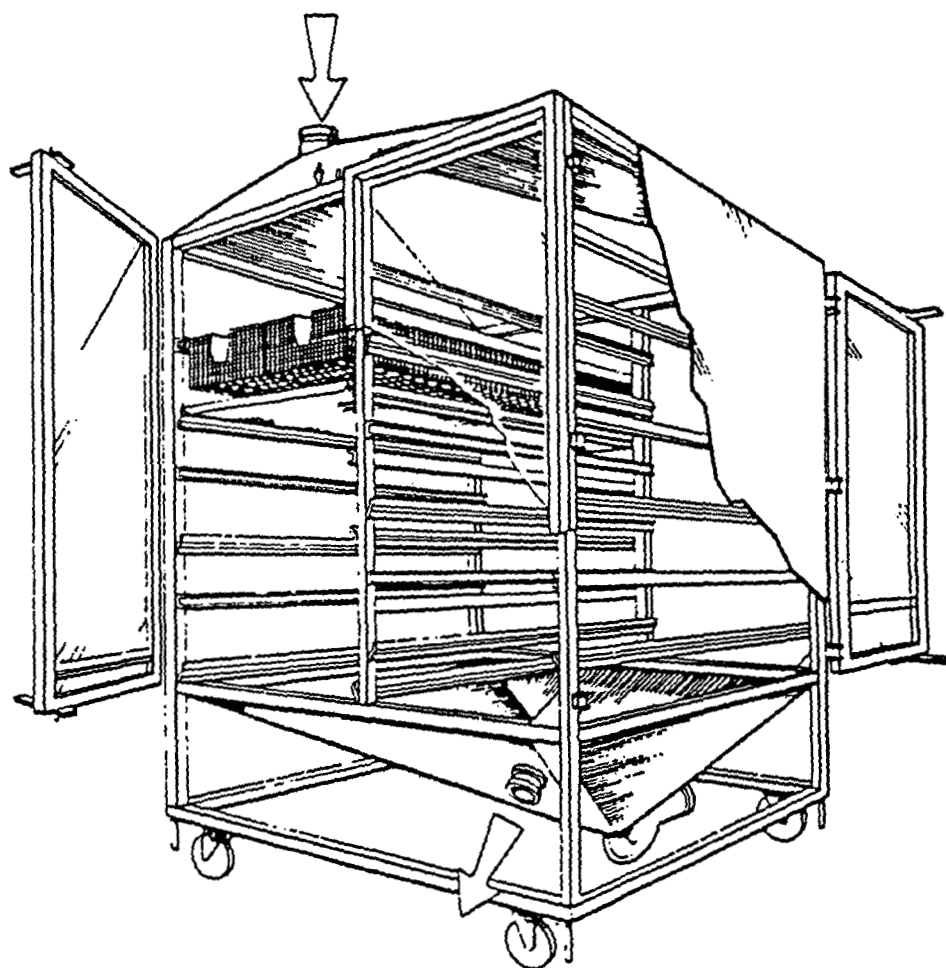
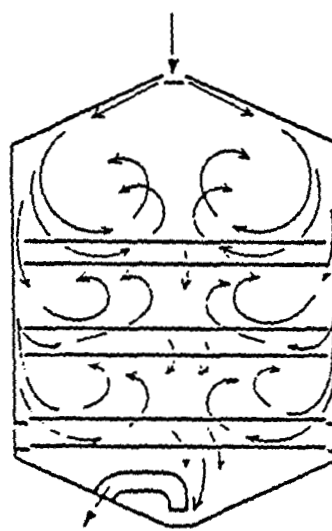


FIGURE 13b  
Hexachlorocyclopentadiene Vapor Generation and Delivery System



FRONT VIEW



SIDE VIEW

FIGURE I4  
Hexachlorocyclopentadiene Inhalation Exposure Chamber

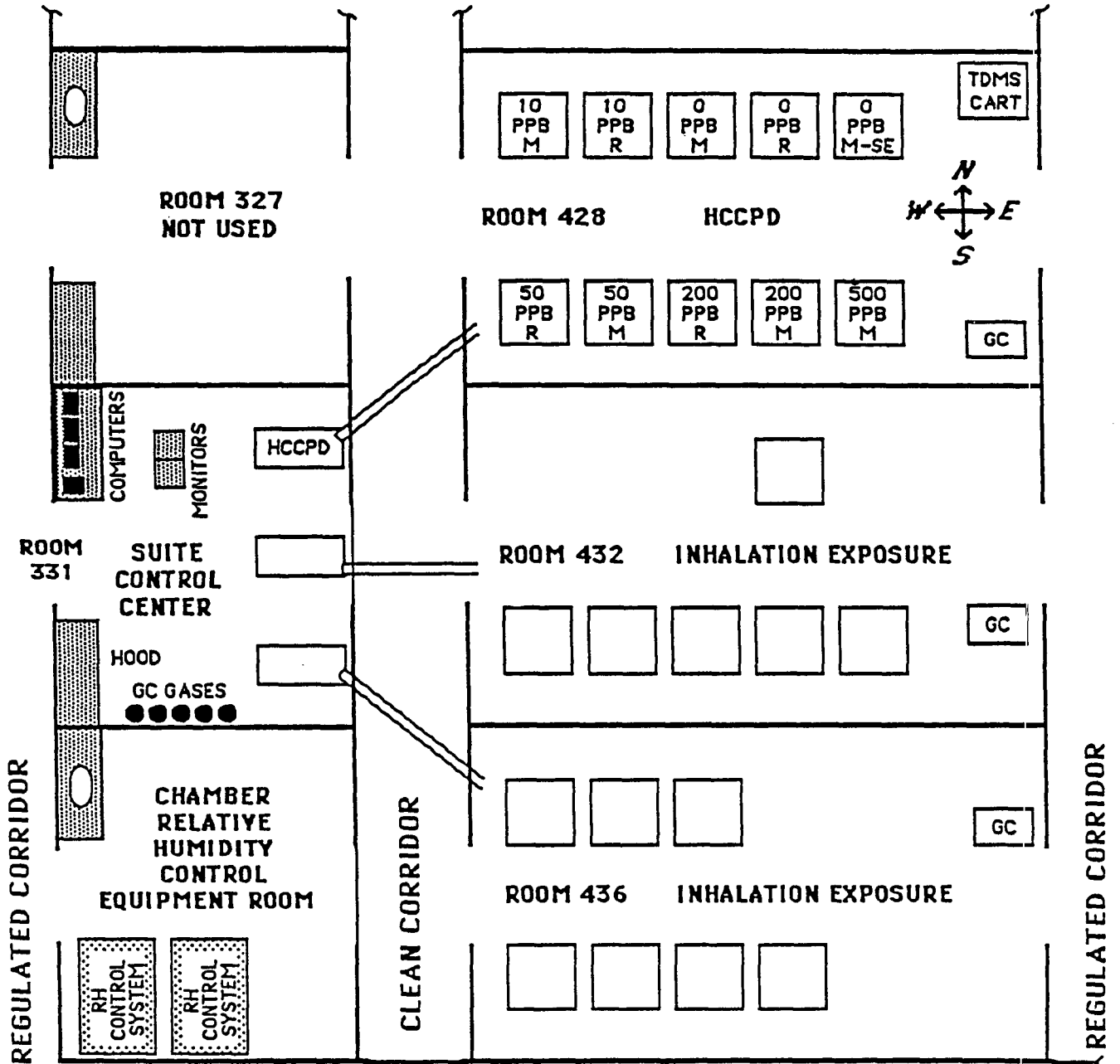


FIGURE 15  
Hexachlorocyclopentadiene Exposure Suite

**TABLE II**  
**Summary of Chamber Concentrations in the 13-Week Inhalation Studies**  
**of Hexachlorocyclopentadiene**

Target Concentration (ppm)	Total Number of Readings	Average Concentration <sup>a</sup> (ppm)
<b>Rat Chambers</b>		
0.04	559	0.039 ± 0.006
0.2	565	0.146 ± 0.017
0.4	571	0.385 ± 0.044
1	216	0.941 ± 0.104
2	130	2.065 ± 0.285
<b>Mouse Chambers</b>		
0.04	547	0.039 ± 0.006
0.2	554	0.146 ± 0.017
0.4	561	0.389 ± 0.041
1	169	0.949 ± 0.110
2	83	2.142 ± 0.295

<sup>a</sup> Mean ± standard deviation

**TABLE I2**  
**Summary of Chamber Concentrations in the 2-Year Inhalation Studies**  
**of Hexachlorocyclopentadiene**

Target Concentration (ppm)	Total Number of Readings	Average Concentration <sup>a</sup> (ppm)
<b>Rat Chambers</b>		
0.01	3,877	0.01 ± 0.00
0.05	4,137	0.05 ± 0.00
0.2	4,118	0.20 ± 0.01
<b>Mouse Chambers</b>		
0.01	4,166	0.01 ± 0.00
0.05	4,148	0.05 ± 0.00
0.2	4,131	0.20 ± 0.01
0.5	1,618	0.50 ± 0.04

<sup>a</sup> Mean ± standard deviation

**TABLE I3**  
**Distribution of Mean Monthly Concentrations in the 2-Year Inhalation Studies**  
**of Hexachlorocyclopentadiene**

Range of Concentration (percent of target)	Number of Months Mean Within Range			
	0.01 ppm	0.05 ppm	0.2 ppm	0.5 ppm
<b>Rat Chambers</b>				
90-95	1	0	0	
95-100	6	7	7	
100-105	17	17	17	
105-110	0	0	0	
<b>Mouse Chambers</b>				
90-95	0	0	0	0
95-100	6	2	2	2
100-105	19	23	23	9
105-110	0	0	0	0

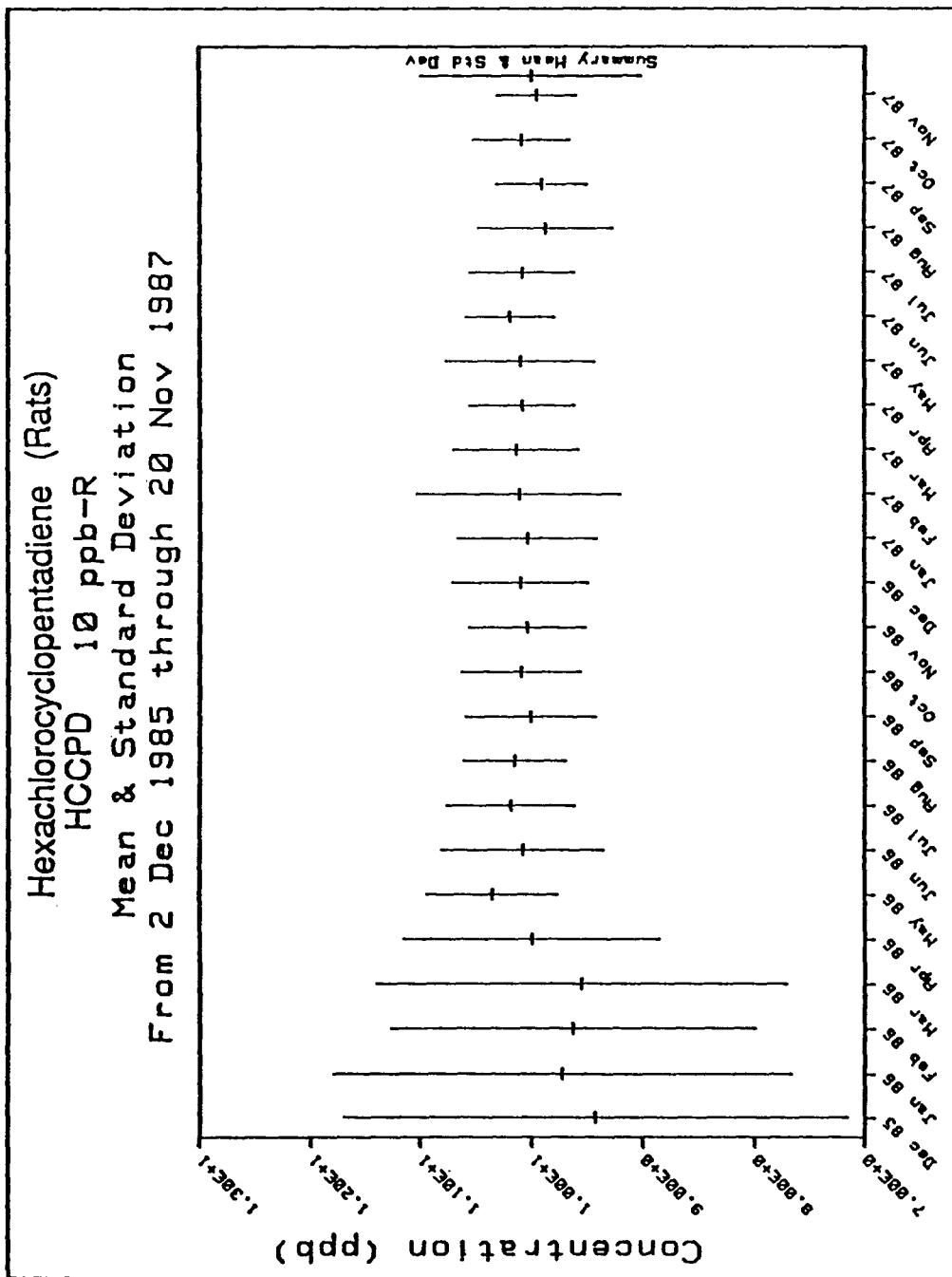


FIGURE I6  
Monthly Mean Concentration and Standard Deviation in the 0.01 ppm  
Hexachlorocyclopentadiene Rat Exposure Chamber for the 2-Year Study

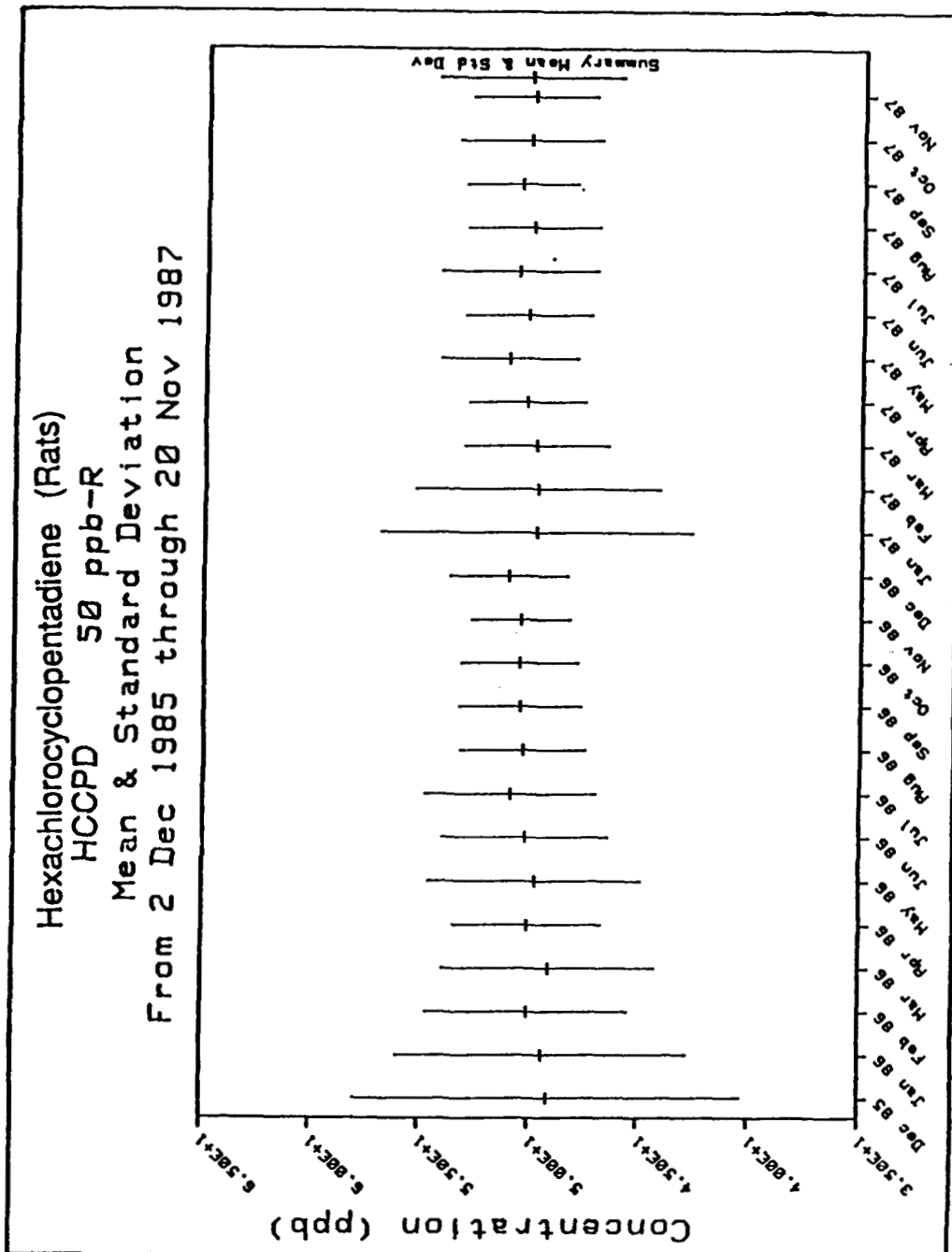


FIGURE I7  
Monthly Mean Concentration and Standard Deviation in the 0.05 ppm  
Hexachlorocyclopentadiene Rat Exposure Chamber for the 2-Year Study

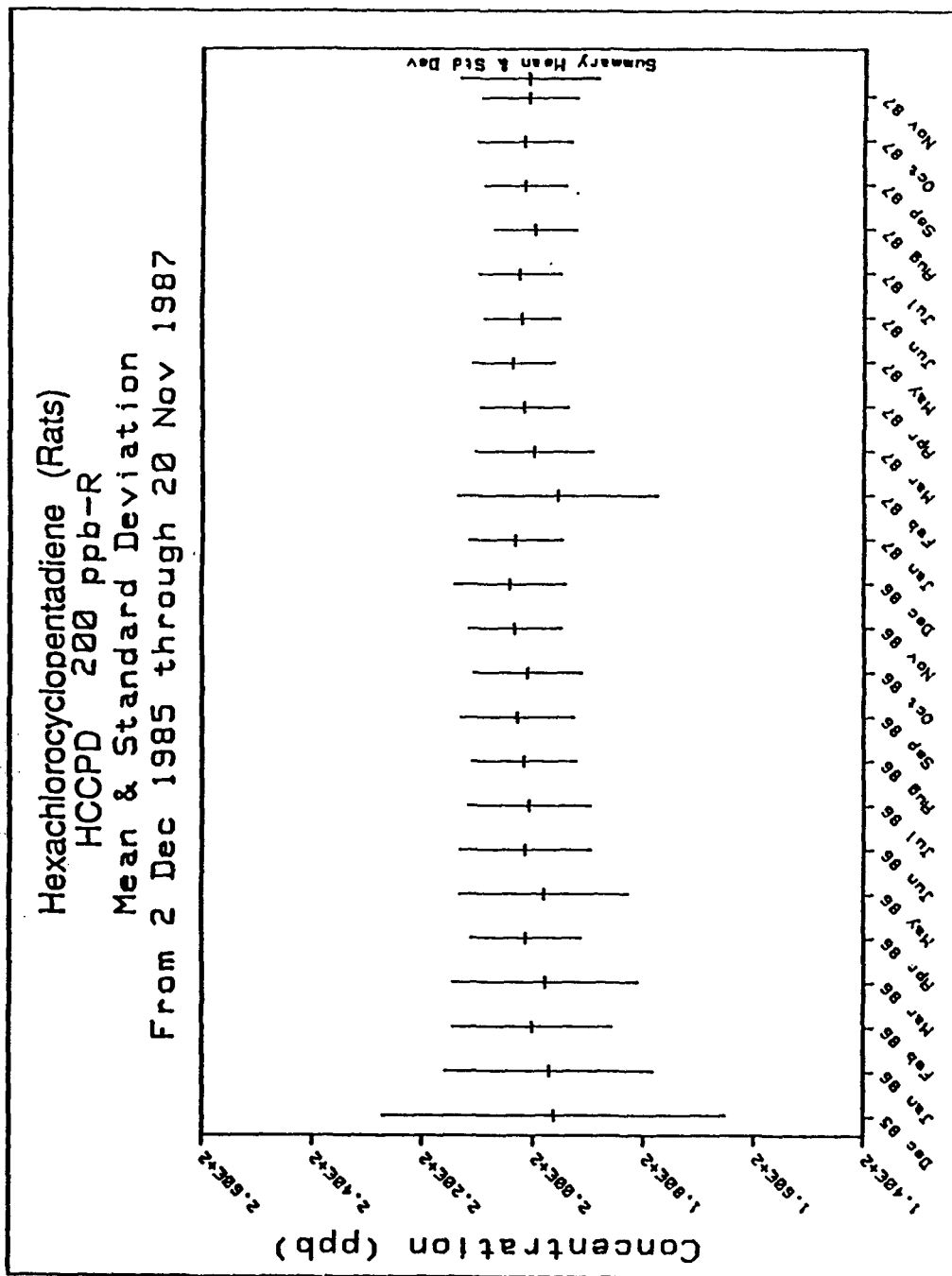
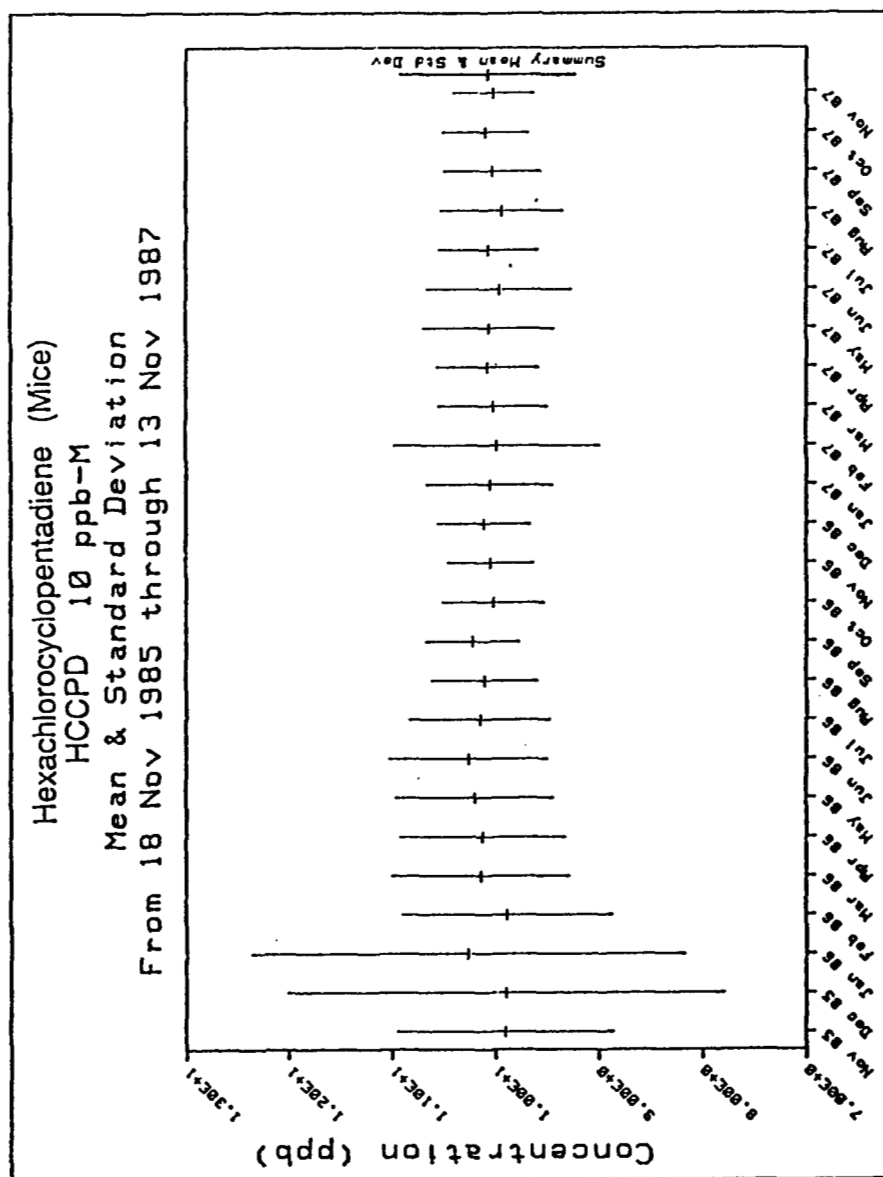


FIGURE 18  
Monthly Mean Concentration and Standard Deviation in the 0.2 ppm  
Hexachlorocyclopentadiene Rat Exposure Chamber for the 2-Year Study





**FIGURE 19**  
Monthly Mean Concentration and Standard Deviation in the 0.01 ppm  
Hexachlorocyclopentadiene Mouse Exposure Chamber for the 2-Year Study

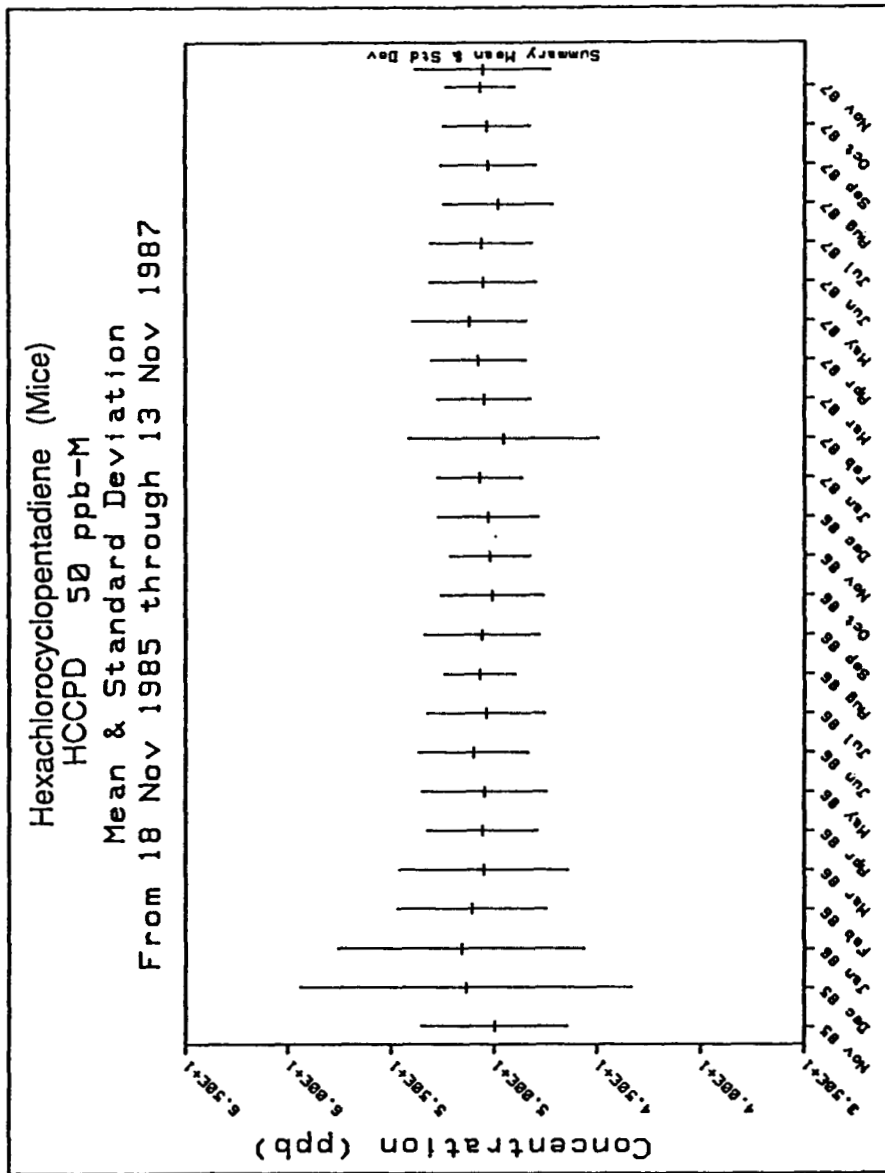


FIGURE I10  
Monthly Mean Concentration and Standard Deviation in the 0.05 ppm  
Hexachlorocyclopentadiene Mouse Exposure Chamber for the 2-Year Study

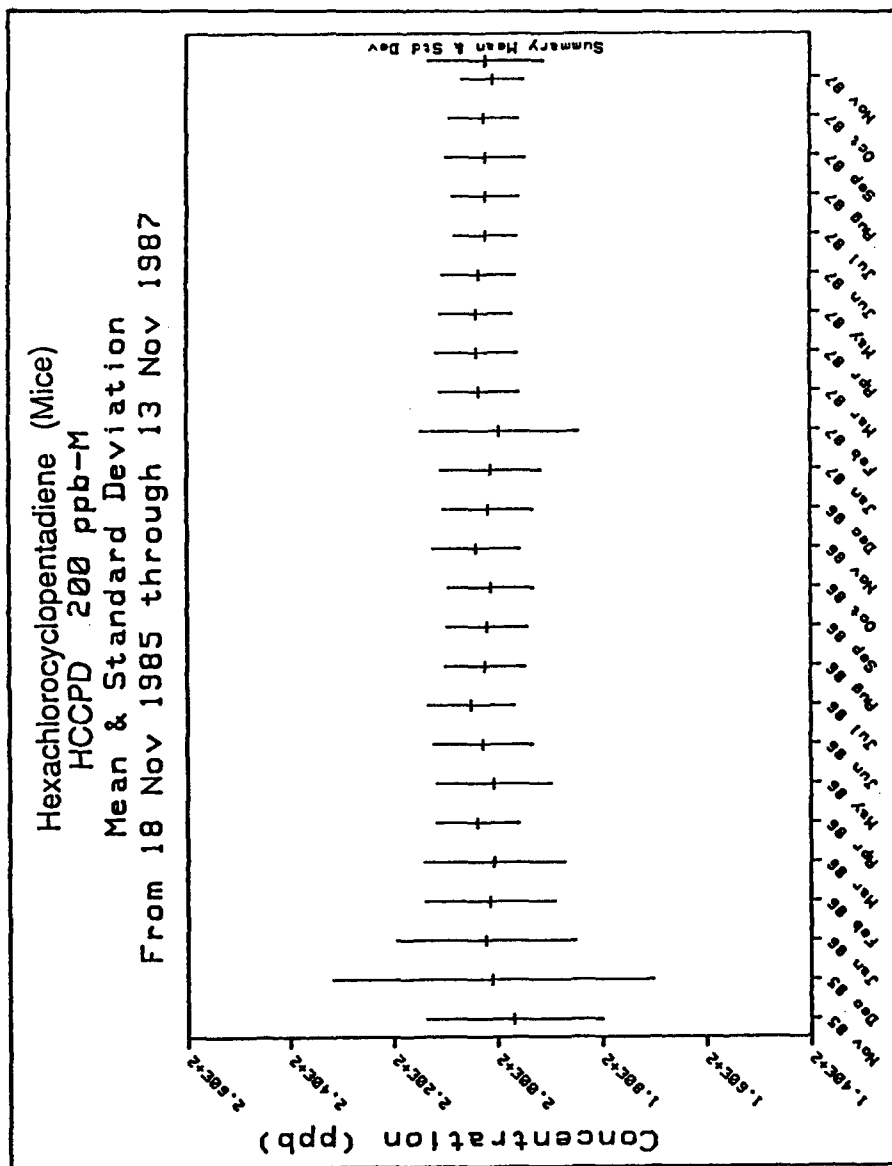


FIGURE I11  
Monthly Mean Concentration and Standard Deviation in the 0.2 ppm  
Hexachlorocyclopentadiene Mouse Exposure Chamber for the 2-Year Study

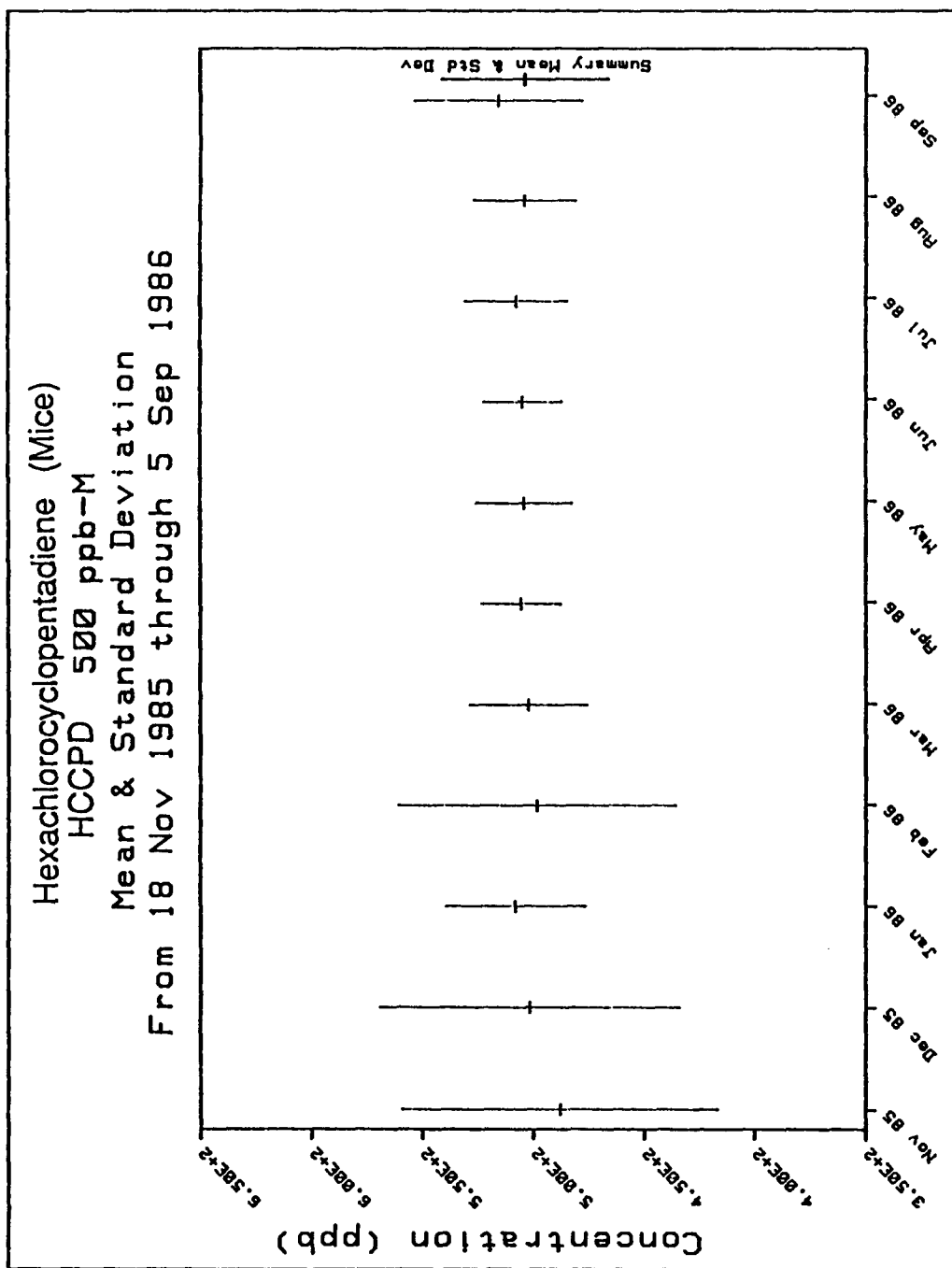


FIGURE II2  
 Monthly Mean Concentration and Standard Deviation in the 0.5 ppm  
 Hexachlorocyclopentadiene Male Mouse Exposure Chamber for the Stop-Exposure Evaluation

**APPENDIX J**  
**INGREDIENTS, NUTRIENT COMPOSITION,**  
**AND CONTAMINANT LEVELS**  
**IN NIH-07 RAT AND MOUSE RATION**

<b>TABLE J1</b>	<b>Ingredients of NIH-07 Rat and Mouse Ration .....</b>	<b>310</b>
<b>TABLE J2</b>	<b>Vitamins and Minerals in NIH-07 Rat and Mouse Ration .....</b>	<b>310</b>
<b>TABLE J3</b>	<b>Nutrient Composition of NIH-07 Rat and Mouse Ration .....</b>	<b>311</b>
<b>TABLE J4</b>	<b>Contaminant Levels in NIH-07 Rat and Mouse Ration .....</b>	<b>312</b>

**TABLE J1**  
**Ingredients of NIH-07 Rat and Mouse Ration<sup>a</sup>**

Ingredients <sup>b</sup>	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

<sup>a</sup> NCI, 1976; NIH, 1978

<sup>b</sup> Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

**TABLE J2**  
**Vitamins and Minerals in NIH-07 Rat and Mouse Ration<sup>a</sup>**

	Amount	Source
<b>Vitamins</b>		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D <sub>3</sub>	4,600,000 IU	D-activated animal sterol
K <sub>3</sub>	2.8 g	Menadione
<i>d</i> - $\alpha$ -Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
<i>d</i> -Pantothenic acid	18.0 g	<i>d</i> -Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B <sub>12</sub>	4,000 $\mu$ g	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	<i>d</i> -Biotin
<b>Minerals</b>		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

<sup>a</sup> Per ton (2,000 lb) of finished product

**TABLE J3**  
**Nutrient Composition of NIH-07 Rat and Mouse Ration**

Nutrient	Mean $\pm$ Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.33 $\pm$ 0.49	21.70 – 23.60	17
Crude fat (% by weight)	5.52 $\pm$ 0.24	4.90 – 6.00	17
Crude fiber (% by weight)	3.35 $\pm$ 0.29	2.70 – 4.00	17
Ash (% by weight)	6.54 $\pm$ 0.30	6.13 – 7.06	17
<b>Amino Acids (% of total diet)</b>			
Arginine	1.287 $\pm$ 0.084	1.100 – 1.390	10
Cystine	0.306 $\pm$ 0.075	0.181 – 0.400	10
Glycine	1.160 $\pm$ 0.050	1.060 – 1.220	10
Histidine	0.580 $\pm$ 0.024	0.531 – 0.608	10
Isoleucine	0.917 $\pm$ 0.034	0.867 – 0.965	10
Leucine	1.972 $\pm$ 0.052	1.850 – 2.040	10
Lysine	1.273 $\pm$ 0.051	1.200 – 1.370	10
Methionine	0.437 $\pm$ 0.115	0.306 – 0.699	10
Phenylalanine	0.994 $\pm$ 0.125	0.665 – 1.110	10
Threonine	0.896 $\pm$ 0.055	0.824 – 0.985	10
Tryptophan	0.223 $\pm$ 0.160	0.107 – 0.671	10
Tyrosine	0.677 $\pm$ 0.105	0.564 – 0.794	10
Valine	1.089 $\pm$ 0.057	0.962 – 1.170	10
<b>Essential Fatty Acids (% of total diet)</b>			
Linoleic	2.389 $\pm$ 0.233	1.830 – 2.570	9
Linolenic	0.277 $\pm$ 0.036	0.210 – 0.320	9
<b>Vitamins</b>			
Vitamin A (IU/kg)	7,622 $\pm$ 2,563	4,700 – 13,000	17
Vitamin D (IU/kg)	4,450 $\pm$ 1,382	3,000 – 6,300	4
$\alpha$ -Tocopherol (ppm)	36.92 $\pm$ 9.32	22.5 – 48.9	9
Thiamine (ppm)	20.14 $\pm$ 2.62	15.0 – 26.0	17
Riboflavin (ppm)	7.92 $\pm$ 0.93	6.10 – 9.00	10
Niacin (ppm)	100.95 $\pm$ 25.92	65.0 – 150.0	9
Pantothenic acid (ppm)	30.30 $\pm$ 3.60	23.0 – 34.6	10
Pyridoxine (ppm)	9.25 $\pm$ 2.62	5.60 – 14.0	10
Folic acid (ppm)	2.51 $\pm$ 0.64	1.80 – 3.70	10
Biotin (ppm)	0.267 $\pm$ 0.049	0.19 – 0.35	10
Vitamin B <sub>12</sub> (ppb)	40.14 $\pm$ 20.04	10.6 – 65.0	10
Choline (ppm)	3,608 $\pm$ 314	2,400 – 3,430	9
<b>Minerals</b>			
Calcium (%)	1.17 $\pm$ 0.11	1.00 – 1.40	17
Phosphorus (%)	0.93 $\pm$ 0.03	0.87 – 1.00	17
Potassium (%)	0.887 $\pm$ 0.067	0.772 – 0.971	8
Chloride (%)	0.526 $\pm$ 0.092	0.380 – 0.635	8
Sodium (%)	0.315 $\pm$ 0.344	0.258 – 0.370	10
Magnesium (%)	0.168 $\pm$ 0.008	0.151 – 0.180	10
Sulfur (%)	0.274 $\pm$ 0.063	0.208 – 0.420	10
Iron (ppm)	356.2 $\pm$ 90.0	255.0 – 523.0	10
Manganese (ppm)	92.24 $\pm$ 5.35	81.70 – 99.40	10
Zinc (ppm)	58.14 $\pm$ 9.91	46.10 – 81.60	10
Copper (ppm)	11.50 $\pm$ 2.40	8.090 – 15.39	10
Iodine (ppm)	3.70 $\pm$ 1.14	1.52 – 5.83	10
Chromium (ppm)	1.71 $\pm$ 0.45	0.85 – 2.09	9
Cobalt (ppm)	0.797 $\pm$ 0.23	0.490 – 1.150	6

**TABLE J4**  
**Contaminant Levels in NIH-07 Rat and Mouse Ration**

	Mean $\pm$ Standard Deviation <sup>a</sup>	Range	Number of Samples
<b>Contaminants</b>			
Arsenic (ppm)	0.57 $\pm$ 0.33	0.14 – 0.98	17
Cadmium (ppm) <sup>b</sup>	0.10 $\pm$ 0.02	0.10 – 0.20	17
Lead (ppm)	0.37 $\pm$ 0.26	0.05 – 0.96	17
Mercury (ppm)	<0.05		17
Selenium (ppm)	0.30 $\pm$ 0.05	0.30 – 0.48	17
Aflatoxins (ppb)	<5.0		17
Nitrate nitrogen (ppm) <sup>c</sup>	20.29 $\pm$ 8.37	12.30 – 41.0	17
Nitrite nitrogen (ppm) <sup>c</sup>	0.50 $\pm$ 0.81	<0.10 – 2.60	17
BHA (ppm) <sup>d</sup>	2.53 $\pm$ 1.01	<2.00 – 5.00	17
BHT (ppm) <sup>d</sup>	1.29 $\pm$ 0.85	<1.00 – 4.00	17
Aerobic plate count (CFU/g) <sup>e</sup>	45,076 $\pm$ 72,968	3,400 – 300,000	17
Coliform (MPN/g) <sup>f</sup>	3.12 $\pm$ 0.33	<3.00 – 4.00	17
<i>E. coli</i> (MPN/g)	3.00		17
Total nitrosoamines (ppb) <sup>g</sup>	9.02 $\pm$ 4.07	3.90 – 12.00	17
<i>N</i> -Nitrosodimethylamine (ppb) <sup>g</sup>	7.68 $\pm$ 3.97	2.90 – 19.00	17
<i>N</i> -Nitrosopyrrolidine (ppb) <sup>g</sup>	1.34 $\pm$ 0.90	1.00 – 4.50	17
<b>Pesticides</b>			
$\alpha$ -BHC <sup>h</sup>	<0.01		17
$\beta$ -BHC	<0.02		17
$\gamma$ -BHC	<0.01		17
$\delta$ -BHC	<0.01		17
Heptachlor	<0.01		17
Aldrin	<0.01		17
Heptachlor epoxide	<0.01		17
DDE	<0.01		17
DDD	<0.01		17
DDT	<0.01		17
HCB	<0.01		17
Mirex	<0.01		17
Methoxychlor	<0.05		17
Dieldrin	<0.01		17
Endrin	<0.01		17
Telodrin	<0.01		17
Chlordane	<0.05		17
Toxaphene	<0.1		17
Estimated PCBs	<0.2		17
Ronnel	<0.01		17
Ethion	<0.02		17
Trithion	<0.05		17
Diazinon	<0.1		17
Methyl parathion	<0.02		17
Ethyl parathion	<0.02		17
Malathion	0.14 $\pm$ 0.12	0.05 – 0.35	17
Endosulfan I	<0.01		17
Endosulfan II	<0.01		17
Endosulfan sulfate	<0.03		17



**TABLE J4**  
**Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)**

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- <sup>a</sup> For values less than the limit of detection, the detection limit is given as the mean.
- <sup>b</sup> The lot milled 30 June 1987 contained 0.20 ppm; all other lots were less than or equal to the detection limit.
- <sup>c</sup> Sources of contamination: alfalfa, grains, and fish meal
- <sup>d</sup> Sources of contamination: soy oil and fish meal
- <sup>e</sup> CFU = colony forming units
- <sup>f</sup> MPN = most probable number; the lots milled 6 January 1986 and 4 February 1986 contained 4.0 MPN; all other lots were less than or equal to the detection limit.
- <sup>g</sup> All values were corrected for percent recovery.
- <sup>h</sup> BHC is hexachlorocyclohexane or benzene hexachloride

**APPENDIX K  
SENTINEL ANIMAL PROGRAM**

**METHODS ..... 316**

## SENTINEL ANIMAL PROGRAM

### METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are all subject to identical environmental conditions. The sentinel animals come from the same production source and weaning groups as the animals used for the studies of chemical compounds.

### Rats

For the 13-week study, samples were obtained from five male and five female controls at terminal sacrifice. These samples were processed appropriately and were submitted to Microbiological Associates, Incorporated (Bethesda, MD), for viral titer screening. The following tests were performed:

<u>Method of Analysis</u>	<u>Time of Analysis</u>
ELISA	
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
PVM (pneumonia virus of mice)	Study termination
Sendai	Study termination

For the 2-year study, 15 male and 15 female rats were selected at the time of randomization and allocation of the animals to the various study groups; 12 males and 12 females were housed in the control chamber and 3 males and 3 females were housed in the 0.01 ppm chamber. Sera were obtained from two male and two female control sentinels at 6 months, five male and five female control sentinels at 12 and 18 months; and all 0.01 ppm sentinels at 6 months. Sera for the 24-month screening were obtained from five 0.05 ppm males and five 0.05 ppm females. Blood from each collection was processed appropriately, shipped to Microbiological Associates, Incorporated, and screened for the following:

<u>Method of Analysis</u>	<u>Time of Analysis</u>
ELISA	
<i>Mycoplasma arthritidis</i>	6 and 24 months
<i>Mycoplasma pulmonis</i>	6 and 24 months
PVM	6, 12, 18, and 24 months
RCV/SDA	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
H-1	6, 12, 18, and 24 months
KRV	6, 12, 18, and 24 months

**Mice**

For the 13-week study, samples were obtained from five male and five female controls at terminal sacrifice. These samples were processed appropriately and were submitted to Microbiological Associates, Incorporated, for viral titer screening. The following tests were performed:

<u>Method of Analysis</u>	<u>Time of Analysis</u>
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus	Study termination
ELISA	
MHV (mouse hepatitis virus)	Study termination
Hemagglutination Inhibition	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination

For the 2-year study, 15 male and 15 female mice were selected at the time of randomization and allocation of the animals to the various study groups and were housed in the control chamber. Sera were obtained from up to five male and five female controls at 6, 12, and 18 months on study. Eight of ten 12-month sera were lost in a centrifuge accident, therefore, sera from five male and five female controls were collected at the 15-month interim evaluation. Sera for the 24-month screening were obtained from five 0.05 ppm males and five 0.05 ppm females. Blood from each collection was processed appropriately, shipped to Microbiological Associates, Incorporated, and screened for the following:

<u>Method of Analysis</u>	<u>Time of Analysis</u>
Complement Fixation	
LCM	6 months
ELISA	
Ectromelia virus	6, 12, 15, 18, and 24 months
GDVII	6, 12, 15, 18, and 24 months
LCM	15, 18, and 24 months
MHV	6, 12, 15, 18, and 24 months
Mouse adenoma virus	6, 12, 15, 18, 24 months
MVM	18 and 24 months
<i>M. arthritidis</i>	6 and 24 months
<i>M. pulmonis</i>	6 and 24 months
PVM	6, 12, 15, 18, and 24 months
Reovirus 3	6, 15, 18, and 24 months
Sendai	6, 12, 15, 18, and 24 months
Hemagglutination Inhibition	
K (papovavirus)	6, 12, 15, 18, and 24 months
MVM	6, 12, and 15 months
Polyoma virus	6, 12, 15, 18, and 24 months
Reovirus 3	12 months

Method of Analysis

## Immunofluorescence Assay

EDIM (epizootic diarrhea of infant mice)

GDVII

LCM

MVM

Reovirus 3

Time of Analysis

6, 12, 15, 18, and 24 months

18 months

12 months

18 months

18 months

All test results were negative.

**NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS  
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TR No.	CHEMICAL	TR No.	CHEMICAL
336	Penicillin VK	385	Methyl Bromide
337	Nitrofurazone	386	Tetranitromethane
338	Erythromycin Stearate	387	Amphetamine Sulfate
339	2-Amino-4-nitrophenol	388	Ethylene Thiourea
340	Iodinated Glycerol	389	Sodium Azide
341	Nitrofurantoin	390	3,3'-Dimethylbenzidine Dihydrochloride
342	Dichlorvos	391	Tris(2-chloroethyl) Phosphate
343	Benzyl Alcohol	392	Chlorinated Water and Chloraminated Water
344	Tetracycline Hydrochloride	393	Sodium Fluoride
345	Roxarsone	394	Acetaminophen
346	Chloroethane	395	Probenecid
347	D-Limonene	396	Monochloroacetic Acid
348	$\alpha$ -Methyldopa Sesquihydrate	397	C.I. Direct Blue 15
349	Pentachlorophenol	398	Polybrominated Biphenyls
350	Tribromomethane	399	Titanocene Dichloride
351	<i>p</i> -Chloroaniline Hydrochloride	400	2,3-Dibromo-1-propanol
352	<i>N</i> -Methylolacrylamide	401	2,4-Diaminophenol Dihydrochloride
353	2,4-Dichlorophenol	402	Furan
354	Dimethoxane	403	Resorcinol
355	Diphenhydramine Hydrochloride	404	5,5-Diphenylhydantoin
356	Furosemide	405	C.I. Acid Red 114
357	Hydrochlorothiazide	406	$\gamma$ -Butyrolactone
358	Ochratoxin A	407	C.I. Pigment Red 3
359	8-Methoxypsoralen	408	Mercuric Chloride
360	<i>N,N</i> -Dimethylaniline	409	Quercetin
361	Hexachloroethane	410	Naphthalene
362	4-Vinyl-1-Cyclohexene Diepoxide	411	C.I. Pigment Red 23
363	Bromoethane (Ethyl Bromide)	412	4,4-Diamino-2,2-stilbenedisulfonic Acid
364	Rhodamine 6G (C.I. Basic Red 1)	413	Ethylene Glycol
365	Pentaerythritol Tetranitrate	414	Pentachloroanisole
366	Hydroquinone	415	Polysorbate 80
367	Phenylbutazone	416	<i>o</i> -Nitroanisole
368	Nalidixic Acid	417	<i>p</i> -Nitrophenol
369	Alpha-Methylbenzyl Alcohol	418	<i>p</i> -Nitroaniline
370	Benzofuran	419	HC Yellow 4
371	Toluene	420	Triamterene
372	3,3-Dimethoxybenzidine Dihydrochloride	421	Talc
373	Succinic Anhydride	422	Coumarin
374	Glycidol	423	Dihydrocoumarin
375	Vinyl Toluene	424	<i>o</i> -Benzyl- <i>p</i> -chlorophenol
376	Allyl Glycidyl Ether	425	Promethazine Hydrochloride
377	<i>o</i> -Chlorobenzal malononitrile	427	Turmeric Oleoresin
378	Benzaldehyde	428	Manganese (II) Sulfate Monohydrate
379	2-Chloroacetophenone	431	Benzyl Acetate
380	Epinephrine Hydrochloride	432	Barium Chloride Dihydrate
381	<i>d</i> -Cavone	434	1,3-Butadiene
382	Furfural	443	Oxazepam
384	1,2,3-Trichloropropane		

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**NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS**  
**PRINTED AS OF JANUARY 1994**

**TR No. CHEMICAL**

201 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)  
 206 1,2-Dibromo-3-chloropropane  
 207 Cytembena  
 208 FD & C Yellow No. 6  
 209 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)  
 210 1,2-Dibromoethane  
 211 C.I. Acid Orange 10  
 212 Di(2-ethylhexyl)adipate  
 213 Butyl Benzyl Phthalate  
 214 Caprolactam  
 215 Bisphenol A  
 216 11-Aminoundecanoic Acid  
 217 Di(2-Ethylhexyl)phthalate  
 219 2,6-Dichloro-*p*-phenylenediamine  
 220 C.I. Acid Red 14  
 221 Locust Bean Gum  
 222 C.I. Disperse Yellow 3  
 223 Eugenol  
 224 Tara Gum  
 225 D & C Red No. 9  
 226 C.I. Solvent Yellow 14  
 227 Gum Arabic  
 228 Vinylidene Chloride  
 229 Guar Gum  
 230 Agar  
 231 Stannous Chloride  
 232 Pentachloroethane  
 233 2-Biphenylamine Hydrochloride  
 234 Allyl Isothiocyanate  
 235 Zearalenone  
 236 *D*-Mannitol  
 237 1,1,1,2-Tetrachloroethane  
 238 Ziram  
 239 Bis(2-chloro-1-Methylethyl)ether  
 240 Propyl Gallate  
 242 Diallyl Phthalate (Mice)  
 243 Trichlorethylene (Rats and Mice)  
 244 Polybrominated Biphenyl Mixture  
 245 Melamine  
 246 Chrysotile Asbestos (Hamsters)  
 247 L-Ascorbic Acid  
 248 4,4'-Methylenedianiline Dihydrochloride  
 249 Amosite Asbestos (Hamsters)  
 250 Benzyl Acetate  
 251 2,4- & 2,6-Toluene Diisocyanate  
 252 Geranyl Acetate  
 253 Allyl Isovalerate  
 254 Dichloromethane (Methylene Chloride)  
 255 1,2-Dichlorobenzene  
 257 Diglycidyl Resorcinol Ether  
 259 Ethyl Acrylate  
 261 Chlorobenzene  
 263 1,2-Dichloropropane  
 266 Monuron  
 267 1,2-Propylene Oxide  
 269 Telone II® (1,3-Dichloropropene)  
 271 HC Blue No. 1  
 272 Propylene

**TR No. CHEMICAL**

273 Trichloroethylene (Four Rat Strains)  
 274 Tris(2-ethylhexyl)phosphate  
 275 2-Chloroethanol  
 276 8-Hydroxyquinoline  
 277 Tremolite  
 278 2,6-Xylidine  
 279 Amosite Asbestos  
 280 Crocidolite Asbestos  
 281 HC Red No. 3  
 282 Chlorodibromomethane  
 284 Diallylphthalate (Rats)  
 285 C.I. Basic Red 9 Monohydrochloride  
 287 Dimethyl Hydrogen Phosphite  
 288 1,3-Butadiene  
 289 Benzene  
 291 Isophorone  
 293 HC Blue No. 2  
 294 Chlorinated Trisodium Phosphate  
 295 Chrysotile Asbestos (Rats)  
 296 Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosphonium Chloride  
 298 Dimethyl Morpholinophosphoramidate  
 299 C.I. Disperse Blue 1  
 300 3-Chloro-2-methylpropene  
 301 *o*-Phenylphenol  
 303 4-Vinylcyclohexene  
 304 Chlorendic Acid  
 305 Chlorinated Paraffins (C<sub>23</sub>, 43% chlorine)  
 306 Dichloromethane (Methylene Chloride)  
 307 Ephedrine Sulfate  
 308 Chlorinated Paraffins (C<sub>12</sub>, 60% chlorine)  
 309 Decabromodiphenyl Oxide  
 310 Marine Diesel Fuel and JP-5 Navy Fuel  
 311 Tetrachloroethylene (Inhalation)  
 312 *n*-Butyl Chloride  
 313 Mirex  
 314 Methyl Methacrylate  
 315 Oxytetracycline Hydrochloride  
 316 1-Chloro-2-methylpropene  
 317 Chlorpheniramine Maleate  
 318 Ampicillin Trihydrate  
 319 1,4-Dichlorobenzene  
 320 Rotenone  
 321 Bromodichloromethane  
 322 Phenylephrine Hydrochloride  
 323 Dimethyl Methylphosphonate  
 324 Boric Acid  
 325 Pentachloronitrobenzene  
 326 Ethylene Oxide  
 327 Xylenes (Mixed)  
 328 Methyl Carbamate  
 329 1,2-Epoxybutane  
 330 4-Hexylresorcinol  
 331 Malonaldehyde, Sodium Salt  
 332 2-Mercaptobenzothiazole  
 333 *N*-Phenyl-2-naphthylamine  
 334 2-Amino-5-nitrophenol  
 335 C.I. Acid Orange 3

**DEPARTMENT OF  
HEALTH & HUMAN SERVICES**

Public Health Service  
National Toxicology Program  
Central Data Management  
P.O. Box 12233, MD A0-01  
Research Triangle Park, NC 27709

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