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$_1$ 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

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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February 1994

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Public Health Service
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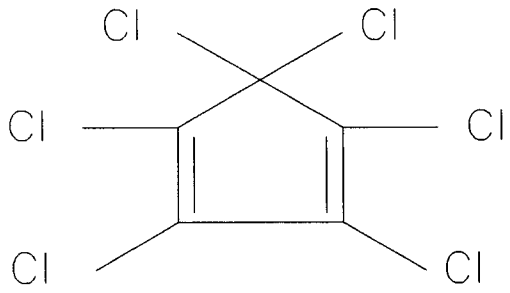
ABSTRACT



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 cyclodiene pesticides. Toxicology and carcinogenesis studies were conducted by exposing male and female F344/N rats and B6C3F$_1$ 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$_1$ 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^3) hexachlorocyclopentadiene. Additional rats were exposed to 0, 0.04, 0.4, or 2 ppm hexachlorocyclopentadiene 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^3) 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^3) 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^3) 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$_1$ 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$_1$ 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 $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 0.01, 0.05, or 0.2 ppm by inhalation (equivalent to 0, 0.11, 0.56, or 2.28 mg/m^3)	0, 0.01, 0.05, or 0.2 ppm by inhalation (equivalent to 0, 0.11, 0.56, or 2.28 mg/m^3)	0, 0.01, 0.05, or 0.2 ppm by inhalation (equivalent to 0, 0.11, 0.56, or 2.28 mg/m^3)	0, 0.01, 0.05, or 0.2 ppm by inhalation (equivalent to 0, 0.11, 0.56, or 2.28 mg/m^3)
Body weights	Exposed groups similar to controls	Exposed groups similar to controls	High dose lower than controls	High dose lower than controls
2-Year survival rates	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
Nonneoplastic effects	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)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence

Genetic toxicology

Salmonella typhimurium gene mutation:	Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537
Sister chromatid exchanges	
Chinese hamster ovary cells *in vitro*:	Positive with and without S9
Chromosomal aberrations	
Chinese hamster ovary cells *in vitro*:	Positive with and without S9
Sex-linked recessive lethal mutation in *Drosophila melanogaster*:	Negative administered in feed or by injection
Mouse peripheral blood erythrocytes *in vivo*:	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$_1$ 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.

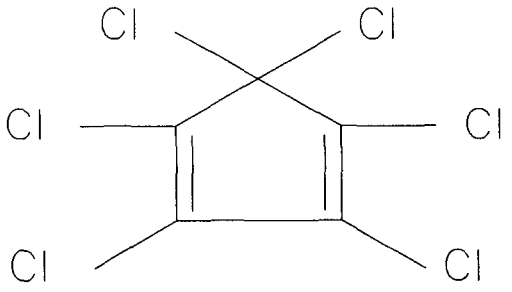
Dr. Ward, the second principal reviewer, also agreed in principle with the proposed conclusions and stated that rats might have been able to tolerate a higher top dose because no effects on body weight gain or survival were observed and because toxic lesions were limited to pigmentation of the respiratory 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° C, a boiling point of 239° C, a density of 1.717 at 15° C (Hawley, 1977), a vapor pressure of 0.08 mm Hg at 25° 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° C followed by fractional distillation or by thermal dechlorination of octachlorocyclopentene at 470° to 480° 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 ± 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$_1$ 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^3) 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 μm, 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^3) 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$_1$ 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 nonneoplastic 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)
Study Laboratory	
Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
Strain and Species	
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source	
Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)
Size of Study Groups	
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)
Time Held Before Studies	
Rats: 14 days Mice: 11 days	Rats: 19 days Mice: 18 days
Average Age When Studies Began	
6 weeks	6-7 weeks
Date of First Exposure	
Rats: 25 October 1983 Mice: 1 November 1983	Rats: 2 December 1985 Mice: 18 November 1985
Duration of Exposure	
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
Date of Last Exposure	
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
Method of Sacrifice	
Pentobarbital sodium	70% CO_2 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)
Necropsy Dates Rats: 25-27 January 1984 Mice: 1-3 February 1984	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
Average Age at Necropsy 19 weeks	15-month interim evaluation: 72-73 weeks 2-year study: 111-112 weeks
Method of Animal Distribution Animals were randomized by weight with a computer randomization program.	Animals were randomized by weight with the XYBION PATH/TOX System.
Animals per Cage 1	1
Method of Animal Identification Ear tag	Toe clip
Diet NIH-07 pelleted rodent diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum* except during exposure period; changed weekly or as necessary; NIH-07 mash (Zeigler Brothers, Inc., Gardners, PA) (special study)	NIH-07 pelleted rodent diet (Zeigler Brothers, Inc., Gardners PA), available *ad libitum* except during exposure period; changed weekly or as necessary
Water Tap water (City of Richland) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*; changed weekly	Same as 13-week studies
Chambers Stainless steel multitiered whole-body exposure chambers (Hazleton Systems, Aberdeen, MD); washed weekly	Same as 13-week studies
Cages Stainless steel (Hazleton Systems, Inc., Aberdeen, MD); changed weekly	Same as 13-week studies
Bedding Catch pans during exposure days and catch pans lined with untreated paper over weekends	Untreated paper cageboard (Techboard® until 12 March 1986, then Techsorb®, Shepherd Specialty Papers, Inc., Kalamazoo, MI); changed daily

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)
Cage Filters	Room High Efficiency Particle Air (HEPA) filter (prefilter and intake) (American Air Filter, Louisville, KY)	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)
Animal Room Environment	Temperature: 20°-21° C Relative humidity: 35%-65% Fluorescent light: 12 hours/day Room air changes: 20 changes/hour	Temperature: 20°-29° C Relative humidity: 21%-88% Fluorescent light: 12 hours/day Room air changes: 9-20 changes/hour
Exposure Concentrations	0, 0.04, 0.15, 0.4, 1, or 2 ppm hexachlorocyclopentadiene by inhalation	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
Type and Frequency of Observation	Animals were observed twice daily, and clinical observations were recorded weekly; animals were weighed initially, weekly, and at the end of the studies.	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.
Necropsy	Necropsy was performed on all animals. Organs weighed (core animals only) were adrenal gland, brain, heart, right kidney, liver, lungs, right testis, and thymus.	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.
Clinical Pathology	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. ***Hematology:*** packed cell volume, hemoglobin, erythrocytes, reticulocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, leukocyte count and differential ***Clinical Chemistry:*** urea nitrogen, creatinine, glucose, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase (except core mice) ***Urinalysis:*** osmolality, creatinine, glucose, protein, volume	Urine was collected over a 16-hour period from all animals (except stop-exposure animals) at the 15-month interim evaluations using metabolism cages. ***Urinalysis:*** volume and specific gravity

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)
Histopathology	
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.	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. 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.

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[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
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[c]	332 ± 9	213 ± 8*	94
0.4	10/10	124 ± 4	326 ± 7*	202 ± 5**	93
1	0/10[d]	127 ± 3	–	–	–
2	0/10[e]	123 ± 3	–	–	–
Female					
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[f]	103 ± 2	–	–	–
2	0/10[g]	101 ± 2	–	–	–

* Significantly different (P≤0.05) from the control group by Williams' test
** P≤0.01
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Final mean body weights were not calculated for groups with 100% mortality.
[c] Nine animals weighed
[d] Week of death: 2, 2, 2, 3, 3, 3, 3, 3, 3, 3
[e] Week of death: 1, 1, 1, 1, 1, 2, 2, 2, 3, 3
[f] Week of death: 2, 2, 2, 2, 2, 2, 3, 3, 3, 4
[g] 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[a]

Dose (ppm)	0	0.15	0.4	1	2
Male					
Nose[b]	10	10	10	10	10
Inflammation, Necrotizing[c]	0	0	2 (2.0)[d]	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)
Female					
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
** $P \leq 0.01$
[a] Animals in the 0.04 ppm group were not examined
[b] Number of animals with organ examined microscopically
[c] Number of animals with lesion
[d] 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
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	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[b]	36	33	45	32
Mean survival (days)[c]	627	616	624	609
Survival analyses[d]	P=0.649	P=0.775	P=0.513N	P=0.679
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	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[a]	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

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] 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.

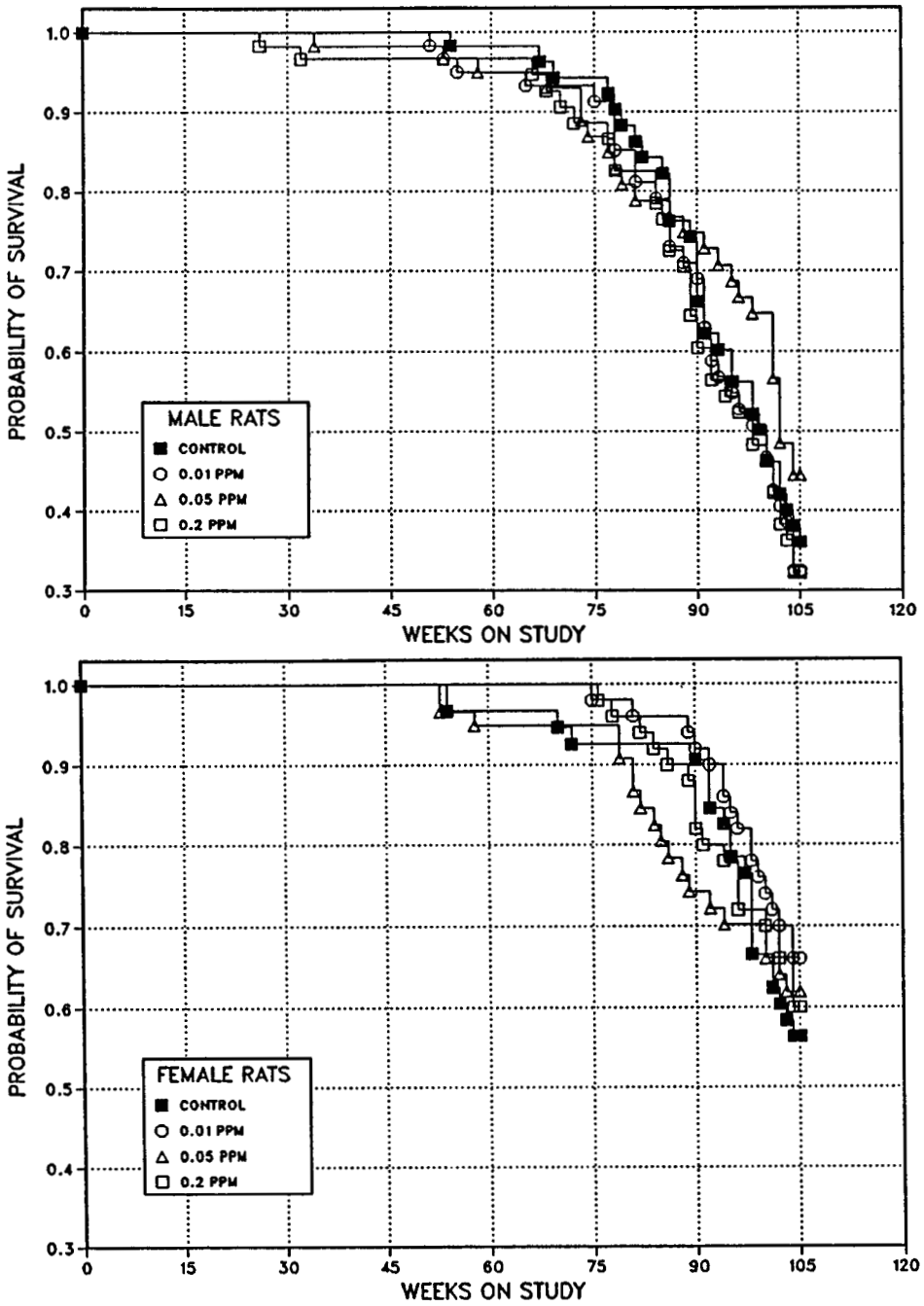


FIGURE 1
Kaplan-Meier Survival Curves for Rats Administered Hexachlorocyclopentadiene by Inhalation for 2 Years

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[a]	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
Mean for weeks											
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	

[a] 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 Av. Wt. (g)	0 ppm No. of Survivors	0.01 ppm Av. Wt. (g)	0.01 ppm Wt. (% of controls)	0.01 ppm No. of Survivors	0.05 ppm Av. Wt. (g)	0.05 ppm Wt. (% of controls)	0.05 ppm No. of Survivors	0.2 ppm Av. Wt. (g)	0.2 ppm Wt. (% of controls)	0.2 ppm 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[a]	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
Mean for weeks											
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	

[a] Interim evaluation occurred during week 66.

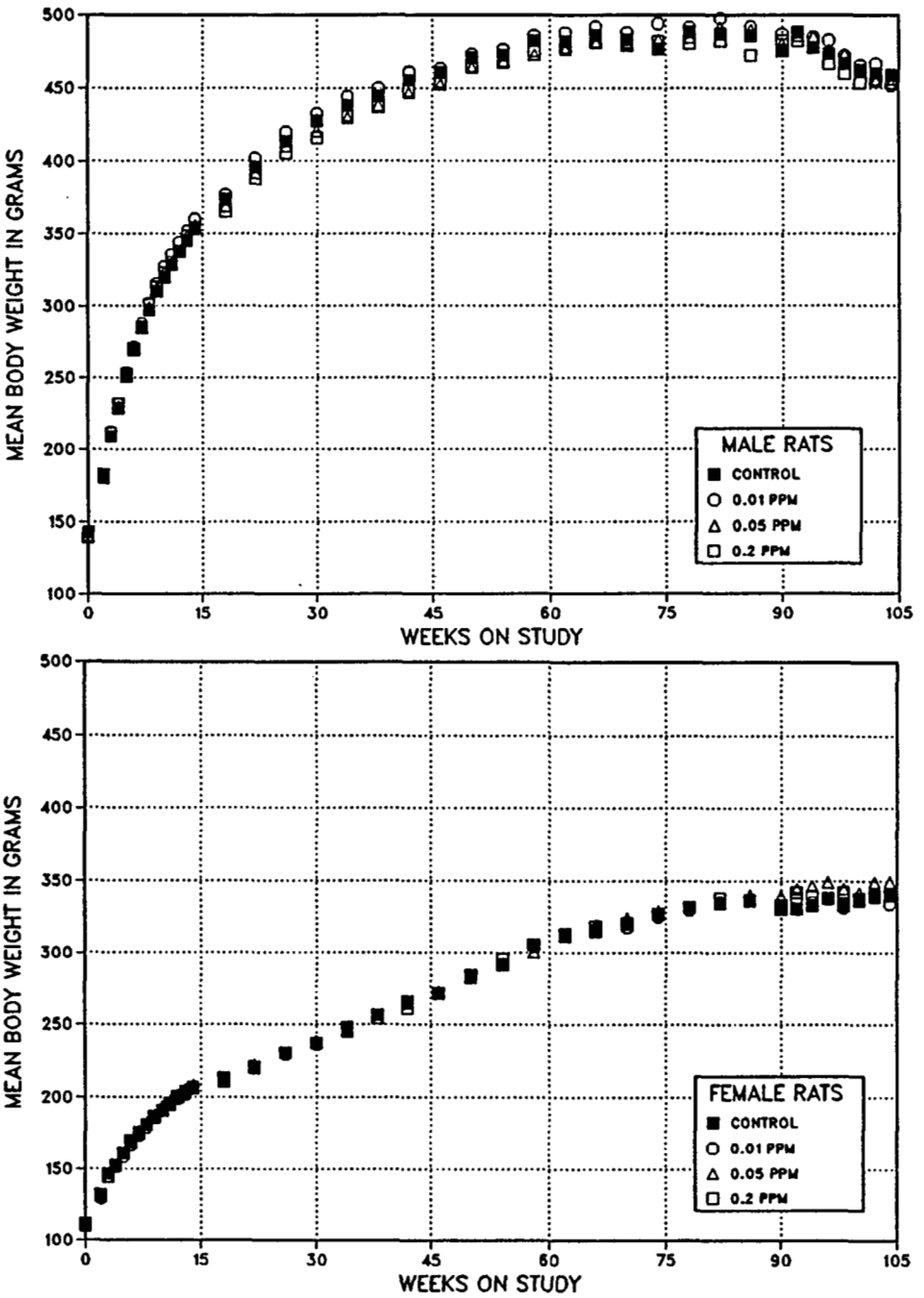


FIGURE 2
Growth Curves for Rats Administered Hexachlorocyclopentadiene by Inhalation for 2 Years

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
Male				
15-Month Interim Evaluation				
Nose[a]	10	10	10	10
Pigmentation[b]	0	8** (1.0)[c]	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)
2-Year Study				
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)

(continued)

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
Female				
15-Month Interim Evaluation				
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)
2-Year Study				
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)
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] 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[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	21.9 ± 0.4	31.9 ± 0.5	10.0 ± 0.6	
0.04	8/10[c]	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[d]	21.4 ± 0.3	29.4 ± 0.6**	7.2 ± 0.7**	92
1	0/10[e]	21.2 ± 0.3	–	–	–
2	0/10[f]	21.1 ± 0.4	–	–	–
Female					
0	4/10[g]	17.4 ± 0.4	26.0 ± 0.9	8.0 ± 0.7	
0.04	9/10[h]	18.0 ± 0.4	27.4 ± 0.7	9.3 ± 0.5	106
0.15	9/10[h]	17.4 ± 0.3	26.1 ± 0.4	8.8 ± 0.2	100
0.4	8/10[i]	17.0 ± 0.4	25.6 ± 0.4	8.6 ± 0.5	99
1	0/10[j]	16.9 ± 0.4	–	–	–
2	0/10[f]	16.6 ± 0.3	–	–	–

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving/number initially in group
[b] 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.
[c] Week of death: 5, 5
[d] Week of death: 1, 1, 1, 1, 2
[e] Week of death: 1, 1, 1, 2, 2, 2, 2, 2, 2, 5
[f] Week of death: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1
[g] Week of death: 8, 8, 8, 8, 8 (due to defective feeder)
[h] Week of death: 1
[i] Week of death: 1, 2
[j] 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
Male						
Nose[a]	10	10	10	10	10	10
Necrosis, Acute[b]	0	0	0	0	1 (4.0)[c]	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)
Female						
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**[d] (4.0)
Metaplasia, Squamous	0	0	0	0	7**[d] (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
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe
[d] 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
Male				
Animals initially in study	60[a]	60	60	60
15-Month interim evaluation[b]	10	10	10	10
Accidental deaths[b]	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[c]	72	70	84	69
Mean survival (days)[d]	510	646	673	647
Survival analyses[e]	P=0.630	P=0.936	P=0.204N	P=0.794
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[b]	10	10	10	10
Accidental deaths[b]	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

[a] Excludes the 30 male mice used as controls in the stop-exposure evaluation
[b] Censored from survival analyses
[c] Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[e] 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.

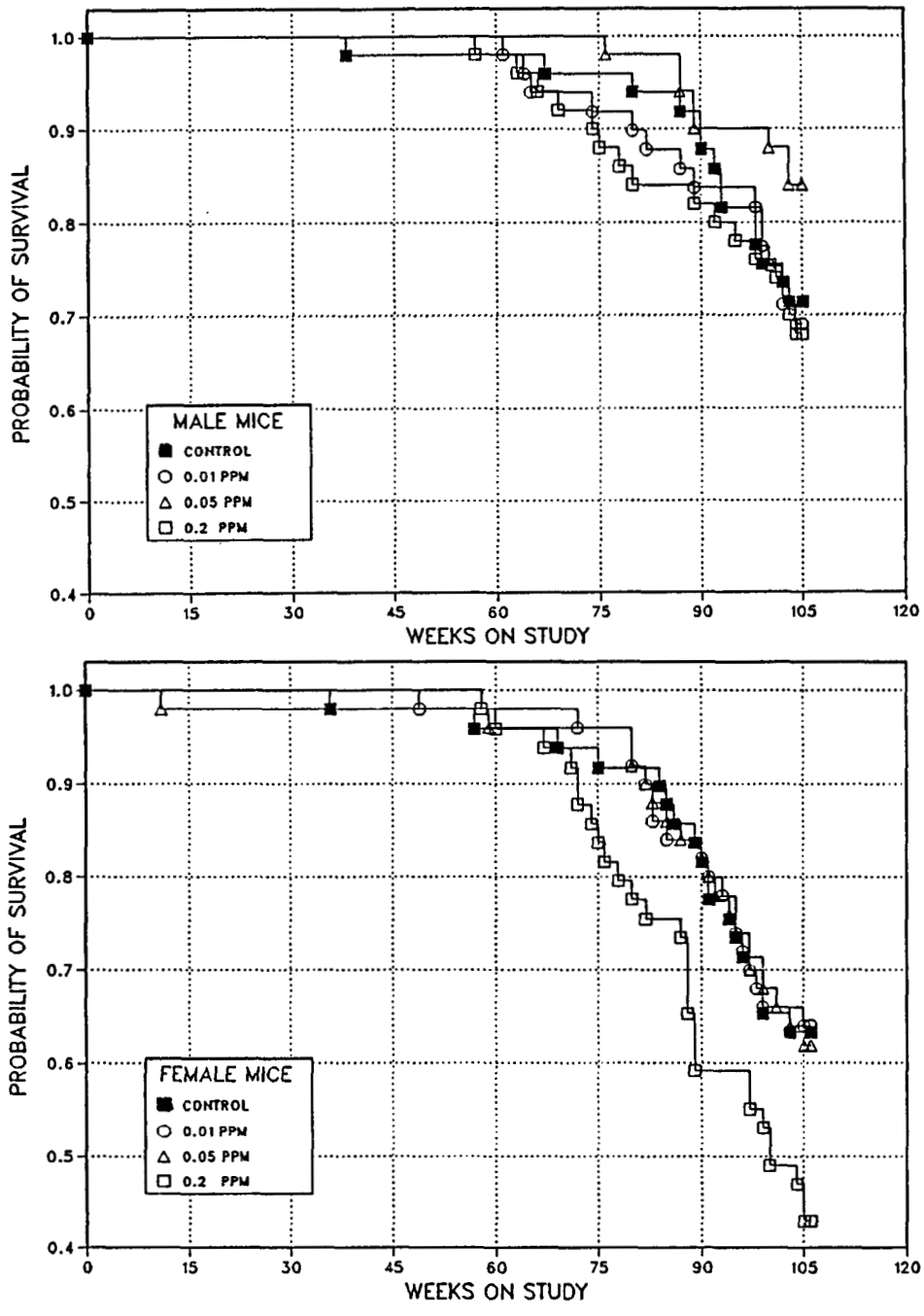


FIGURE 3
Kaplan-Meier Survival Curves for Mice Administered Hexachlorocyclopentadiene by Inhalation for 2 Years

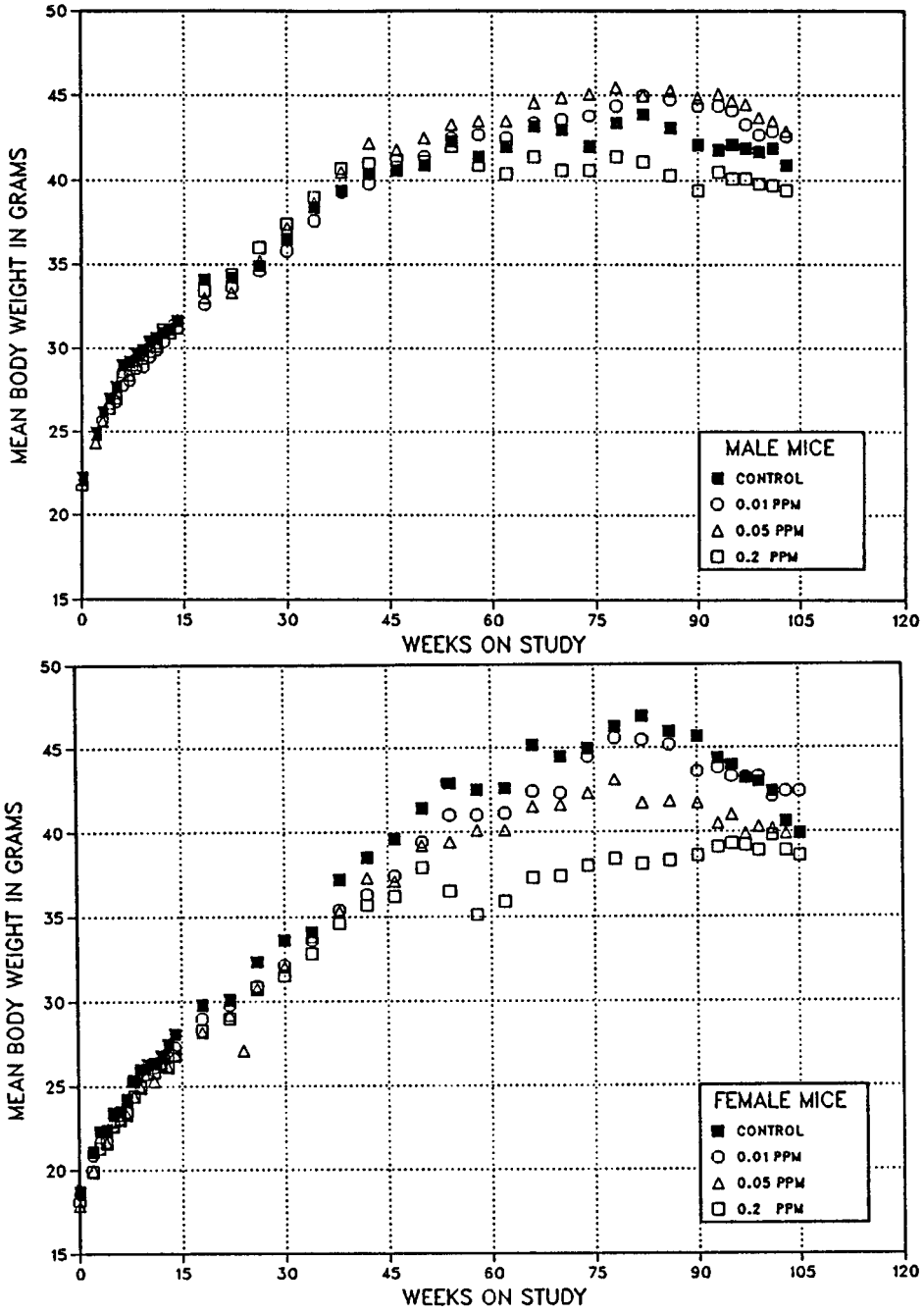


FIGURE 4
Growth Curves for Mice Administered Hexachlorocyclopentadiene by Inhalation for 2 Years

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[a]	36.5	79	35.8	98	60	37.2	102	60	37.4	103	60
34[a]	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[a]	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[a]	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
Mean for weeks											
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	

[a] 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[a]	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
Mean for weeks											
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	

[a] 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 $B6C3F_1$ 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
Male				
15-Month Interim Evaluation				
Nose[a]	10	10	10	10
Inflammation, Suppurative[b]	0	0	1 (1.0)[c]	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)
2-Year Study				
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
Female				
15-Month Interim Evaluation				
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)
2-Year Study				
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)
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] 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[a]	80	50	90	70
27-Week interim evaluation[b]	10	–[c]	–	10	–
34-Week interim evaluation[b]	10	10	–	10	–
43-Week interim evaluation[b]	10	10	–	10	10
15-Month interim evaluation[b]	10	10	–	10	10
Accidental deaths[b]	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[d]	72	71	67	82	70
Mean survival (days)[e]	509	555	673	522	554
Survival analyses[f]		P=1.000	P=0.652	P=0.311N	P=0.500

[a] Includes 60 controls from the core study
[b] Censored from survival analyses
[c] No interim evaluation scheduled for this group
[d] Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice
[e] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[f] 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.

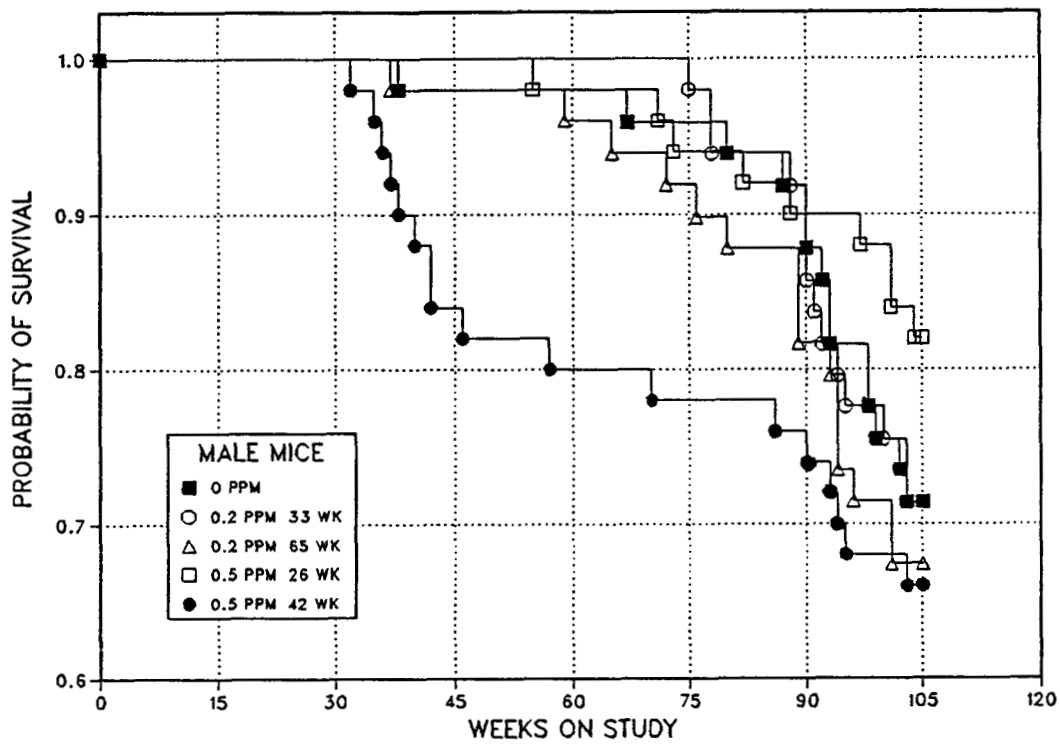


FIGURE 5
Kaplan-Meier Survival Curves for Male Stop-Exposure Mice Administered Hexachlorocyclopentadiene by Inhalation

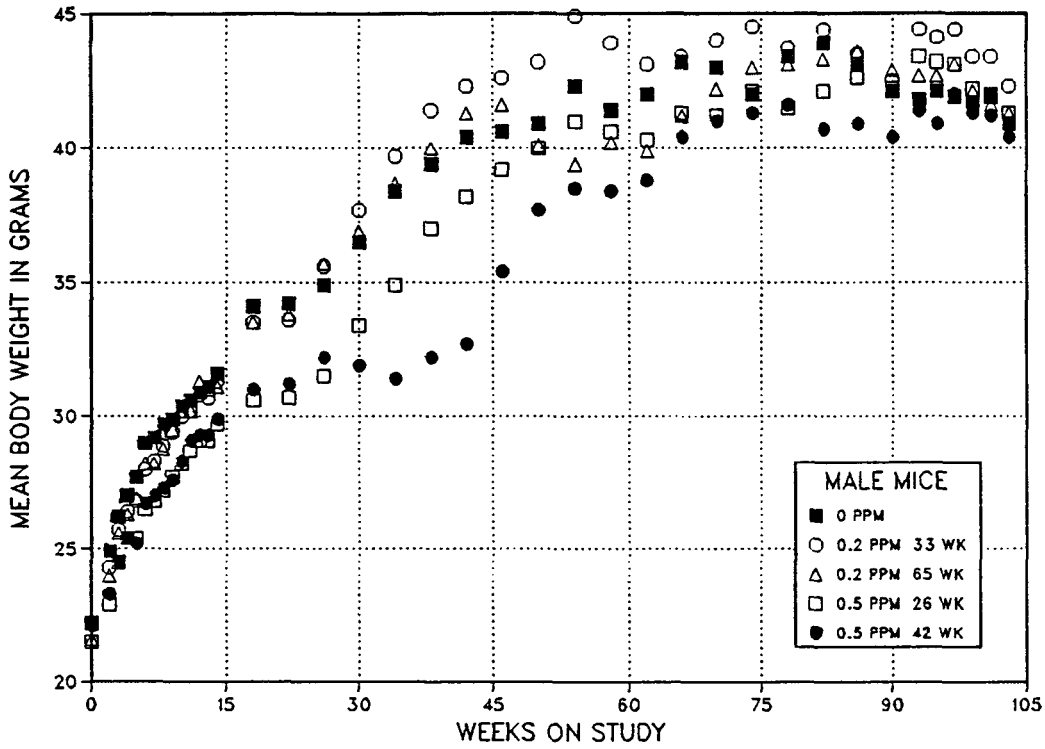


FIGURE 6
Growth Curves for Male Stop-Exposure Mice Administered Hexachlorocyclopentadiene by Inhalation

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[a]	36.5	79	37.7	103	80	36.9	101	50
34[a]	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[a]	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[a]	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
Mean for weeks								
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[a]	36.5	79	33.4	92	80	31.9	87	70
34[a]	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[a]	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[a]	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
Mean for weeks								
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	

[a] 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[a]	50	50	49	50
Inflammation, Suppurative[b]	0	2 (2.5)[c]	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[d]	11	13	17	16

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean ± standard deviation): 139/624 (22.3% ± 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[a]	50	50	50
Inflammation, Suppurative[b]	0	7* (2.0)[c]	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[d]	0	5*	6*
Alveolar/bronchiolar Adenoma or Carcinoma[e]	11	14	14

* Significantly different (P≤0.05) from the control group by the logistic regression test
** P≤0.01
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean ± standard deviation): 45/624 (7.2% ± 5.5%), range 0%-16%
[e] Historical incidence: 139/624 (22.3% ± 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$_1$ 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$_1$ 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$_1$ 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 hexachlorocyclopentadiene 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^3) 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 contaminants 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 (Wildemauwe *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$_1$ 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.

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

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	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
15-Month Interim Evaluation				
Alimentary System				
None				
Cardiovascular System				
None				
Endocrine System				
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%)	
General Body System				
None				
Genital System				
Testes	(10)	(2)	(1)	(10)
Interstitial cell, adenoma	2 (20%)	2 (100%)		5 (50%)
Interstitial cell, adenoma, multiple	7 (70%)		1 (100%)	5 (50%)
Hematopoietic System				
None				
Integumentary System				
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
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
Skeletal muscle			(1)	
Sarcoma			1 (100%)	
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Sarcoma, metastatic, skeletal muscle			1 (10%)	
Special Senses System				
None				
Urinary System				
Urinary bladder	(10)			(10)
Papilloma	1 (10%)			
2-Year Study				
Alimentary System				
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)
Cardiovascular System				
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
2-Year Study (continued)				
Endocrine System				
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%)
General Body System				
None				
Genital System				
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%)	
Hematopoietic System				
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
2-Year Study (continued)				
Integumentary System				
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%)
Musculoskeletal System				
Skeletal muscle	(1)		(1)	(2)
Rhabdomyosarcoma	1 (100%)			
Nervous System				
Brain	(50)	(35)	(29)	(50)
Glioma malignant				1 (2%)
Granular cell tumor malignant			1 (3%)	
Respiratory System				
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%)
Special Senses System				
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
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(37)	(36)	(50)
Nephroblastoma		1 (3%)		
Urinary bladder	(50)	(34)	(27)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	29 (58%)	33 (66%)	26 (52%)	29 (58%)
Mesothelioma malignant	1 (2%)	5 (10%)		2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
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	

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Number of animals with any tissue examined microscopically
[c] 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

Number of Days on Study	3 7 3	4 6 4	4 8 1	5 3 6	5 4 4	5 4 8	5 6 5	5 6 9	5 9 1	5 9 7	5 9 7	6 0 0	6 1 7	6 2 4	6 2 5	6 2 6	6 2 8	6 3 3	6 3 5	6 5 1	6 6 0	6 6 1	6 8 1	6 8 3	6 9 1
Carcass ID Number	0 0 4 4	0 1 5 1	0 1 5 4	0 0 6 3	0 1 3 1	0 0 4 1	0 0 9 2	0 1 3 2	0 0 8 4	0 1 0 3	0 1 2 1	0 1 1 1	0 1 4 3	0 0 9 3	0 0 5 4	0 0 7 2	0 0 2 2	0 0 5 3	0 0 6 2	0 1 2 4	0 1 1 4	0 0 1 3	0 1 1 1	0 1 0 3	0 1 1 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+
Adenocarcinoma, mucinous	X																								
Fibroma																					X				
Intestine small, ileum	+	+	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery		+			+					+	+											+		+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+				+											+			+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																					X			X	
Pheochromocytoma benign																	X							X	
Pheochromocytoma benign, multiple																		X							
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Carcinoma																X									X
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X				X			X	X					X			X	X				X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X								X	
General Body System																									
None																									

+: 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)

Number of Days on Study	6 9 4	6 9 8	7 1 2	7 1 2	7 1 9	7 2 4	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 1 1 2	0 0 3 1	0 0 7 4	0 0 9 1	0 0 7 1	0 0 3 2	0 0 8 3	0 0 1 1	0 0 1 2	0 0 1 4	0 0 2 1	0 0 2 3	0 0 3 4	0 0 4 3	0 0 6 1	0 0 6 4	0 0 8 1	0 0 8 2	0 0 9 4	0 1 0 2	0 1 1 2	0 1 2 3	0 1 3 3	0 1 4 2	0 1 4 4	0 1 5 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma, mucinous																										1
Fibroma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X																							1
Mesentery						+										+	+	+			+		+			12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																	+									1
Cardiovascular System																										
Blood vessel							+																			5
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										2
Pheochromocytoma benign	X			X		X					X	X			X		X		X		X		X			12
Pheochromocytoma benign, multiple																										1
Bilateral, pheochromocytoma benign					X																	X				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X										X			X		X						X		X		7
Carcinoma			X												X											4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X			X	X				X		X			X			X	X			X	X	23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma	X							X																X		5
General Body System																										
None																										

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

Number of Days on Study	3 7 3	4 6 4	4 8 1	5 3 6	5 4 4	5 4 8	5 6 5	5 6 9	5 9 1	5 9 7	5 9 7	6 0 0	6 1 7	6 2 4	6 2 5	6 2 6	6 2 8	6 3 3	6 3 5	6 5 1	6 6 0	6 6 1	6 8 1	6 8 3	6 9 1
Carcass ID Number	0 0 4 4	0 1 5 1	0 1 5 4	0 0 6 3	0 1 3 1	0 0 4 1	0 0 9 2	0 1 3 2	0 0 8 4	0 1 0 3	0 1 2 1	0 1 1 1	0 1 4 3	0 0 9 3	0 0 5 4	0 0 7 2	0 0 2 2	0 0 5 3	0 0 6 2	0 1 2 4	0 1 1 4	0 0 1 3	0 1 0 1	0 1 5 2	0 1 0 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X																	X				X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X		X		X			X		X					X	X	X			
Interstitial cell, adenoma				X													X						X		
Interstitial cell, adenoma, multiple																X		X	X						
Hematopoietic System																									
Blood																		+							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+																
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma				X																					
Fibrosarcoma										X															
Squamous cell papilloma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																							
Rhabdomyosarcoma		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Pheochromocytoma malignant, metastatic, adrenal medulla																					X				
Nose	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	6 9 4	6 9 8	7 1 2	7 1 2	7 1 9	7 2 4	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 1 1 2	0 0 3 1	0 0 7 4	0 0 9 1	0 0 7 1	0 0 3 2	0 0 8 3	0 0 1 1	0 0 1 2	0 0 1 4	0 0 2 1	0 0 2 3	0 0 3 4	0 0 4 3	0 0 6 1	0 0 6 4	0 0 8 1	0 0 8 2	0 0 9 4	0 0 0 2	0 1 2 3	0 1 3 3	0 1 4 2	0 1 4 4	0 1 5 3	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X												X											X		6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X			X	X		X	X			X			X	X		X	X	X		X	X	X		23
Interstitial cell, adenoma			X	X						X	X		X	X			X				X				X	12
Interstitial cell, adenoma, multiple																										3
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+																					2
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma					X																					2
Fibrosarcoma																										1
Squamous cell papilloma																						X				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X		X														X				X			X		5
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

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

Number of Days on Study	3	4	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	7	6	8	3	4	4	6	6	9	9	9	0	1	2	2	2	2	3	3	5	6	6	8	8	9
	3	4	1	6	4	8	5	9	1	7	7	0	7	4	5	6	8	3	5	1	0	1	1	3	1
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
	0	1	1	0	1	0	0	1	0	1	1	1	1	0	0	0	0	0	0	1	1	0	1	1	1
	4	5	5	6	3	4	9	3	8	0	2	1	4	9	5	7	2	5	6	2	1	1	0	5	0
	4	1	4	3	1	1	2	2	4	3	1	1	3	3	4	2	2	3	2	4	4	3	1	2	4
Special Senses System																									
Eye		+			+										+										
Zymbal's gland						+																			
Carcinoma						X																			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X	X		X	X	X			X	X	X	X		X	X	X	
Mesothelioma malignant																									

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

Number of Days on Study	6 9 4	6 9 8	7 1 2	7 1 2	7 1 9	7 2 4	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 1 1 2	0 0 3 1	0 0 7 4	0 0 9 1	0 0 7 1	0 0 3 2	0 0 8 3	0 0 1 1	0 0 1 2	0 0 1 4	0 0 2 1	0 0 2 3	0 0 3 4	0 0 4 3	0 0 6 1	0 0 6 4	0 0 8 1	0 0 8 2	0 0 9 4	0 0 0 2	0 1 2 3	0 1 3 3	0 1 4 2	0 1 4 4	0 1 5 3	Total Tissues/ Tumors
Special Senses System																										
Eye																					+					4
Zymbal's gland						+																				2
Carcinoma						X																				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
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: 0.01 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.01 ppm (continued)

Number of Days on Study	6 9 5	6 9 8	7 0 4	7 0 5	7 0 9	7 1 9	7 2 4	7 2 4	7 2 6	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 4 4 1	0 4 4 4	0 4 3 4	0 3 6 1	0 3 2 3	0 3 8 4	0 3 2 4	0 3 6 2	0 4 5 1	0 4 3 3	0 3 3 1	0 3 4 2	0 3 4 3	0 3 4 3	0 3 5 3	0 3 7 4	0 3 8 3	0 3 9 1	0 3 9 3	0 4 0 3	0 4 1 4	0 4 2 2	0 4 2 3	0 4 4 3	0 4 4 4	0 4 5 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+																	34
Intestine large, colon	+	+	+	+	+	+	+	+	+																	34
Intestine large, rectum	+	+	+	+	+	+	+	+	+																	34
Intestine large, cecum	+	+	+	+	+	+	+	+	+																	32
Intestine small, duodenum	+	+	+	+	+	+	+	+	+																	34
Intestine small, jejunum	+	+	+	+	+	+	+	+	+																	33
Intestine small, ileum	+	+	+	+	+	+	+	+	+																	32
Liver	+	+	+	+	+	+	+	+	+	+						+			+	+	+					39
Hepatocellular adenoma																										1
Mesentery	+		+			+			+															+	+	+	11
Pancreas	+	+	+	+	+	+	+	+	+																	34
Salivary glands	+	+	+	+	+	+	+	+	+																	34
Stomach, forestomach	+	+	+	+	+	+	+	+	+							+		+								36
Stomach, glandular	+	+	+	+	+	+	+	+	+							+										35
Tooth			+																							1
Cardiovascular System																										
Blood vessel																										3
Heart	+	+	+	+	+	+	+	+	+																	34
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+																	33
Adrenal medulla	+	+	M	+	+	+	+	+	+			+														34
Pheochromocytoma malignant				X																						1
Pheochromocytoma benign							X					X														7
Bilateral, pheochromocytoma benign	X	X																								3
Islets, pancreatic	+	+	+	+	+	+	+	+	+																	34
Adenoma						X	X		X																	5
Carcinoma																										2
Parathyroid gland	+	+	M	+	M	+	+	+	+																	30
Pituitary gland	+	+	+	+	+	+	+	+	+		+									+		+	+	+		39
Carcinoma, metastatic, Zymbal's gland																										1
Pars distalis, adenoma	X	X			X	X	X	X	X		X									X		X	X	X		23
Thyroid gland	+	+	+	+	+	+	+	+	+										+							35
C-cell, adenoma									X																	3
C-cell, carcinoma																										1
Follicular cell, adenoma																			X							1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.01 ppm (continued)

Number of Days on Study	3 5 5	3 7 0	3 7 9	4 5 1	5 2 3	5 4 0	5 4 1	5 4 4	5 6 4	5 6 5	5 8 4	5 9 7	6 0 0	6 0 0	6 1 5	6 2 8	6 3 4	6 3 5	6 3 6	6 3 9	6 3 9	6 4 9	6 6 2	6 7 0	6 8 1
Carcass ID Number	0 4 0 1	0 3 1 4	0 3 8 1	0 3 7 2	0 3 3 2	0 3 7 3	0 3 2 1	0 3 4 4	0 3 9 2	0 4 2 4	0 3 1 2	0 4 1 3	0 3 8 2	0 3 9 4	0 4 3 2	0 4 1 2	0 3 5 1	0 4 0 2	0 3 2 2	0 3 1 1	0 3 5 2	0 4 3 1	0 3 6 3	0 3 1 3	0 3 5 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																						X			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X								X				X			X				
Interstitial cell, adenoma	X							X	X	X		X			X		X			X					X
Interstitial cell, adenoma, multiple																						X	X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+										+					+	+							
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma								X																	
Squamous cell papilloma																							X		
Sebaceous gland, carcinoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, Zymbal's gland			X																			X			
Mesothelioma malignant, metastatic, testes																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.01 ppm (continued)

Number of Days on Study	6 9 5	6 9 8	7 0 4	7 0 5	7 0 9	7 1 9	7 2 4	7 2 4	7 2 6	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 4 4 1	0 4 4 4	0 4 3 4	0 3 6 1	0 3 2 3	0 3 8 4	0 3 2 4	0 3 6 2	0 4 5 1	0 3 3 3	0 3 4 1	0 3 4 2	0 3 4 3	0 3 5 3	0 3 7 4	0 3 8 3	0 3 9 1	0 3 9 3	0 4 0 3	0 4 1 4	0 4 2 2	0 4 2 3	0 4 4 3	0 4 4 4	0 4 5 2	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+														+			35
Mesothelioma malignant, metastatic, testes																										1
Preputial gland	+	+	+	+	+	+	+	+	+		+				+					+				+		38
Carcinoma																				X						2
Prostate	+	+	+	+	+	+	+	+	+												+					35
Seminal vesicle	+	+	+	+	+	+	+	+	+															+		35
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+	48
Bilateral, interstitial cell, adenoma	X		X	X			X			X	X	X	X	X		X	X	X		X	X		X	X	X	21
Interstitial cell, adenoma								X							X												11
Interstitial cell, adenoma, multiple																										2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+																	34
Lymph node																		+						+		6
Lymph node, bronchial	+	+	+	+	+	+	+	+	+														+			32
Lymph node, mandibular	+	+	+	+	+	+	+	+	M										+							32
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+																+	35
Lymph node, mediastinal	+	+	+	+	M	+	+	+	M																	32
Spleen	+	+	+	+	+	+	+	+	+		+	+			+			+			+	+			+	41
Thymus	+	+	+	+	M	+	+	+	M																	32
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+																	34
Skin	+	+	+	+	+	+	+	+	+		+	+			+				+							38
Fibroma															X											1
Fibrosarcoma																										1
Squamous cell papilloma																										1
Sebaceous gland, carcinoma												X														1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+																	34
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+									+								35
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X						X							2
Carcinoma, metastatic, Zymbal's gland																										2
Mesothelioma malignant, metastatic, testes																							X			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.01 ppm (continued)

Number of Days on Study	3 5 5	3 7 0	3 7 9	4 5 1	5 2 3	5 4 0	5 4 1	5 4 4	5 6 4	5 6 5	5 8 4	5 9 7	6 0 0	6 0 0	6 1 5	6 2 8	6 3 4	6 3 5	6 3 6	6 3 9	6 3 9	6 4 9	6 6 2	6 7 0	6 8 1
Carcass ID Number	0 4 0 1	0 3 1 4	0 3 8 1	0 3 7 2	0 3 3 2	0 3 7 3	0 3 2 1	0 3 4 4	0 3 9 2	0 3 2 4	0 4 1 2	0 3 1 3	0 4 1 2	0 3 8 2	0 3 9 4	0 4 3 2	0 4 1 2	0 3 5 1	0 4 0 2	0 3 2 2	0 3 1 1	0 3 5 2	0 4 3 1	0 3 6 3	0 3 1 3	0 3 5 4
Special Senses System																									
Eye																								+	
Harderian gland																						+			
Duct, carcinoma																						X			
Zymbal's gland			+																			+			
Carcinoma			X																			X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X		X			X	X	X	X	X	X		X	X	X	X	X	X	X		X
Mesothelioma malignant												X										X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.01 ppm (continued)

Number of Days on Study	6 9 5	6 9 8	7 0 4	7 0 5	7 0 9	7 1 9	7 2 4	7 2 4	7 2 6	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 4 4 1	0 4 0 4	0 4 3 4	0 3 6 1	0 3 2 3	0 3 8 4	0 3 2 4	0 3 6 2	0 4 5 1	0 3 3 3	0 3 4 1	0 3 4 2	0 3 4 3	0 3 5 3	0 3 7 4	0 3 8 3	0 3 9 1	0 3 9 3	0 4 0 3	0 4 1 4	0 4 2 2	0 4 2 3	0 4 4 3	0 4 4 4	0 4 5 2	Total Tissues/ Tumors
Special Senses System																										
Eye				+																						2
Harderian gland																										1
Duct, carcinoma																										1
Zymbal's gland																										2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+												+	+	+			37
Nephroblastoma																					X					1
Urinary bladder	+	+	+	+	+	+	+	+	+																	34
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X	X	X	X	X			X	X			X			X		X	X			X	X	33
Mesothelioma malignant			X						X														X			5

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

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

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

Number of Days on Study	7 1 2	7 2 3	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 0 4	0 6 1 3	0 6 5 3	0 6 2 1	0 6 2 2	0 6 2 4	0 6 3 1	0 6 4 3	0 6 5 1	0 6 7 3	0 6 7 4	0 6 8 1	0 6 8 4	0 6 9 2	0 7 0 2	0 7 1 1	0 7 1 3	0 7 1 1	0 7 2 2	0 7 2 4	0 7 3 2	0 7 3 4	0 7 4 1	0 7 5 1	0 7 5 2	0 7 5 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+																							28
Intestine large, colon	+	+	+																							25
Intestine large, rectum	+	+	+																							24
Intestine large, cecum	+	+	+																							23
Intestine small, duodenum	+	+	+																							26
Intestine small, jejunum	+	+	+																							23
Intestine small, ileum	+	+	+																							24
Liver	+	+	+		+	+			+	+	+	+	+						+						+	36
Hepatocellular adenoma			X																							1
Mesentery			+			+	+						+													8
Pancreas	+	+	+		+			+																+		30
Pharynx						+																				3
Papilloma																										1
Squamous cell carcinoma																										1
Salivary glands	+	+	+																							27
Stomach, forestomach	+	+	+	+								+													+	30
Stomach, glandular	+	+	+	+								+													+	30
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+																							27
Endocrine System																										
Adrenal cortex	+	+	+																							27
Carcinoma																										1
Adrenal medulla	+	+	+	+																						28
Pheochromocytoma malignant																										1
Pheochromocytoma benign	X																									6
Bilateral, pheochromocytoma benign		X		X																						5
Islets, pancreatic	+	+	+		+				+																	29
Adenoma	X								X																	5
Carcinoma																										1
Parathyroid gland	+	+	+																							25
Pituitary gland	+	+	+	+	+			+	+	+		+				+	+	+	+				+	+		38
Pars distalis, adenoma	X	X	X	X	X				X	X						X	X		X				X	X		23
Thyroid gland	+	+	+		+												+	+		+						32
C-cell, adenoma					X												X	X								5
C-cell, carcinoma																				X						2
General Body System																										
None																										

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

Number of Days on Study	2 3 4 4 5 5 5 5 5 5 5 6 6 6 6 6 7 7 7 7 7 7 7 3 6 0 7 0 0 1 3 4 4 6 9 1 3 4 6 6 8 0 0 0 0 0 1 1 3 5 2 1 6 6 6 5 1 7 5 7 1 5 9 4 6 0 1 4 5 5 9 0 2
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 6 6 7 7 6 6 6 7 7 6 6 6 7 7 7 6 6 7 6 7 7 7 6 6 6 5 9 3 3 3 4 6 4 0 8 9 4 2 4 5 1 4 0 7 1 1 4 1 2 8 2 3 3 1 2 4 1 2 3 3 4 2 1 4 3 2 1 1 2 2 4 3 4 3 2
Genital System	
Epididymis	+ A +
Preputial gland	+ +
Carcinoma	
Prostate	+ A +
Seminal vesicle	+ A +
Testes	+ A +
Bilateral, interstitial cell, adenoma	X X X X X
Interstitial cell, adenoma	X X X X X X X
Interstitial cell, adenoma, multiple	X
Hematopoietic System	
Bone marrow	+ A +
Lymph node	+ + + + + + +
Lymph node, bronchial	+ A M +
Lymph node, mandibular	+ A +
Lymph node, mesenteric	+ A +
Lymph node, mediastinal	+ A +
Carcinoma, metastatic, thyroid gland	X
Spleen	+ A +
Thymus	+ A +
Integumentary System	
Mammary gland	+ A +
Skin	+ +
Fibroma	
Neurofibrosarcoma	
Sarcoma	X
Musculoskeletal System	
Bone	+ A +
Skeletal muscle	
Nervous System	
Brain	+ A +
Granular cell tumor malignant	X
Respiratory System	
Larynx	+ A + + + + + + + + + + + + + + A + + + + + + + +
Lung	+ +
Alveolar/bronchiolar adenoma	
Carcinoma, metastatic, thyroid gland	
Hemangiosarcoma, metastatic, uncertain primary site	
Nose	+ A +
Trachea	+ A + + + + + + + + + + + + + + A + + + + + + + +

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

Number of Days on Study	7 1 2	7 2 3	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 0 4	0 6 1 3	0 6 5 3	0 6 2 1	0 6 2 2	0 6 2 4	0 6 3 1	0 6 4 3	0 6 5 1	0 6 7 3	0 6 7 4	0 6 8 1	0 6 8 4	0 6 9 2	0 7 0 2	0 7 1 1	0 7 1 3	0 7 2 2	0 7 2 4	0 7 3 2	0 7 3 4	0 7 4 1	0 7 5 1	0 7 5 2	0 7 5 4	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+																							27
Preputial gland	+	+	+			+									+											30
Carcinoma															X											1
Prostate	+	+	+													+	+			+						30
Seminal vesicle	+	+	+														+			+						29
Testes	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, interstitial cell, adenoma					X	X	X	X		X	X		X		X	X	X	X	X		X		X			19
Interstitial cell, adenoma			X						X			X		X						X		X		X	X	13
Interstitial cell, adenoma, multiple																										1
Hematopoietic System																										
Bone marrow	+	+	+																							27
Lymph node	+		+	+		+													+							11
Lymph node, bronchial	+	+	+								+							+								28
Lymph node, mandibular	+	+	+								+			+											+	30
Lymph node, mesenteric	+	+	+					+			+				+										+	31
Lymph node, mediastinal	+	+	+								+															28
Carcinoma, metastatic, thyroid gland																										1
Spleen	+	+	+		+	+		+	+		+	+	+					+		+					+	37
Thymus	+	+	+															+								28
Integumentary System																										
Mammary gland	+	+	+																							27
Skin	+	+	+						+	+	+				+			+						+		34
Fibroma		X																						X		2
Neurofibrosarcoma										X																1
Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+																							27
Skeletal muscle			+																							1
Nervous System																										
Brain	+	+	+	+													+									29
Granular cell tumor malignant																										1
Respiratory System																										
Larynx	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X								X													2
Carcinoma, metastatic, thyroid gland																				X						1
Hemangiosarcoma, metastatic, uncertain primary site				X																						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

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

Number of Days on Study	2	3	4	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7
	3	6	0	7	0	0	1	3	4	4	6	9	1	3	4	6	6	8	0	0	0	0	0	1	1
	3	5	2	1	6	6	6	5	1	7	5	7	1	5	9	4	6	0	1	4	5	5	9	0	2
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
	6	6	7	7	6	6	6	7	7	6	6	6	7	7	7	6	6	7	6	7	7	7	6	6	6
	5	9	3	3	3	4	6	4	0	8	9	4	2	4	5	1	4	0	7	1	1	4	1	2	8
	2	3	3	1	2	4	1	2	3	3	4	2	1	4	3	2	1	1	2	2	4	3	4	3	2
Special Senses System																									
Ear						+																			
Eye									+	+				+											
Harderian gland										+				+											
Zymbal's gland						+																			
Carcinoma						X																			
Urinary System																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra															+										
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X	X	X		X			X		X	X	X	X	X	X	X	X	X	

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

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

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

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

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 8 3	6 9 5	7 0 4	7 0 4	7 0 9	7 1 2	7 1 9	7 2 3	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 9 9 2	0 9 1 4	0 9 8 4	1 0 1 4	0 9 6 2	1 0 5 1	1 0 5 3	0 9 9 4	1 0 3 1	0 9 1 1	0 9 2 1	0 9 2 4	0 9 4 2	0 9 5 2	0 9 6 4	0 9 8 2	1 0 1 2	1 0 1 3	1 0 2 1	1 0 2 4	1 0 3 3	1 0 4 1	1 0 4 4	1 0 5 2	1 0 5 4	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																									1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X				X																		3
Mesentery											+		+			+		+			+	+			14
Oral mucosa																									1
Squamous cell carcinoma																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																		+							1
Cardiovascular System																									
Blood vessel																									2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																									1
Pheochromocytoma benign		X	X			X	X	X						X					X			X		X	13
Bilateral, pheochromocytoma benign				X							X				X										4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X		X									X			X		X					X		X	10
Carcinoma								X	X																2
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	33
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X							X			3
C-cell, carcinoma					X				X	X															3
Follicular cell, adenoma																X						X			3
General Body System																									
None																									

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

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 8 3	6 9 5	7 0 4	7 0 4	7 0 9	7 1 2	7 1 9	7 2 3	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 9 9 2	0 9 1 4	0 9 8 4	1 0 1 4	0 9 6 2	1 0 5 1	1 0 5 3	0 9 9 4	1 0 3 1	0 9 1 1	0 9 2 1	0 9 2 4	0 9 4 2	0 9 5 2	0 9 6 4	0 9 8 2	1 0 1 2	1 0 2 3	1 0 3 1	1 0 4 4	1 0 4 3	1 0 3 1	1 0 4 4	1 0 5 2	1 0 5 4	Total Tissues/ Tumors
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma													X							X					2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X		X						X	X	X	X					X		X	X	X	X	X	19
Interstitial cell, adenoma						X		X		X							X	X		X						15
Hematopoietic System																									
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
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																					X				1
Fibroma					X												X	X							3
Neurofibroma																			X						1
Neurofibrosarcoma																									1
Squamous cell carcinoma																									1
Squamous cell papilloma													X												1
Sebaceous gland, carcinoma												X													1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									2
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																									1
Spinal cord																									1

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	1 8 0	2 2 0	4 6 0	4 7 4	4 8 5	5 0 0	5 3 4	5 4 1	5 4 2	5 8 2	5 8 5	5 8 9	6 0 0	6 0 0	6 1 2	6 1 7	6 2 0	6 2 1	6 2 8	6 2 8	6 3 9	6 3 9	6 5 3	6 6 8	6 8 1
Carcass ID Number	0 9 4 3	0 9 8 1	1 0 4 2	0 9 4 4	0 9 2 2	0 9 1 2	0 9 4 1	1 0 3 2	0 9 3 4	0 9 3 3	0 9 3 3	0 9 2 3	0 9 5 3	0 9 1 3	1 0 0 3	0 0 6 3	0 9 9 1	0 9 2 3	1 0 1 2	1 0 3 2	0 9 7 2	0 9 9 2	0 9 5 4	1 0 0 4	1 0 4 3	0 9 7 1	0 9 9 3
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X					
Alveolar/bronchiolar carcinoma																										
Squamous cell carcinoma, metastatic, skin							X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, papillary																										
Squamous cell carcinoma, metastatic, oral mucosa																										X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear										+																
Eye				+				+	+				+													+
Harderian gland																										+
Adenoma																										
Zymbal's gland							+																			
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X		X	X	X	X			X		X	X	X		X		X				X		
Mesothelioma malignant									X														X			

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 8 3	6 9 5	7 0 4	7 0 4	7 0 9	7 1 2	7 1 9	7 2 3	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 9 9 2	0 9 1 4	0 9 8 4	1 0 1 4	0 9 6 2	1 0 5 1	1 0 5 3	0 9 9 4	1 0 3 1	0 9 1 1	0 9 2 1	0 9 2 4	0 9 4 2	0 9 5 2	0 9 6 4	0 9 8 2	1 0 1 2	1 0 1 3	1 0 2 1	1 0 2 4	1 0 3 3	1 0 4 1	1 0 4 4	1 0 5 2	1 0 5 4	Total Tissues/ Tumors
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X						X								3
Alveolar/bronchiolar carcinoma									X			X													2
Squamous cell carcinoma, metastatic, skin																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, papillary																					X				1
Squamous cell carcinoma, metastatic, oral mucosa																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Ear																									1
Eye				+								+													7
Harderian gland																					+				2
Adenoma																					X				1
Zymbal's gland																									1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X	X	X		X	X	X	X	X	X	X	X						X	X				29
Mesothelioma malignant																									2

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
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	15/50 (30%)	10/50 (20%)	11/50 (22%)	17/50 (34%)
Adjusted rate[b]	58.2%	31.8%	31.4%	60.7%
Terminal rate[c]	8/18 (44%)	1/16 (6%)	1/22 (5%)	6/16 (38%)
First incidence (days)	628	565	471	617
Life table test[d]	P=0.109	P=0.247N	P=0.148N	P=0.314
Logistic regression test[d]	P=0.108	P=0.203N	P=0.225N	P=0.311
Cochran-Armitage test[d]	P=0.145			
Fisher exact test[d]		P=0.178N	P=0.247N	P=0.415
Liver: Hepatocellular Adenoma				
Overall rate	1/50 (2%)	1/39 (3%)[e]	1/36 (3%)[e]	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
Lung: Alveolar/bronchiolar Adenoma				
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
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
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
Pancreatic Islets: Adenoma				
Overall rate	7/50 (14%)	5/34 (15%)[e]	5/29 (17%)[e]	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
Pancreatic Islets: Carcinoma				
Overall rate	4/50 (8%)	2/34 (6%)[e]	1/29 (3%)[e]	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
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	11/50 (22%)	7/34 (21%)[e]	6/29 (21%)[e]	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
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	23/50 (46%)	23/39 (59%)[e]	23/38 (61%)[e]	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
Preputial Gland: Carcinoma				
Overall rate	6/50 (12%)	2/38 (5%)[e]	1/30 (3%)[e]	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
Skin: Fibroma				
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
Skin: Squamous Cell Papilloma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
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	–[f]	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
Testes: Adenoma				
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
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/49 (10%)	3/35 (9%)[e]	5/32 (16%)[e]	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
Thyroid Gland (C-cell): Carcinoma				
Overall rate	0/49 (0%)	1/35 (3%)[e]	2/32 (6%)[e]	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
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/49 (10%)	3/35 (9%)[e]	7/32 (22%)[e]	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
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/49 (0%)	1/35 (3%)[e]	0/32 (0%)[e]	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
All Organs: Mononuclear Cell Leukemia				
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
All Organs: Malignant Mesothelioma				
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
All Organs: Benign Neoplasms				
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
All Organs: Malignant Neoplasms				
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
All Organs: Benign or Malignant Neoplasms				
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	-[g]	-
Cochran-Armitage test	P=0.471			
Fisher exact test		P=0.500N	P=0.247N	P=1.000N

(T)Terminal sacrifice
[a] 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.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] 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.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not appropriate.
[f] Not applicable; no neoplasms in animal group
[g] Value of statistic cannot be computed.

TABLE A4
Historical Incidence of Pituitary Gland Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-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
Overall Historical Incidence			
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%

[a] 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[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	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
15-Month Interim Evaluation				
Alimentary System				
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%)			
Cardiovascular System				
Heart	(10)			(10)
Cardiomyopathy	4 (40%)			3 (30%)
Endocrine System				
Thyroid gland	(10)		(1)	(10)
Ultimobranchial cyst	1 (10%)			1 (10%)
C-cell, hyperplasia	1 (10%)			
Follicular cell, cyst	1 (10%)			
General Body System				
None				
Genital System				
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
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node	(1)			
Renal, hemorrhage	1 (100%)			
Lymph node, mediastinal	(10)			(10)
Hemorrhage	1 (10%)			
Spleen	(10)			(10)
Ectopic tissue				1 (10%)
Integumentary System				
Skin	(10)			(10)
Cyst epithelial inclusion	1 (10%)			
Ulcer	1 (10%)			
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
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%)	
Special Senses System				
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
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(1)		(10)
Nephropathy, chronic	9 (90%)	1 (100%)		10 (100%)
2-Year Study				
Alimentary System				
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
2-Year Study (continued)				
Alimentary System (continued)				
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%)
Cardiovascular System				
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%)		
Endocrine System				
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
2-Year Study (continued)				
Endocrine System (continued)				
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%)
General Body System				
None				
Genital System				
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%)
Hematopoietic System				
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
2-Year Study (continued)				
Hematopoietic System (continued)				
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%)		
Integumentary System				
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%)		
Musculoskeletal System				
Bone	(50)	(34)	(27)	(50)
Fibrous osteodystrophy	1 (2%)			
Inflammation, suppurative			1 (4%)	
Skeletal muscle	(1)		(1)	(2)
Mineralization				1 (50%)
Nervous System				
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%)	
Respiratory System				
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
2-Year Study (continued)				
Respiratory System (continued)				
Lung	(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%)
Nose	(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%)
Trachea	(48)	(50)	(48)	(50)
Inflammation, suppurative		1 (2%)		
Pigmentation				5 (10%)
Special Senses System				
Eye	(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%)
Urinary System				
Kidney	(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
2-Year Study (continued)				
Urinary System (continued)				
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%)

[a] 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

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	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
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(3)		(10)
Hepatocellular adenoma		1 (33%)		
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)		(5)	(10)
Pars distalis, adenoma	1 (10%)		2 (40%)	2 (20%)
General Body System				
None				
Genital System				
Uterus	(10)		(10)	(10)
Polyp stromal			1 (10%)	
Hematopoietic System				
None				
Integumentary System				
Mammary gland	(10)	(1)	(1)	(10)
Fibroadenoma	1 (10%)	1 (100%)	1 (100%)	
Musculoskeletal System				
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
15-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
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%)	
Cardiovascular System				
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
2-Year Study (continued)				
Endocrine System				
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%)		
General Body System				
None				
Genital System				
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%)			
Hematopoietic System				
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
2-Year Study (continued)				
Integumentary System				
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%)
Musculoskeletal System				
Bone	(50)	(17)	(19)	(50)
Mandible, squamous cell carcinoma, metastatic, pharynx			1 (5%)	
Nervous System				
None				
Respiratory System				
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%)
Special Senses System				
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
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Carcinoma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	16 (32%)	14 (28%)	18 (36%)	21 (42%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
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

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Number of animals with any tissue examined microscopically
[c] 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

Number of Days on Study	3 7 6	3 7 6	4 8 8	5 0 2	6 2 5	6 3 9	6 3 9	6 4 0	6 5 3	6 6 0	6 6 3	6 7 7	6 8 0	6 8 1	6 8 1	6 8 3	6 8 6	7 0 3	7 0 5	7 0 9	7 1 9	7 2 6	7 3 3	7 3 3	7 3
Carcass ID Number	0 2 5 2	0 3 0 2	0 2 2 1	0 2 1 1	0 2 1 4	0 2 3 4	0 2 5 1	0 2 9 3	0 1 7 3	0 2 0 3	0 3 0 4	0 3 1 3	0 2 7 2	0 1 6 2	0 1 5 4	0 2 6 1	0 2 4 2	0 1 8 4	0 2 4 1	0 2 7 1	0 2 9 4	0 1 9 3	0 1 6 1	0 1 6 3	0 1 6 4
Alimentary System																									
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																				
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
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		
Pars intermedia, adenoma														X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma					X																		X		
Follicular cell, adenoma																									
General Body System																									
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)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 1 7 1	0 1 7 4	0 1 8 3	0 1 9 1	0 1 9 2	0 2 0 1	0 2 2 3	0 2 2 4	0 2 3 1	0 2 3 2	0 2 3 3	0 2 4 3	0 2 4 4	0 2 5 3	0 2 6 2	0 2 6 3	0 2 6 6	0 2 7 3	0 2 7 7	0 2 8 1	0 2 8 2	0 2 8 4	0 2 9 1	0 2 9 2	0 3 0 1	0 3 0 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery					+					+														+	+	9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Pharynx								+									+									3
Squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Carcinoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma benign				X																		X			X	5
Bilateral, pheochromocytoma benign	X																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																X			2
Parathyroid gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X			X			X		X	X	X	X			X	X			X	X	X		31
Pars intermedia, adenoma																				X						2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X					X				X									X	6
Follicular cell, adenoma																X										1
General Body System																										
None																										

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

Number of Days on Study	3 7 6	3 7 6	4 8 8	5 0 2	6 2 5	6 3 9	6 3 9	6 4 0	6 5 3	6 6 0	6 6 3	6 7 7	6 8 0	6 8 1	6 8 1	6 8 3	6 8 6	7 0 3	7 0 5	7 0 9	7 1 9	7 2 6	7 3 3	7 3 3	7 3 3
Carcass ID Number	0 2 5 2	0 3 0 2	0 2 2 2	0 2 1 1	0 2 1 4	0 2 3 4	0 2 5 1	0 2 9 3	0 1 7 3	0 2 0 3	0 3 0 4	0 2 1 3	0 1 7 2	0 1 6 2	0 2 5 4	0 2 6 1	0 2 4 2	0 1 8 4	0 2 4 1	0 2 7 1	0 2 9 4	0 1 9 3	0 1 6 1	0 1 6 3	0 1 6 4
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																				X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																	X								
Sarcoma stromal																									
Bilateral, polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma													X												
Adenocarcinoma, multiple																									
Fibroadenoma			X										X							X			X	X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland																									
Alveolar/bronchiolar adenoma																						X			
Carcinoma, metastatic, Zymbal's gland																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 1 7 1	0 1 7 4	0 1 8 3	0 1 9 1	0 1 9 2	0 2 0 1	0 2 2 3	0 2 2 4	0 2 3 1	0 2 3 2	0 2 3 3	0 2 4 3	0 2 4 4	0 2 5 3	0 2 6 2	0 2 6 3	0 2 7 3	0 2 7 4	0 2 8 1	0 2 8 2	0 2 8 4	0 2 9 1	0 2 9 2	0 3 0 1	0 3 0 3	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma				X						X							X					X				5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign								X																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X					X																				3
Sarcoma stromal			X																							1
Bilateral, polyp stromal														X												1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	M	+	M	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	42
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma			X																							2
Adenocarcinoma, multiple															X											1
Fibroadenoma				X	X		X										X					X	X	X		12
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland			X																							1
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, Zymbal's gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	3	3	4	5	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	7	7	8	0	2	3	3	4	5	6	6	7	8	8	8	8	8	0	0	0	1	2	3	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	2	1	2	3	2	1	1	2	2	2	1	2	2	2	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
Special Senses System																									
Eye														+										+	
Harderian gland														+											
Adenoma														X											
Zymbal's gland																									+
Carcinoma																									X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						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 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	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	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	Total
	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	Tissues/
	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	Tumors
Special Senses System																										
Eye			+																				+			4
Harderian gland																										1
Adenoma																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
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

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

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 5 0 2	0 5 0 3	0 5 0 4	0 5 1 1	0 5 1 1	0 5 2 2	0 5 3 3	0 5 3 1	0 5 4 2	0 5 4 3	0 5 4 4	0 5 5 1	0 5 5 4	0 5 6 2	0 5 6 3	0 5 6 4	0 5 7 2	0 5 7 3	0 5 8 1	0 5 8 2	0 5 8 3	0 5 8 4	0 5 9 2	0 6 0 2	0 6 0 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus									+																	18
Intestine large, colon																										17
Intestine large, rectum																										17
Intestine large, cecum																										17
Intestine small, duodenum																										17
Intestine small, jejunum																										17
Intestine small, ileum																										17
Liver			+	+		+		+	+				+				+	+	+		+			+		31
Hepatocellular adenoma			X																							1
Mesentery																		+						+	+	6
Pancreas																										17
Salivary glands																										17
Stomach, forestomach																		+	+							18
Stomach, glandular																		+								17
Tongue																										1
Carcinoma																										1
Cardiovascular System																										
Heart																										17
Endocrine System																										
Adrenal cortex												+							+		+					21
Carcinoma												X														1
Adrenal medulla												M							+		+					19
Pheochromocytoma malignant																			X							1
Pheochromocytoma benign																										2
Islets, pancreatic							+																			18
Adenoma							X																			1
Parathyroid gland																										17
Pituitary gland	+	+	+	+			+	+	+	+	+			+	+		+	+				+		+	+	39
Pars distalis, adenoma	X	X	X				X	X			X			X	X		X	X				X		X	X	30
Pars intermedia, adenoma																										1
Pars nervosa, hamartoma																										1
Thyroid gland		+															+									19
C-cell, adenoma																										3
C-cell, carcinoma																	X									1
Follicular cell, carcinoma		X																								1
General Body System																										
None																										
Genital System																										
Clitoral gland			+	+			+										+	+								22
Carcinoma							X											X								5
Ovary																										18
Uterus									+			+							+							22
Polyp stromal												X							X							5

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

Number of Days on Study	5 2 1	5 6 5	6 2 1	6 2 5	6 3 8	6 5 4	6 5 4	6 5 9	6 6 8	6 8 1	6 8 3	6 9 1	6 9 4	7 0 5	7 0 9	7 2 4	7 2 4	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 4 8 1	0 5 6 1	0 5 7 4	0 5 9 4	0 5 3 4	0 5 1 4	0 5 2 3	0 5 1 3	0 5 2 2	0 5 1 2	0 4 8 3	0 5 9 1	0 4 6 3	0 5 2 4	0 5 5 3	0 5 9 3	0 6 0 1	0 4 6 2	0 4 7 1	0 4 7 2	0 4 7 3	0 4 7 4	0 4 8 2	0 4 9 1	0 4 9 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Lymph node																+									
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+		+	+
Adenoacanthoma															X										
Adenocarcinoma																						X			
Fibroadenoma							X			X														X	X
Fibroadenoma, multiple								X												X	X	X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Carcinoma, metastatic, adrenal cortex																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									+
Harderian gland											+														
Duct, carcinoma											X														
Zymbal's gland			+																						
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	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: 0.01 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 5 0 2	0 5 0 3	0 5 0 4	0 5 1 1	0 5 2 1	0 5 3 2	0 5 3 3	0 5 4 1	0 5 4 2	0 5 4 3	0 5 4 4	0 5 5 1	0 5 5 4	0 5 6 2	0 5 6 3	0 5 6 4	0 5 7 2	0 5 7 3	0 5 8 1	0 5 8 2	0 5 8 3	0 5 8 4	0 5 9 2	0 6 0 2	0 6 0 4	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow																										17
Lymph node										+																2
Lymph node, bronchial																										17
Lymph node, mandibular																										17
Lymph node, mesenteric																										17
Lymph node, mediastinal																										17
Spleen								+	+						+				+							21
Thymus																										17
Integumentary System																										
Mammary gland		+		+	+					+					+			+	+	+	+	+	+		33
Adenoacanthoma																										1
Adenocarcinoma																										1
Fibroadenoma		X		X						X					X			X	X	X		X	X		13
Fibroadenoma, multiple					X																X					6
Skin																										17
Musculoskeletal System																										
Bone																										17
Nervous System																										
Brain								+																		18
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																	X									1
Carcinoma, metastatic, adrenal cortex												X														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																										1
Duct, carcinoma																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder																										17
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X	X														X			14

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

Number of Days on Study	3 6 6	3 6 7	4 0 2	5 4 9	5 5 0	5 6 1	5 6 2	5 6 9	5 8 5	5 9 0	5 9 7	6 1 1	6 1 8	6 4 2	6 5 2	6 9 5	7 0 5	7 1 9	7 3 8	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 9 0 1	0 7 6 3	0 8 4 4	0 8 8 3	0 7 8 1	0 9 0 3	0 8 6 3	0 7 8 3	0 8 3 2	0 8 1 2	0 8 5 3	0 7 7 4	0 9 0 2	0 7 9 4	0 7 6 2	0 8 2 2	0 8 4 2	0 7 9 2	0 8 1 3	0 7 7 1	0 7 7 3	0 7 8 2	0 7 8 4	0 7 9 2
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine large, cecum	+	+	+	+	+	A	+	+	+	A	+	+	A	+	A	+	+	+						
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	A	+	A	+	+	+						
Intestine small, ileum	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	
Hepatocellular carcinoma																						X		
Mesentery								+	+		+			+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Pharynx								+																
Squamous cell carcinoma								X																
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+						
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Tongue								+																
Squamous cell carcinoma, metastatic, pharynx								X																
Tooth											+													
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Alveolar/bronchiolar carcinoma, metastatic, lung											X													
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Pheochromocytoma malignant																								
Pheochromocytoma benign							X				X							X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		
Pars distalis, adenoma	X								X	X		X	X	X	X	X		X		X	X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
C-cell, adenoma							X																	
C-cell, carcinoma				X						X						X								
General Body System																								
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	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 9 3	0 8 0 1	0 8 0 2	0 8 0 3	0 8 0 4	0 8 2 1	0 8 2 3	0 8 2 4	0 8 3 1	0 8 3 3	0 8 4 1	0 8 4 3	0 8 5 1	0 8 5 2	0 8 6 1	0 8 6 2	0 8 7 1	0 8 7 2	0 8 7 4	0 8 8 2	0 8 8 4	0 8 9 1	0 8 9 2	0 8 9 3	0 9 0 4	Total Tissues/ Tumors
Alimentary System																										
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
Cardiovascular System																										
Heart																										19
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal cortex																										19
Adrenal medulla																							+			20
Pheochromocytoma malignant																							X			1
Pheochromocytoma benign																										3
Islets, pancreatic																										19
Parathyroid gland																										19
Pituitary gland					+	+			+		+	+	+	+		+	+		+	+				+		33
Pars distalis, adenoma					X	X			X		X	X	X	X		X	X		X	X				X		23
Thyroid gland																										19
C-cell, adenoma																										1
C-cell, carcinoma																										3
General Body System																										
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 6 6	3 6 7	4 0 2	5 4 9	5 5 0	5 6 1	5 6 2	5 6 9	5 8 5	5 9 0	5 9 7	6 1 1	6 1 8	6 4 2	6 5 2	6 9 5	6 9 9	7 0 9	7 1 8	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 9 0 1	0 7 6 3	0 8 4 4	0 8 8 3	0 7 8 1	0 9 0 3	0 8 6 3	0 7 8 3	0 8 3 2	0 8 1 2	0 8 5 3	0 7 7 4	0 9 0 2	0 7 9 4	0 7 6 2	0 8 2 2	0 8 4 2	0 7 9 1	0 8 1 3	0 7 7 1	0 7 7 3	0 7 8 2	0 7 8 4	0 7 9 2
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+		+	+		
Carcinoma																						X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal															X		X							
Vagina															+									
Hematopoietic System																								
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											X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	+
Thymus	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+					
Alveolar/bronchiolar carcinoma, metastatic, lung											X													
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+			+	+
Adenocarcinoma																		X					X	
Fibroadenoma				X		X						X			X				X					X
Fibroadenoma, multiple																		X						
Skin	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+					
Neurofibrosarcoma					X																			
Squamous cell papilloma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Mandible, squamous cell carcinoma, metastatic, pharynx								X																
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma											X													
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)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 9 3	0 8 0 1	0 8 0 2	0 8 0 3	0 8 0 4	0 8 2 1	0 8 2 3	0 8 2 4	0 8 3 1	0 8 3 3	0 8 4 1	0 8 4 3	0 8 5 1	0 8 5 2	0 8 6 1	0 8 6 2	0 8 7 1	0 8 7 2	0 8 7 4	0 8 8 2	0 8 8 4	0 8 9 1	0 8 9 2	0 8 9 3	0 9 0 4	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+			+	+					+			+					+				+				27
Carcinoma										X			X													3
Ovary				+				+				+									+					24
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal											X				X											4
Vagina																										1
Hematopoietic System																										
Bone marrow																										19
Lymph node																										1
Lymph node, bronchial																										16
Lymph node, mandibular																										18
Lymph node, mesenteric																										18
Lymph node, mediastinal																										17
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Spleen			+	+	+								+		+											26
Thymus																										16
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	+								+								+	+			+			+	+	28
Adenocarcinoma																					X			X		4
Fibroadenoma	X								X								X	X			X				X	12
Fibroadenoma, multiple																										1
Skin							+																			19
Neurofibrosarcoma																										1
Squamous cell papilloma							X																			1
Musculoskeletal System																										
Bone																										19
Mandible, squamous cell carcinoma, metastatic, pharynx																										1
Nervous System																										
Brain																										19
Respiratory System																										
Larynx	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma																										1
Pheochromocytoma malignant, metastatic																							X			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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	
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	
	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	
Special Senses System																									
Eye								+				+					+		+						
Lids, fibroma																	X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear	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)

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

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

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	5 2 8	5 4 1	5 6 9	5 8 8	5 9 7	6 1 7	6 2 5	6 2 6	6 2 8	6 3 5	6 5 8	6 6 7	6 6 7	6 6 8	6 9 6	7 1 0	7 1 0	7 2 4	7 2 6	7 2 6	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 1 7 4	1 1 6 1	1 1 2 4	1 1 9 4	1 2 0 3	1 1 2 1	1 0 8 4	1 1 3 2	1 1 9 2	1 1 1 2	1 1 5 3	1 1 4 4	1 1 7 2	1 0 9 4	1 1 4 2	1 1 0 3	1 1 4 4	1 1 1 1	1 1 1 4	1 1 7 1	1 0 6 1	0 0 6 2	0 0 6 3	0 0 6 4	0 0 7 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+							+		+							
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Carcinoma, metastatic, thyroid gland																				X					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																				X					
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma								X																	
Fibroadenoma	X		X							X	X												X	X	
Fibroadenoma, multiple									X																
Sarcoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue, sarcoma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																				X					
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																				X					
Special Senses System																									
Eye							+	+																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			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: 0.2 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 0 7 2	1 0 7 3	1 0 7 4	1 0 8 1	1 0 8 2	1 0 8 3	1 0 9 1	1 0 9 2	1 0 9 3	1 1 0 1	1 1 2 2	1 1 3 1	1 1 3 3	1 1 5 1	1 1 5 2	1 1 6 3	1 1 6 4	1 1 7 3	1 1 8 1	1 1 8 2	1 1 8 4	1 1 9 1	1 1 9 3	1 2 0 1	1 2 0 2	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, thyroid gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, thyroid gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+		44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Fibroadenoma					X																		X			8
Fibroadenoma, multiple								X			X			X							X					5
Sarcoma											X															1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma			X																							1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Special Senses System																										
Eye																			+		+					4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X			X	X			X	X	X			X		X		X	X	X	X				21

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
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	6/50 (12%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate[b]	19.2%	5.1%	7.9%	5.5%
Terminal rate[c]	4/28 (14%)	0/33 (0%)	0/30 (0%)	1/30 (3%)
First incidence (days)	681	681	562	617
Life table test[d]	P=0.247N	P=0.099N	P=0.250N	P=0.124N
Logistic regression test[d]	P=0.237N	P=0.115N	P=0.256N	P=0.128N
Cochran-Armitage test[d]	P=0.237N			
Fisher exact test[d]		P=0.134N	P=0.243N	P=0.134N
Clitoral Gland: Carcinoma				
Overall rate	5/49 (10%)	5/22 (23%)[e]	3/27 (11%)[e]	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
Mammary Gland: Fibroadenoma				
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
Mammary Gland: Carcinoma				
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
Mammary Gland: Fibroadenoma or Carcinoma				
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
Pancreatic Islets: Adenoma				
Overall rate	2/50 (4%)	1/18 (6%)[e]	0/19 (0%)[e]	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
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	31/50 (62%)	30/39 (77%)[e]	23/33 (70%)[e]	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
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/50 (12%)	3/19 (16%)[e]	1/19 (5%)[e]	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
Thyroid Gland (C-cell): Carcinoma				
Overall rate	0/50 (0%)	1/19 (5%)[e]	3/19 (16%)[e]	4/50 (8%)
Adjusted rate	0.0%			12.8%
Terminal rate	0/28 (0%)			3/30 (10%)
First incidence (days)	-[f]			726
Life table test				P=0.074
Logistic regression test				P=0.072
Cochran-Armitage test				
Fisher exact test				P=0.059
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	6/50 (12%)	4/19 (21%)[e]	4/19 (21%)[e]	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
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/19 (5%)[e]	0/19 (0%)[e]	0/50 (0%)
Adjusted rate	3.6%			0.0%
Terminal rate	1/28 (4%)			0/30 (0%)
First incidence (days)	730 (T)			–
Life table test				P=0.486N
Logistic regression test				P=0.486N
Cochran-Armitage test				
Fisher exact test				P=0.500N
Uterus: Stromal Polyp				
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
Uterus: Stromal Polyp or Stromal Sarcoma				
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
All Organs: Mononuclear Cell Leukemia				
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
All Organs: Benign Neoplasms				
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
All Organs: Malignant Neoplasms				
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
All Organs: Benign or Malignant Neoplasms				
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

[a] 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.

[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] 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.

[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not appropriate.

[f] 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[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	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
15-Month Interim Evaluation				
Alimentary System				
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%)	
Cardiovascular System				
Heart	(10)			(10)
Thrombosis	1 (10%)			
Endocrine System				
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%)
General Body System				
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
15-Month Interim Evaluation (continued)				
Genital System				
Ovary	(10)			(10)
Cyst				1 (10%)
Uterus	(10)		(10)	(10)
Dilatation			2 (20%)	
Endometrium, hyperplasia				1 (10%)
Hematopoietic System				
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%)
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
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
15-Month Interim Evaluation (continued)				
Respiratory System (continued)				
Trachea	(10)	(10)	(10)	(10)
Inflammation, chronic		1 (10%)	1 (10%)	
Special Senses System				
Eye	(1)		(1)	
Cataract	1 (100%)			
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	1 (10%)	1 (10%)	2 (20%)	
Nephropathy, chronic	10 (100%)	10 (100%)	10 (100%)	10 (100%)
2-Year Study				
Alimentary System				
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
2-Year Study (continued)				
Alimentary System (continued)				
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%)
Cardiovascular System				
Heart	(50)	(17)	(19)	(50)
Cardiomyopathy	4 (8%)		1 (5%)	4 (8%)
Thrombosis	1 (2%)		1 (5%)	
Endocrine System				
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%)
General Body System				
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
2-Year Study (continued)				
Genital System				
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%)
Hematopoietic System				
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%)		
Integumentary System				
Mammary gland	(50)	(33)	(28)	(50)
Inflammation, suppurative				1 (2%)
Skin	(50)	(17)	(19)	(50)
Abscess				1 (2%)
Ulcer		1 (6%)		1 (2%)
Musculoskeletal System				
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
2-Year Study (continued)				
Nervous System				
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%)	
Respiratory System				
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%)
Special Senses System				
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
2-Year Study (continued)				
Urinary System				
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%)

[a] 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

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	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
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma	2 (20%)			
Hepatocellular adenoma	3 (30%)	2 (20%)	2 (20%)	1 (10%)
Cardiovascular System				
None				
Endocrine System				
Islets, pancreatic	(10)			(10)
Adenoma	1 (10%)			
General Body System				
None				
Genital System				
None				
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
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
15-Month Interim Evaluation (continued)				
Respiratory System				
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%)
Special Senses System				
None				
Urinary System				
Urinary bladder	(10)		(1)	(10)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Lymphoma malignant histiocytic			1 (10%)	
2-Year Study				
Alimentary System				
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)
Cardiovascular System				
Heart	(50)	(17)	(8)	(50)
Endocrine System				
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
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(49)	(16)	(8)	(49)
Carcinoma	1 (2%)			
Thyroid gland	(48)	(19)	(12)	(50)
Follicular cell, adenoma	1 (2%)		3 (25%)	2 (4%)
General Body System				
None				
Genital System				
Epididymis	(50)	(17)	(8)	(50)
Fibrosarcoma			1 (13%)	
Testes	(50)	(18)	(9)	(50)
Interstitial cell, adenoma		1 (6%)	1 (11%)	1 (2%)
Hematopoietic System				
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)
Integumentary System				
Skin	(50)	(18)	(10)	(50)
Fibrosarcoma			1 (10%)	
Hemangiosarcoma			1 (10%)	
Papilloma				1 (2%)
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
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
2-Year Study (continued)				
Special Senses System				
Harderian gland	(7)	(4)	(7)	(2)
Adenoma	7 (100%)	3 (75%)	5 (71%)	2 (100%)
Adenoma, two			2 (29%)	
Urinary System				
Kidney	(50)	(22)	(12)	(50)
Urinary bladder	(50)	(18)	(16)	(50)
Systemic Lesions				
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%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
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

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Number of animals with any tissue examined microscopically
[c] 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 3 7	2 6 4	4 6 4	5 5 4	6 0 7	6 2 6	6 2 7	6 4 3	6 4 8	6 4 9	6 8 1	6 8 2	6 8 9	7 1 1	7 1 7	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	0 1 1 3	0 1 0 4	0 1 5 1	0 1 6 5	0 0 3 5	0 0 5 2	0 0 7 1	0 1 6 4	0 0 1 3	0 0 1 4	0 0 9 4	0 1 3 4	0 1 4 2	0 0 4 2	0 1 6 1	0 0 2 1	0 0 2 3	0 0 3 2	0 0 3 4	0 0 4 3	0 0 4 4	0 0 5 1	0 0 5 3	0 0 5 3	0 0 7 3
Alimentary System																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
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																									
General Body System																									
None																									
Genital System																									
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)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 0 0 7 4	0 0 0 7 5	0 0 0 8 3	0 0 0 8 4	0 0 0 9 1	0 0 0 9 2	0 0 0 9 3	0 0 1 0 1	0 0 1 0 3	0 0 1 0 5	0 0 1 1 1	0 0 1 2 3	0 0 1 2 4	0 0 1 2 5	0 0 1 3 2	0 0 1 3 3	0 0 1 4 1	0 0 1 4 3	0 0 1 4 5	0 0 1 6 2	0 0 1 6 3	0 0 1 7 4	0 0 1 7 5	0 0 1 8 1	0 0 1 8 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma					X																					1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma						X													X				X			7
Hepatocellular adenoma		X	X			X			X	X	X			X				X		X			X		X	19
Mesentery													+													4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	M	+	+	+	M	+	+	M	M	M	+	+	+	M	M	M	+	M	M	+	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma													X													1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma															X											1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										4
Preputial gland					+		+																			9
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

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

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

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 0 7 4	0 0 7 5	0 0 8 3	0 0 8 4	0 0 9 1	0 0 9 2	0 0 9 3	0 1 0 1	0 1 0 3	0 1 1 5	0 1 2 1	0 1 2 3	0 1 2 4	0 1 2 5	0 1 3 2	0 1 3 3	0 1 4 1	0 1 4 3	0 1 4 5	0 1 6 2	0 1 6 3	0 1 7 4	0 1 7 5	0 1 8 1	0 1 8 2	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	41
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
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
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	49
Alveolar/bronchiolar adenoma		X										X	X		X								X			11
Hepatocellular carcinoma, metastatic, liver						X																	X			3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye											+															2
Harderian gland										+	+					+						+				7
Adenoma										X	X					X						X				7
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
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

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

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	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 3 3 3	0 3 3 5	0 3 4 1	0 3 4 2	0 3 5 1	0 3 5 2	0 3 5 4	0 3 5 5	0 3 6 1	0 3 6 2	0 3 7 1	0 3 7 2	0 3 7 5	0 3 8 2	0 3 8 3	0 3 9 1	0 3 9 2	0 4 0 2	0 4 0 3	0 4 0 4	0 4 0 5	0 4 1 1	0 4 1 2	0 4 1 3	0 4 2 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus																										17
Gallbladder																										17
Intestine large, colon																										17
Intestine large, rectum																										17
Intestine large, cecum																										17
Intestine small, duodenum																										17
Intestine small, jejunum															+											18
Intestine small, ileum																										19
Liver	+	+		+				+			+		+				+	+		+			+			32
Hemangiosarcoma																										1
Hepatocellular carcinoma								X					X													7
Hepatocellular adenoma	X	X		X							X						X	X				X			X	13
Hepatocellular adenoma, multiple																				X						1
Mesentery									+							+						+				5
Pancreas						+																				18
Salivary glands																										17
Stomach, forestomach				+									+	+												19
Squamous cell papilloma																										1
Stomach, glandular																										16
Tooth				+														+								2
Cardiovascular System																										
Heart																										17
Endocrine System																										
Adrenal cortex																										17
Adrenal medulla																										17
Islets, pancreatic																										17
Parathyroid gland																										12
Pituitary gland																										16
Thyroid gland	+																						+			19
General Body System																										
None																										
Genital System																										
Epididymis																										17
Penis																										3
Preputial gland			+						+																	5
Prostate																										17
Seminal vesicle																					+					18
Testes										+																18
Interstitial cell, adenoma										X																1

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	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	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	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
	3	4	3	4	3	3	4	3	3	3	4	3	4	3	3	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
Hematopoietic System																									
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	+	+	+	+	+	+	+	+	+	+							
Integumentary System																									
Mammary gland	+	M	M	+	M	M	M	M	M	M	+	M	M	M	M	M	M								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Musculoskeletal System																									
Bone	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Skeletal muscle	+																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Peripheral nerve	+																								
Spinal cord	M									+															
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X						X						X
Alveolar/bronchiolar adenoma, multiple																					X		X		
Alveolar/bronchiolar carcinoma																								X	
Hemangiosarcoma, metastatic, liver												X													
Hepatocellular carcinoma, metastatic, liver						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																				+					
Adenoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed									X				X		X			X							X

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	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 3 3 3	0 3 3 5	0 3 4 1	0 3 4 2	0 3 5 1	0 3 5 2	0 3 5 4	0 3 5 5	0 3 6 1	0 3 6 2	0 3 7 1	0 3 7 2	0 3 7 5	0 3 8 2	0 3 8 3	0 3 9 1	0 3 9 2	0 4 0 2	0 4 0 3	0 4 0 4	0 4 0 5	0 4 1 1	0 4 1 2	0 4 1 3	0 4 2 5	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow																										17
Lymph node																								+		5
Lymph node, bronchial																										17
Lymph node, mandibular																										13
Lymph node, mesenteric																								+	+	21
Lymph node, mediastinal																										16
Spleen																										18
Thymus																										16
Integumentary System																										
Mammary gland																										3
Skin		+																								18
Musculoskeletal System																										
Bone																										16
Skeletal muscle																										1
Nervous System																										
Brain																										17
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Larynx																										17
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X					X						X			X									7
Alveolar/bronchiolar adenoma, multiple																				X						3
Alveolar/bronchiolar carcinoma																	X									2
Hemangiosarcoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland				+												+						+				4
Adenoma																X						X				3
Urinary System																										
Kidney							+														+	+	+			22
Urinary bladder																			+							18
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										5

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

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

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 5 9 3	0 5 9 4	0 5 9 5	0 6 0 2	0 6 0 4	0 6 1 1	0 6 1 2	0 6 1 3	0 6 1 4	0 6 1 5	0 6 2 1	0 6 2 2	0 6 2 3	0 6 2 4	0 6 2 5	0 6 3 1	0 6 3 2	0 6 4 1	0 6 4 5	0 6 5 1	0 6 5 2	0 6 5 4	0 6 6 3	0 6 6 4	0 6 6 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus																										8
Gallbladder																										7
Intestine large, colon																										8
Intestine large, rectum																										8
Intestine large, cecum																										8
Intestine small, duodenum																										8
Intestine small, jejunum																+										9
Intestine small, ileum							+																			9
Liver	+	+	+		+	+		+	+	+	+	+		+		+	+	+	+				+	+		37
Hepatocellular carcinoma									X		X					X		X								10
Hepatocellular adenoma		X	X			X		X	X	X		X							X				X	X		19
Hepatocellular adenoma, two					X																					2
Mesentery					+																					2
Pancreas																										8
Salivary glands																										7
Stomach, forestomach							+							+												12
Squamous cell papilloma														X												1
Stomach, glandular																										8
Tooth																					+					1
Cardiovascular System																										
Heart																										8
Endocrine System																										
Adrenal cortex																										8
Adrenal medulla																										8
Islets, pancreatic																										8
Parathyroid gland																										6
Pituitary gland																										8
Thyroid gland														+								+				12
Follicular cell, adenoma														X												3
General Body System																										
None																										
Genital System																										
Epididymis																										8
Fibrosarcoma																										1
Penis																										1
Preputial gland																								+		4
Prostate																										8
Seminal vesicle																										9
Testes																										9
Interstitial cell, adenoma																										1

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

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

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 5 9 3	0 5 9 4	0 5 9 5	0 6 0 2	0 6 0 4	0 6 1 1	0 6 1 2	0 6 1 3	0 6 1 4	0 6 1 5	0 6 2 1	0 6 2 2	0 6 2 3	0 6 2 4	0 6 2 5	0 6 3 1	0 6 3 2	0 6 4 1	0 6 4 5	0 6 5 1	0 6 5 2	0 6 5 4	0 6 6 3	0 6 6 4	0 6 6 5	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow																										8
Lymph node														+												3
Lymph node, bronchial																										6
Lymph node, mandibular																										3
Lymph node, mesenteric														+		+	+	+								13
Lymph node, mediastinal																										8
Spleen															+		+									13
Thymus																										7
Integumentary System																										
Mammary gland																										
Skin						+											+							+		10
Fibrosarcoma						X																				1
Hemangiosarcoma																	X									1
Musculoskeletal System																										
Bone																									+	9
Nervous System																										
Brain																										8
Respiratory System																										
Larynx																										8
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X		X		X												X				X			8
Alveolar/bronchiolar adenoma, multiple																										2
Alveolar/bronchiolar carcinoma													X	X	X	X										4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland						+			+		+															7
Adenoma						X			X																	5
Adenoma, two											X															2
Urinary System																										
Kidney													+				+	+			+					12
Urinary bladder																		+		+	+			+		16
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																X										4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.2 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.2 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 2 1	0 8 2 2	0 8 2 3	0 8 3 2	0 8 3 3	0 8 4 1	0 8 4 2	0 8 5 1	0 8 5 3	0 8 5 4	0 8 6 1	0 8 6 2	0 8 6 3	0 8 6 5	0 8 7 1	0 8 7 2	0 8 7 3	0 8 7 4	0 8 7 5	0 8 8 1	0 8 8 3	0 8 9 2	0 8 9 4	0 8 9 5	0 8 9 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatocellular carcinoma						X									X											9
Hepatocellular carcinoma, multiple																										1
Hepatocellular carcinoma, two																										1
Hepatocellular adenoma							X	X									X				X					10
Hepatocellular adenoma, two																										1
Mesentery																									+	2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																					X					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth							+								+											2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma NOS																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	M	M	M	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	+	M	M	+	M	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X																								2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										3
Preputial gland																										4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma								X																		1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.2 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene: 0.2 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 2 1	0 8 2 2	0 8 2 3	0 8 3 2	0 8 3 3	0 8 4 1	0 8 4 2	0 8 5 1	0 8 5 3	0 8 5 4	0 8 6 1	0 8 6 2	0 8 6 3	0 8 6 5	0 8 7 1	0 8 7 2	0 8 7 3	0 8 7 4	0 8 7 5	0 8 8 1	0 8 8 3	0 8 9 2	0 8 9 4	0 8 9 5	0 9 0 1	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
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	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X			X		X				X								X					12
Alveolar/bronchiolar adenoma, multiple																				X			X			3
Alveolar/bronchiolar carcinoma			X																							1
Hepatocellular carcinoma, metastatic, liver																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye								+																		3
Harderian gland																										2
Adenoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic							X	X																		2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										2

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
Harderian Gland: Adenoma				
Overall rate[a]	7/50 (14%)	3/50 (6%)	7/50 (14%)	2/50 (4%)
Adjusted rate[b]	19.0%	9.1%	16.7%	5.6%
Terminal rate[c]	6/35 (17%)	3/33 (9%)	7/42 (17%)	1/34 (3%)
First incidence (days)	627	731 (T)	731 (T)	715
Life table test[d]	P=0.130N	P=0.183N	P=0.478N	P=0.090N
Logistic regression test[d]	P=0.130N	P=0.168N	P=0.531N	P=0.086N
Cochran-Armitage test[d]	P=0.126N			
Fisher exact test[d]		P=0.159N	P=0.613N	P=0.080N
Liver: Hepatocellular Adenoma				
Overall rate	19/50 (38%)	14/32 (44%)[e]	21/37 (57%)[e]	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
Liver: Hepatocellular Carcinoma				
Overall rate	7/50 (14%)	7/32 (22%)[e]	10/37 (27%)[e]	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
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	24/50 (48%)	21/32 (66%)[e]	28/37 (76%)[e]	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
Lung: Alveolar/bronchiolar Adenoma				
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
Lung: Alveolar/bronchiolar Carcinoma				
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)	-[f]	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
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
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
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/48 (2%)	0/19 (0%)[e]	3/12 (25%)[e]	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
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)				
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
All Organs: Benign Neoplasms				
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
All Organs: Malignant Neoplasms				
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
All Organs: Benign or Malignant Neoplasms				
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
[a] 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.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] 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.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not appropriate.
[f] Not applicable; no neoplasms in animal group

TABLE C4
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
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
o-Chlorobenzalmalononitrile	7/49	7/49	14/49
Overall Historical Incidence			
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%

[a] 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[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	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
15-Month Interim Evaluation				
Alimentary System				
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%)
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
Epididymis	(10)			(10)
Inflammation, chronic				1 (10%)
Testes	(10)			(10)
Atrophy	1 (10%)			
Hematopoietic System				
Lymph node, mesenteric	(10)	(1)		(10)
Hemorrhage		1 (100%)		
Integumentary System				
Skin	(10)		(1)	(10)
Alopecia			1 (100%)	
Musculoskeletal System				
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
15-Month Interim Evaluation (continued)				
Nervous System				
Brain	(10)			(10)
Mineralization	3 (30%)			5 (50%)
Respiratory System				
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%)
Special Senses System				
None				
Urinary System				
Kidney	(10)			(10)
Inflammation, suppurative	1 (10%)			
Nephropathy, chronic	1 (10%)			
Urinary bladder	(10)		(1)	(10)
Dilatation	1 (10%)			
2-Year Study				
Alimentary System				
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
2-Year Study (continued)				
Alimentary System (continued)				
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%)		
Cardiovascular System				
Heart	(50)	(17)	(8)	(50)
Inflammation, subacute		1 (6%)		
Arteriole, mineralization				1 (2%)
Atrium, thrombosis	1 (2%)			
Endocrine System				
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
2-Year Study (continued)				
General Body System				
None				
Genital System				
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%)
Hematopoietic System				
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
2-Year Study (continued)				
Integumentary System				
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%)	
Musculoskeletal System				
Bone	(50)	(16)	(9)	(50)
Arthrosis			1 (11%)	
Nervous System				
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%)		
Respiratory System				
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
2-Year Study (continued)				
Special Senses System				
None				
Urinary System				
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%)

[a] 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

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	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
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular adenoma	1 (10%)			1 (10%)
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
None				
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
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
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma			1 (10%)	1 (10%)
Special Senses System				
Harderian gland				(1)
Adenoma				1 (100%)
Urinary System				
None				
2-Year Study				
Alimentary System				
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%)			
Cardiovascular System				
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
2-Year Study (continued)				
Endocrine System				
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%)	
General Body System				
Tissue NOS		(1)		
Sarcoma, metastatic, skin		1 (100%)		
Genital System				
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%)	
Hematopoietic System				
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
2-Year Study (continued)				
Integumentary System				
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%)		
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Osteosarcoma			1 (2%)	
Skeletal muscle		(1)	(1)	(2)
Fibrosarcoma, metastatic, skin		1 (100%)		
Nervous System				
Brain	(49)	(50)	(50)	(50)
Meninges, fibrosarcoma		1 (2%)		
Respiratory System				
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%)		
Special Senses System				
Harderian gland	(7)	(6)	(4)	(1)
Adenocarcinoma	1 (14%)			
Adenoma	4 (57%)	5 (83%)	4 (100%)	1 (100%)
Adenoma, two		1 (17%)		
Urinary System				
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
2-Year Study (continued)				
Systemic Lesions				
Multiple organs[b]	(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%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
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		

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Number of animals with any tissue examined microscopically
[c] 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

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

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	2 4 9	3 9 6	4 8 3	5 2 0	5 8 4	5 8 9	5 9 8	6 2 0	6 2 9	6 3 3	6 3 4	6 5 7	6 6 0	6 7 2	6 8 7	6 9 1	6 9 3	7 1 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	0 2 5 1	0 2 6 2	0 2 9 5	0 2 1 4	0 2 9 2	0 2 2 4	0 2 4 2	0 3 0 5	0 2 9 3	0 2 0 2	0 1 9 3	0 2 2 2	0 2 6 3	0 1 9 5	0 2 5 4	0 2 6 5	0 2 6 1	0 2 8 3	0 1 9 1	0 1 9 2	0 1 9 4	0 2 0 1	0 2 0 3	0 2 1 1
Genital System																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X
Granulosa cell tumor benign																X								
Histiocytic sarcoma			X											X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Hemangioma							X																	
Histiocytic sarcoma		X	X											X										
Hematopoietic System																								
Blood											+													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+					+						+	+								
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X										
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X										
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma								X																
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X					
Alveolar/bronchiolar carcinoma								X								X								
Hepatocellular carcinoma, metastatic, liver											X													
Histiocytic sarcoma			X											X		X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 2 1 2	0 2 1 3	0 2 1 5	0 2 2 1	0 2 2 3	0 2 2 4	0 2 2 1	0 2 2 3	0 2 2 4	0 2 2 5	0 2 2 2	0 2 2 3	0 2 2 5	0 2 3 5	0 2 3 6	0 2 3 7	0 2 3 7	0 2 3 7	0 2 3 7	0 2 3 8	0 2 3 8	0 2 3 8	0 2 3 9	0 3 3 0	0 3 3 0	0 3 3 0	Total Tissues/ Tumors
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X														1
Granulosa cell tumor benign																											1
Histiocytic sarcoma																											2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X														1
Hemangioma																											1
Histiocytic sarcoma																											3
Hematopoietic System																											
Blood																											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node													+					+								+	7
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+		42
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma							X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma				X				X												X							4
Alveolar/bronchiolar carcinoma																			X								3
Hepatocellular carcinoma, metastatic, liver																											1
Histiocytic sarcoma																											3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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	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
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
	2	2	2	2	2	2	2	3	2	2	1	2	2	1	2	2	2	2	1	1	1	2	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
Special Senses System																								
Eye																								
Harderian gland		+														+	+							
Adenocarcinoma																	X							
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X	X											X		X								
Lymphoma malignant lymphocytic				X																				
Lymphoma malignant mixed					X				X					X	X	X								

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	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
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	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	Total
	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	Tissues/
	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	Tumors
Special Senses System																										
Eye					+																					1
Harderian gland					+		+														+				+	7
Adenocarcinoma																										1
Adenoma					X		X														X				X	4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										4
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed				X			X						X					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

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

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 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 4 5 1	0 4 6 1	0 4 6 4	0 4 7 3	0 4 7 4	0 4 7 5	0 4 8 5	0 4 9 3	0 4 9 5	0 5 0 1	0 5 0 5	0 5 1 1	0 5 1 2	0 5 1 3	0 5 1 4	0 5 2 1	0 5 2 3	0 5 2 4	0 5 2 5	0 5 3 1	0 5 3 3	0 5 3 4	0 5 3 5	0 5 4 2	0 5 4 5	Total Tissues/ Tumors
Alimentary System																										
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																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Hemangiosarcoma																										1
Hepatocellular carcinoma																										2
Hepatocellular adenoma		X	X	X		X	X			X	X				X						X					10
Histiocytic sarcoma																										1
Mesentery														+												4
Fibrosarcoma, metastatic, skin																										1
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma								X																		1
Parathyroid gland	M	+	+	+	+	M	+	+	M	+	M	+	M	+	M	+	+	+	+	M	M	+	M	+	+	22
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X		X															3
Carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																		X								1

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	3	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	4	0	5	5	7	7	7	9	2	3	4	6	6	6	7	8	8	3	3	3	3	3	3	3
	0	3	5	8	2	6	7	3	9	3	6	0	0	8	3	0	8	0	7	7	7	7	7	7
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
	4	4	5	4	4	4	4	4	5	5	5	4	4	4	4	4	5	5	4	4	4	4	4	4
	3	6	3	9	7	8	7	8	4	0	2	5	9	6	9	8	4	0	3	3	4	4	4	4
	5	3	2	1	1	1	2	2	1	4	2	3	4	5	2	3	3	2	2	3	1	2	3	4	5
General Body System																								
Tissue NOS													+											
Sarcoma, metastatic, skin													X											
Genital System																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Hemangioma																								
Teratoma NOS	X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Hemangioma														X										
Histiocytic sarcoma																	X							
Endometrium, polyp, moderate										X														
Hematopoietic System																								
Blood																			+					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X														
Lymph node				+			+					+				+	+						+	
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	M	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X								X														
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																		X						
Myxosarcoma																								
Subcutaneous tissue, sarcoma													X											
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																		+						
Fibrosarcoma, metastatic, skin																		X						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, fibrosarcoma									X															
Peripheral nerve																		+						

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 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 4 5 1	0 4 6 1	0 4 6 4	0 4 7 3	0 4 7 4	0 4 7 5	0 4 8 5	0 4 9 3	0 4 9 5	0 5 0 1	0 5 0 5	0 5 1 1	0 5 1 2	0 5 1 3	0 5 1 4	0 5 2 1	0 5 2 3	0 5 2 4	0 5 2 5	0 5 3 1	0 5 3 3	0 5 3 4	0 5 3 5	0 5 4 2	0 5 4 5	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										1
Sarcoma, metastatic, skin																										1
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma														X												1
Hemangioma																				X						1
Teratoma NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma						X																				1
Hemangioma																										1
Histiocytic sarcoma																										1
Endometrium, polyp, moderate																										1
Hematopoietic System																										
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
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										1
Myxosarcoma																								X		1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Fibrosarcoma, metastatic, skin																										1
Nervous System																										
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)

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

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 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 4 5 1	0 4 6 1	0 4 6 4	0 4 7 3	0 4 7 4	0 4 7 5	0 4 8 5	0 4 9 3	0 4 9 5	0 5 0 1	0 5 0 5	0 5 1 1	0 5 1 2	0 5 1 3	0 5 1 4	0 5 2 1	0 5 2 3	0 5 2 4	0 5 2 5	0 5 3 1	0 5 3 3	0 5 3 4	0 5 3 5	0 5 4 2	0 5 4 5	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X		X													3
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic, skin																										1
Hemangiosarcoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucosa, squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																+										1
Harderian gland		+									+					+										6
Adenoma		X									X					X										5
Adenoma, two																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
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

Number of Days on Study	0	4	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	7	1	5	5	7	7	9	0	2	3	4	5	6	7	7	8	0	1	1	3	3	3	3	3	3
	4	1	4	4	4	5	2	4	5	5	3	4	0	4	4	8	6	5	8	0	6	6	6	6	6
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
	7	7	7	7	6	7	7	7	6	7	7	7	7	7	7	6	6	7	7	7	6	6	6	6	6
	3	3	0	3	8	5	4	8	8	0	1	6	7	2	8	8	7	3	7	8	7	7	7	7	8
	5	3	1	4	1	4	2	5	4	3	2	5	2	3	4	5	5	2	5	1	1	2	3	4	2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma									X	X									X						
Hepatocellular adenoma																			X						X
Hepatocellular adenoma, two																									
Mesentery					+		+								+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	M	+	+	+	M	+	M	+	M	+	+	M	M	M	+	+	+	M	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma												X											X		
Carcinoma							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma													X					X					X		
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Uterus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X						X					
Hemangioma, mild																									
Endometrium, polyp stromal, moderate																									

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

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 6 8 3	0 6 9 1	0 7 0 2	0 7 0 4	0 7 0 5	0 7 1 1	0 7 1 3	0 7 1 4	0 7 2 1	0 7 2 2	0 7 2 5	0 7 4 1	0 7 4 3	0 7 4 4	0 7 4 5	0 7 5 2	0 7 5 5	0 7 6 1	0 7 6 3	0 7 6 4	0 7 7 1	0 7 7 3	0 7 7 4	0 7 8 2	0 7 8 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																			X							4
Hepatocellular adenoma			X								X				X						X					6
Hepatocellular adenoma, two									X																	1
Mesentery						+		+													+					6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X														X							X				5
Carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma						X									X								X			6
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Hemangioma, mild											X															1
Endometrium, polyp stromal, moderate										X																1

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

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

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

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

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

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

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	6 9 6	7 2 4	7 3 0	7 3 0	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 9 3 5	0 9 8 4	0 9 7 5	1 0 2 1	0 9 1 5	0 9 2 1	0 9 3 4	0 9 4 3	0 9 4 4	0 9 5 5	0 9 6 2	0 9 6 4	0 9 7 4	0 9 9 1	0 9 9 2	0 9 9 3	0 9 9 5	1 0 0 2	1 0 0 3	1 0 0 4	1 0 0 5	1 0 1 1	1 0 1 4	1 0 1 5	1 0 2 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																		X								1
Hepatocellular adenoma		X	X													X									X	5
Mesentery																							+			2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma								X					X													2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	M	+	M	+	+	+	+	+	28
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X		X		X										3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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
	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	9	9	0	9	9	9	9	9	9	9	0	0	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
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+	+																				
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+																								
Spinal cord	+																								
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X		X		X
Alveolar/bronchiolar carcinoma																									
Nose	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Trachea	+	+	A	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed		X		X					X															X	

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	6 9 6	7 2 4	7 3 0	7 3 0	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 9 3 5	0 9 8 4	0 9 7 5	1 0 2 1	0 9 1 5	0 9 2 1	0 9 3 4	0 9 4 3	0 9 4 4	0 9 5 5	0 9 6 2	0 9 6 4	0 9 7 4	0 9 9 1	0 9 9 2	0 9 9 3	0 9 9 5	0 0 2 2	1 0 3 3	1 0 4 4	1 0 5 5	1 0 1 1	1 1 1 4	1 1 1 5	1 2 2 2	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+		+																						5
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	43
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma								X																		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma										X																4
Alveolar/bronchiolar carcinoma						X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Special Senses System																										
Harderian gland																									+	1
Adenoma																									X	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																X										1
Lymphoma malignant mixed		X		X				X					X													8

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
Harderian Gland: Adenoma				
Overall rate[a]	4/50 (8%)	6/50 (12%)	4/50 (8%)	1/50 (2%)
Adjusted rate[b]	12.9%	18.8%	12.1%	4.8%
Terminal rate[c]	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[d]	P=0.164N	P=0.387	P=0.631	P=0.311N
Logistic regression test[d]	P=0.130N	P=0.387	P=0.634N	P=0.311N
Cochran-Armitage test[d]	P=0.070N			
Fisher exact test[d]		P=0.370	P=0.643N	P=0.181N
Harderian Gland: Adenoma or Carcinoma				
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
Liver: Hepatocellular Adenoma				
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
Liver: Hepatocellular Carcinoma				
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
Liver: Hepatocellular Adenoma or Carcinoma				
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
Lung: Alveolar/bronchiolar Adenoma				
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
Lung: Alveolar/bronchiolar Carcinoma				
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
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
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
Pituitary Gland (Pars Distalis): Adenoma				
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
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
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
Thyroid Gland (Follicular Cell): Adenoma				
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	–[e]
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
All Organs: Hemangioma or Hemangiosarcoma				
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
All Organs: Histiocytic Sarcoma				
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
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)				
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
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
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
All Organs: Benign Neoplasms				
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
All Organs: Malignant Neoplasms				
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
All Organs: Benign or Malignant Neoplasms				
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
[a] 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.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] 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.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Thyroid Gland (Follicular Cell) Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
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
o-Chlorobenzalmalononitrile	2/49	0/49	2/49
Overall Historical Incidence			
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%

[a] 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[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	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
15-Month Interim Evaluation				
Alimentary System				
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%)
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
Ovary	(10)	(2)	(2)	(10)
Cyst	2 (20%)	2 (100%)	2 (100%)	1 (10%)
Uterus	(10)		(2)	(10)
Endometrium, hyperplasia			2 (100%)	1 (10%)
Hematopoietic System				
Lymph node, mandibular	(8)			(9)
Hyperplasia, lymphoid				1 (11%)
Spleen	(10)			(10)
Hyperplasia, lymphoid	1 (10%)			
Integumentary System				
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
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
Brain	(10)			(10)
Mineralization	3 (30%)			3 (30%)
Respiratory System				
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%)
Special Senses System				
Eye			(1)	
Cornea, edema			1 (100%)	
Urinary System				
Kidney	(10)			(10)
Congestion				1 (10%)
Cyst	1 (10%)			
Infiltration cellular, lymphocyte	1 (10%)			
2-Year Study				
Alimentary System				
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
2-Year Study (continued)				
Alimentary System (continued)				
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%)
Cardiovascular System				
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
2-Year Study (continued)				
Endocrine System				
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%)
General Body System				
None				
Genital System				
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%)
Hematopoietic System				
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
2-Year Study (continued)				
Hematopoietic System (continued)				
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%)
Integumentary System				
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%)		
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Developmental malformation			1 (2%)	1 (2%)
Fibrous osteodystrophy	1 (2%)			
Fracture			1 (2%)	
Nervous System				
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
2-Year Study (continued)				
Respiratory System				
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%)
Special Senses System				
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%)
Urinary System				
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%)		

[a] 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

TABLE E1
Summary of the Incidence of Neoplasms in Male Mice in the Stop-Exposure Evaluation of Hexachlorocyclopentadiene[a]

	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)
Disposition Summary						
Animals initially in study	90[b]	60	80	50	90	70
27-Week interim evaluation[c]	10				10	
34-Week interim evaluation[d]	10		10		10	
43-Week interim evaluation[e]	10		10		10	10
15-Month interim evaluation	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
43-Week Interim Evaluation						
Alimentary System						
Liver	(10)		(10)		(10)	(10)
Hepatocellular adenoma	1 (10%)					1 (10%)
Respiratory System						
Lung	(10)		(10)		(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)		1 (10%)			
15-Month Interim Evaluation						
Alimentary System						
Liver	(10)	(10)				
Hepatocellular carcinoma	2 (20%)					
Hepatocellular adenoma	3 (30%)	1 (10%)				
Cardiovascular System						
None						
Endocrine System						
Islets, pancreatic	(10)	(10)				
Adenoma	1 (10%)					
General Body System						
None						
Genital System						
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)
15-Month Interim Evaluation (continued)						
Hematopoietic System						
None						
Integumentary System						
None						
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
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%)
Special Senses System						
None						
Urinary System						
Urinary bladder		(10)				
Systemic Lesions						
Multiple organs[f]		(10)				
2-Year Study						
Alimentary System						
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)
2-Year Study (continued)						
Alimentary System (continued)						
Stomach, forestomach	(50)	(50)				
Squamous cell papilloma		1 (2%)				
Cardiovascular System						
Heart	(50)	(50)				
Endocrine System						
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%)	
General Body System						
None						
Genital System						
Epididymis	(50)	(50)				
Testes	(50)	(50)				
Interstitial cell, adenoma		1 (2%)				
Hematopoietic System						
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)		
Integumentary System						
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)
2-Year Study (continued)						
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
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)		
Special Senses System						
Harderian gland	(7)	(2)	(4)	(3)	(4)	(3)
Adenoma	7 (100%)	2 (100%)	4 (100%)	3 (100%)	4 (100%)	1 (33%)
Carcinoma						1 (33%)
Urinary System						
Kidney	(50)	(50)				
Urinary bladder	(50)	(50)				
Systemic Lesions						
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%)	
Neoplasm Summary						
Total animals with primary neoplasms[g]						
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)
Neoplasm Summary (continued)						
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			

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Includes 60 controls from the core study
[c] No neoplasms were observed at any site in any animal at the 27-week interim evaluation.
[d] No neoplasms were observed at any site in any animal at the 34-week interim evaluation.
[e] No neoplasms were observed at any other site in any animal at the 43-week interim evaluation.
[f] Number of animals with any tissue examined microscopically
[g] 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)
Harderian Gland: Adenoma				
Overall rate[a]	7/50 (14%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted rate[b]	19.0%	11.0%	8.5%	5.6%
Terminal rate[c]	6/35 (17%)	3/35 (9%)	2/33 (6%)	1/34 (3%)
First incidence (days)	627	696	654	715
Life table test[d]	P=0.051N	P=0.263N	P=0.187N	P=0.090N
Logistic regression test[d]	P=0.048N	P=0.260N	P=0.178N	P=0.086N
Cochran-Armitage test[d]	P=0.043N			
Fisher exact test[d]		P=0.262N	P=0.159N	P=0.080N
Lung: Alveolar/bronchiolar Adenoma				
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
Lung: Alveolar/bronchiolar Carcinoma				
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)	–[e]	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
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
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
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)				
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)
All Organs: Benign Neoplasms				
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
All Organs: Malignant Neoplasms				
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
All Organs: Benign or Malignant Neoplasms				
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
[a] 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.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] 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.
[e] 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)
Harderian Gland: Adenoma			
Overall rate[a]	7/50 (14%)	4/50 (8%)	1/50 (2%)
Adjusted rate[b]	19.0%	9.8%	3.0%
Terminal rate[c]	6/35 (17%)	4/41 (10%)	1/33 (3%)
First incidence (days)	627	729 (T)	729 (T)
Life table test[d]	P=0.024N	P=0.185N	P=0.041N
Logistic regression test[d]	P=0.032N	P=0.222N	P=0.048N
Cochran-Armitage test[d]	P=0.025N		
Fisher exact test[d]		P=0.262N	P=0.030N
Harderian Gland: Adenoma or Carcinoma			
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
Lung: Alveolar/bronchiolar Adenoma			
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
Lung: Alveolar/bronchiolar Carcinoma			
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)	-[e]	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
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
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)
All Organs: Benign Neoplasms			
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
All Organs: Malignant Neoplasms			
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
All Organs: Benign or Malignant Neoplasms			
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
[a] 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.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] 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.
[e] 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)
Harderian Gland: Adenoma		
Overall rate[a]	3/50 (6%)	4/50 (8%)
Adjusted rate[b]	8.5%	9.8%
Terminal rate[c]	2/33 (6%)	4/41 (10%)
First incidence (days)	654	729 (T)
Life table test[d]		P=0.613
Logistic regression test[d]		P=0.559
Fisher exact test[d]		P=0.500
Lung: Alveolar/bronchiolar Adenoma		
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
Lung: Alveolar/bronchiolar Carcinoma		
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
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
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
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)		
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)
All Organs: Benign Neoplasms		
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
All Organs: Malignant Neoplasms		
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
All Organs: Benign or Malignant Neoplasms		
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
[a] 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.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] 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)
Lung: Alveolar/bronchiolar Adenoma		
Overall rate[a]	15/50 (30%)	10/50 (20%)
Adjusted rate[b]	37.5%	29.2%
Terminal rate[c]	10/34 (29%)	9/33 (27%)
First incidence (days)	393	647
Life table test[d]		P=0.226N
Logistic regression test[d]		P=0.336N
Fisher exact test[d]		P=0.178N
Lung: Alveolar/bronchiolar Carcinoma		
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
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
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
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)		
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	–[e]
Life table test		P=0.080N
Logistic regression test		P=0.143N
Fisher exact test		P=0.059N
All Organs: Benign Neoplasms		
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)
All Organs: Malignant Neoplasms		
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
All Organs: Benign or Malignant Neoplasms		
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
[a] 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.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] 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.
[e] 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[a]

	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)
Disposition Summary						
Animals initially in study	90[b]	60	80	50	90	70
27-Week interim evaluation	10				10	
34-Week interim evaluation	10		10		10	
43-Week interim evaluation	10		10		10	10
15-Month interim evaluation	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

27-Week Interim Evaluation

Alimentary System
None

Cardiovascular System
None

Endocrine System
None

General Body System
None

Genital System
None

Hematopoietic System
None

Integumentary System
None

Musculoskeletal System
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)
27-Week Interim Evaluation (continued)						
Nervous System						
None						
Respiratory System						
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%)	
Special Senses System						
None						
Urinary System						
Kidney	(1)					
Renal tubule, cytoplasmic alteration	1 (100%)					
34-Week Interim Evaluation						
Alimentary System						
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%)	
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
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)
34-Week Interim Evaluation (continued)						
Genital System						
Testes	(10)		(10)		(10)	
Atrophy	1 (10%)		1 (10%)			
Hematopoietic System						
Lymph node, mandibular	(6)		(9)		(8)	
Congestion	1 (17%)					
Lymph node, mesenteric	(10)		(10)		(10)	
Hyperplasia, lymphoid			1 (10%)			
Integumentary System						
None						
Musculoskeletal System						
None						
Nervous System						
Brain	(10)		(10)		(10)	
Mineralization	1 (10%)					
Respiratory System						
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%)	
Special Senses System						
None						
Urinary System						
Kidney	(10)		(10)		(10)	
Inflammation, subacute			1 (10%)		1 (10%)	
43-Week Interim Evaluation						
Alimentary System						
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)
43-Week Interim Evaluation (continued)						
Alimentary System (continued)						
Stomach, glandular	(10)		(10)		(10)	(10)
Inflammation, subacute						1 (10%)
Cardiovascular System						
None						
Endocrine System						
Adrenal cortex	(10)		(10)		(10)	(10)
Hyperplasia	1 (10%)					
General Body System						
None						
Genital System						
Testes	(10)		(10)		(10)	(10)
Atrophy					1 (10%)	
Hematopoietic System						
Lymph node, bronchial	(9)		(8)		(8)	(7)
Hyperplasia, lymphoid						1 (14%)
Integumentary System						
None						
Musculoskeletal System						
None						
Nervous System						
Brain	(10)		(10)		(10)	(10)
Mineralization			2 (20%)		2 (20%)	1 (10%)
Respiratory System						
Lung	(10)		(10)		(10)	(10)
Congestion	1 (10%)		3 (30%)			
Inflammation, subacute					1 (10%)	1 (10%)
Inflammation, suppurative						5 (50%)
Mucosa, pigmentation			10 (100%)		9 (90%)	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)
43-Week Interim Evaluation (continued)						
Respiratory System (continued)						
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%)
Special Senses System						
None						
Urinary System						
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%)					
15-Month Interim Evaluation						
Alimentary System						
Liver	(10)	(10)				
Cytoplasmic alteration		2 (20%)				
Inflammation, subacute	1 (10%)	1 (10%)				
Stomach, forestomach	(10)	(10)				
Hyperkeratosis		2 (20%)				
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
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)
15-Month Interim Evaluation (continued)						
Hematopoietic System						
None						
Integumentary System						
None						
Musculoskeletal System						
None						
Nervous System						
Brain	(10)	(10)				
Mineralization	3 (30%)	5 (50%)				
Respiratory System						
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%)
Special Senses System						
None						
Urinary System						
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)
2-Year Study						
Alimentary System						
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%)			
Cardiovascular System						
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)
2-Year Study (continued)						
Endocrine System						
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%)
General Body System						
None						
Genital System						
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%)				
Hematopoietic System						
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)
2-Year Study (continued)						
Hematopoietic System (continued)						
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%)	
Integumentary System						
Skin	(50)	(50)	(48)	(46)	(48)	(36)
Alopecia	2 (4%)					2 (6%)
Edema		1 (2%)				
Inflammation, suppurative	4 (8%)					
Prepuce, inflammation, suppurative	1 (2%)					
Musculoskeletal System						
None						
Nervous System						
Brain	(50)	(50)				
Compression	1 (2%)					
Inflammation, subacute		1 (2%)				
Inflammation, suppurative		1 (2%)				
Mineralization	13 (26%)	10 (20%)				
Respiratory System						
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%)				
Interstitium, 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)
2-Year Study (continued)						
Respiratory System (continued)						
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%)
Special Senses System						
None						
Urinary System						
Kidney	(50)	(50)				
Casts	1 (2%)					
Cyst	1 (2%)	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%)				

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Includes 60 controls from the core study

APPENDIX F
GENETIC TOXICOLOGY

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 ± 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 ($P\leq0.05$) difference for one dose point and a significant trend ($P\leq0.015$) 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 μL) 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_1 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 $B6C3F_1$ 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 μg/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$_1$ mice exposed to hexachlorocyclopentadiene by inhalation for 13 weeks (Table F5).

TABLE F1
Mutagenicity of Hexachlorocyclopentadiene in *Salmonella typhimurium*[a]

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

TABLE F1
Mutagenicity of Hexachlorocyclopentadiene in *Salmonella typhimurium* (continued)

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

[a] Study performed at SRI, International. The detailed protocol and these data are presented in Haworth *et al.* (1983).
[b] Revertants are presented as mean ± standard error from three plates. All trials were repeated. Because the data are published elsewhere, only one trial per experimental condition is presented here.
[c] 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[a]

Compound	Dose μg/mL	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Trial 1								
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[c]
Trial 2								
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*
	0.10	50	1,041	468	0.44	9.4	26.0	22.78*
	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*
								P<0.001
+S9								
Trial 1								
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≤0.01)
[a] 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).
[b] SCEs/chromosome of culture exposed to hexachlorocyclopentadiene relative to those of culture exposed to solvent
[c] 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[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1 - Harvest time: 12.0 hours Summary: Weakly Positive					**Trial 1** - Harvest time: 13.0 hours 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[b]	0	0.00	0.0	10.0	136[b]	43	0.32	21.3*
				P=0.011[c]					P<0.001
					Trial 2 - Harvest time 13.0 hours 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≤0.05)

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

[b] Due to severe chemical-induced toxicity, fewer than 200 cells could be scored for aberrations.

[c] 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[a]

Route of Exposure	Dose (ppm)	Incidence of Deaths (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			
				Mating 1	Mating 2	Mating 3	Total[b]
Study 1							
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%)
Study 2							
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%)

[a] 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).
[b] 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[a]

Dose (ppm)	Micronucleated Cells/1,000 Cells PCE	NCE	PCE (%)[b]
Male			
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[c]	P=0.467	P=0.848	
ANOVA[d]			P=0.146
Female			
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	P=0.968	P=0.312	
ANOVA			P=0.191

[a] 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).

[b] Percent PCEs among total erythrocyte population

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

[d] Exposed groups do not differ from the control by *t*-test on ranks.

APPENDIX G
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
Male				
n	10	10	10	10
Necropsy body wt	344 ± 5	330 ± 8	329 ± 9	319 ± 7*
Adrenal Gland				
Absolute	0.042 ± 0.002	0.041 ± 0.005[b]	0.038 ± 0.003	0.045 ± 0.003
Relative	0.12 ± 0.00	0.13 ± 0.01[b]	0.12 ± 0.01	0.14 ± 0.01
Brain				
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
Heart				
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**
R. Kidney				
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*
Liver				
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
Lungs				
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**
R. Testis				
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**
Thymus				
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
Female				
n	10	10	10	10
Necropsy body wt	195 ± 6	191 ± 4	198 ± 3	190 ± 3
Adrenal Gland				
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
Brain				
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
Heart				
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
R. Kidney				
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
Liver				
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
Lungs				
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
Thymus				
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
** $P \leq 0.01$
[a] 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.
[b] 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[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Male				
n	10	10	10	10
Necropsy body wt	485 ± 6	481 ± 7	462 ± 8	481 ± 6
Brain				
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
R. Kidney				
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
Liver				
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
Lungs				
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*
Female				
n	10	10	10	10
Necropsy body wt	310 ± 10	324 ± 9	324 ± 8	312 ± 6
Brain				
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
R. Kidney				
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
Liver				
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
Lungs				
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
** $P \leq 0.01$
[a] 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[a]

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
Male				
n	10	5	10	5
Necropsy body wt	31.4 ± 0.5	31.1 ± 0.8	29.3 ± 0.5**	29.1 ± 0.5*
Adrenal Gland				
Absolute	0.002 ± 0.000[b]	0.003 ± 0.000*[c]	0.003 ± 0.000*	0.003 ± 0.000
Relative	0.07 ± 0.01[b]	0.10 ± 0.01*[c]	0.10 ± 0.01*	0.10 ± 0.02*
Brain				
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
Heart				
Absolute	0.141 ± 0.005	0.143 ± 0.007	0.145 ± 0.006[b]	0.144 ± 0.009
Relative	4.50 ± 0.15	4.47 ± 0.20	4.92 ± 0.22[b]	4.96 ± 0.26
R. Kidney				
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
Liver				
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*
Lungs				
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**
R. Testis				
Absolute	0.118 ± 0.002[b]	0.130 ± 0.009	0.113 ± 0.003	0.117 ± 0.003
Relative	3.80 ± 0.08[b]	4.20 ± 0.38	3.85 ± 0.10	4.02 ± 0.04
Thymus				
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
Female				
n	4	9	9	8
Necropsy body wt	25.3 ± 1.3	25.0 ± 0.8	24.3 ± 0.3	23.5 ± 0.5
Adrenal Gland				
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
Brain				
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
Heart				
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
R. Kidney				
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
Liver				
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
Lungs				
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
Thymus				
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≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] 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.
[b] n=9
[c] 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[a]

	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≤0.05) from the control group by Williams' or Dunnett's test
[a] 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[a]

	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≤0.01) from the control group by Williams' or Dunnett's test
[a] 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[a]

	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
** $P \leq 0.01$
[a] 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[a]

	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[b]	1.888 ± 0.064	1.684 ± 0.058*	1.668 ± 0.120**
Relative	49.08 ± 3.03[b]	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
** $P \leq 0.01$
[a] 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).
[b] 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[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Male				
n	10	10	10	10
Necropsy body wt	42.5 ± 1.3	40.7 ± 1.4	42.7 ± 1.4	40.8 ± 1.7
Brain				
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
R. Kidney				
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
Liver				
Absolute	2.054 ± 0.084[b]	1.774 ± 0.101	1.907 ± 0.082	1.739 ± 0.055*
Relative	49.08 ± 3.03[b]	43.59 ± 2.11	44.95 ± 2.40	42.87 ± 0.71
Lungs				
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
Female				
n	10	10	10	10
Necropsy body wt	45.1 ± 1.5	39.4 ± 1.5*	41.0 ± 1.7*	37.9 ± 1.6**
Brain				
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**
R. Kidney				
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
Liver				
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
Lungs				
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
** $P \leq 0.01$
[a] 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).
[b] n=9

APPENDIX H
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE H1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
Male				
n	10	10	10	10
Hematology				
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 (10^6/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 (10^6/μL)	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.1 ± 0.0
Leukocytes (10^3/μL)	3.79 ± 0.11	3.29 ± 0.17	3.72 ± 0.29	3.59 ± 0.25
Segmented neutrophils (10^3/μL)	1.12 ± 0.15	0.95 ± 0.08	1.17 ± 0.18	0.94 ± 0.08
Lymphocytes (10^3/μL)	2.55 ± 0.12	2.27 ± 0.16	2.47 ± 0.17	2.51 ± 0.19
Monocytes (10^3/μL)	0.07 ± 0.01	0.03 ± 0.01**	0.03 ± 0.01**[b]	0.08 ± 0.02
Eosinophils (10^3/μL)	0.04 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.05 ± 0.01
Clinical Chemistry				
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[b]	84 ± 3**	88 ± 2**	92 ± 3**
Lactate dehydrogenase (IU/L)	941 ± 136	711 ± 68	717 ± 36	670 ± 70
Female				
n	10	10	10	10
Hematology				
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 (10^6/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 (10^6/μL)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0[b]	0.1 ± 0.0
Leukocytes (10^3/μL)	3.52 ± 0.24	3.20 ± 0.18	3.47 ± 0.26	3.20 ± 0.19
Segmented neutrophils (10^3/μL)	0.87 ± 0.09	0.73 ± 0.05	0.70 ± 0.06[b]	0.69 ± 0.10
Lymphocytes (10^3/μL)	2.58 ± 0.19	2.42 ± 0.16	2.54 ± 0.19	2.44 ± 0.15
Monocytes (10^3/μL)	0.04 ± 0.01	0.04 ± 0.00	0.03 ± 0.01	0.02 ± 0.01
Eosinophils (10^3/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
Female (continued)				
n	10	10	10	10
Clinical Chemistry				
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≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. No data were collected for 1 and 2 ppm males and females due to 100% mortality.
[b] n=9

TABLE H2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
Male				
Hematology				
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 (10^6/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 (10^6/μL)				
Week 13	0.2 ± 0.0	0.2 ± 0.1	0.1 ± 0.0	
Leukocytes (10^3/μL)				
Week 13	4.35 ± 0.31	4.58 ± 0.44	4.16 ± 0.41	
Segmented neutrophils (10^3/μL)				
Week 13	1.08 ± 0.19	1.23 ± 0.11	1.02 ± 0.15	
Lymphocytes (10^3/μL)				
Week 13	3.16 ± 0.34	3.20 ± 0.39	3.04 ± 0.36	
Monocytes (10^3/μL)				
Week 13	0.04 ± 0.02	0.08 ± 0.04	0.05 ± 0.02	
Eosinophils (10^3/μL)				
Week 13	0.07 ± 0.03	0.07 ± 0.01	0.05 ± 0.01	
Clinical Chemistry				
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[b]	19.0 ± 0.9	19.6 ± 1.5	98.5 ± 28.5*[c]
Day 46	21.0 ± 1.2	18.8 ± 0.9	24.6 ± 1.9	–[d]
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*[b]
Day 16	0.80 ± 0.06[b]	0.73 ± 0.04	0.73 ± 0.01	0.72 ± 0.06[c]
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[b]	218 ± 26	201 ± 7	52 ± 19[c]
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
Male (continued)				
Clinical Chemistry (continued)				
n	5	5	5	5
Albumin (g/dL)				
Day 4	3.7 ± 0.2	4.0 ± 0.1	3.9 ± 0.1	4.0 ± 0.1
Day 16	4.0 ± 0.0[b]	4.0 ± 0.2	4.0 ± 0.1	3.3 ± 0.2[c]
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	–
Alanine aminotransferase (IU/L)				
Day 4	37 ± 3	38 ± 5	33 ± 3	485 ± 301[b]
Day 16	33 ± 3[b]	35 ± 2	31 ± 1	290 ± 186[c]
Day 46	36 ± 4	31 ± 1	39 ± 2	–
Week 13	44 ± 2	41 ± 3	39 ± 3	–
Aspartate aminotransferase (IU/L)				
Day 4	93 ± 10	100 ± 16	96 ± 8	711 ± 444*[b]
Day 16	80 ± 2[b]	85 ± 5	85 ± 2	304 ± 151*[c]
Day 46	94 ± 7	83 ± 5	94 ± 4	–
Week 13	122 ± 5	109 ± 9	98 ± 10*	–
Lactate dehydrogenase (IU/L)				
Day 4	737 ± 202	972 ± 361	625 ± 109	2,246 ± 1,095[b]
Day 16	765 ± 83[b]	706 ± 166	757 ± 68	832 ± 82[c]
Day 46	871 ± 122	773 ± 114	753 ± 127	–
Week 13	1,275 ± 182	1,110 ± 89	579 ± 81**	–
Urinalysis				
n	5	5	5	5
Osmolality (mOsm/kg)				
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[e]
Day 46	1,821 ± 75	1,458 ± 167	1,771 ± 89	–
Week 13	1,227 ± 65	959 ± 90	1,425 ± 37	–
Creatinine (mg/dL)				
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[e]
Day 46	98.56 ± 4.27	83.90 ± 3.28*	85.26 ± 3.36*	–
Week 13	104.26 ± 8.65	99.62 ± 9.11	110.58 ± 7.79	–
Creatinine (mg/100 g/16 hr)				
Day 4	3.14 ± 0.27	3.04 ± 0.20	1.77 ± 0.35*	0.88 ± 0.13**
Day 16	2.66 ± 0.25	2.36 ± 0.13	2.73 ± 0.20	0.29[e]
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
Male (continued)				
Urinalysis (continued)				
n	5	5	5	5
Glucose (mg/dL)				
Day 4	40 ± 5	40 ± 6	48 ± 9	46 ± 5[b]
Day 16	72 ± 4[b]	46 ± 11	53 ± 4	106[e]
Day 46	64 ± 4	59 ± 5	55 ± 7	–
Week 13	23 ± 4	18 ± 3	37 ± 4	–
Glucose (mg/100 g/16 hr)				
Day 4	2.2 ± 0.3	2.1 ± 0.2	1.2 ± 0.2*	0.5 ± 0.1**[b]
Day 16	2.5 ± 0.2[b]	1.5 ± 0.2*	1.8 ± 0.2*	0.4[e]
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	–
Protein (mg/dL)				
Day 4	48 ± 10	40 ± 9	34 ± 13	97 ± 45[b]
Day 16	145 ± 8	118 ± 36	135 ± 4[b]	240[e]
Day 46	163 ± 11	145 ± 8	188 ± 24	–
Week 13	129 ± 10	110 ± 20	224 ± 46	–
Protein (mg/100 g/16 hr)				
Day 4	3 ± 1	2 ± 0	1 ± 0*	1 ± 1[b]
Day 16	5 ± 1	4 ± 1	4 ± 1	1[e]
Day 46	4 ± 0	4 ± 0	6 ± 0	–
Week 13	4 ± 2	2 ± 0	4 ± 0	–
Volume (mL/16 hr)				
Day 4	7.9 ± 1.4	7.1 ± 1.4	4.0 ± 1.4	1.0 ± 0.1**[b]
Day 16	7.0 ± 0.9	6.3 ± 0.6	5.7 ± 0.5	0.2 ± 0.1*[c]
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	–
Female				
Hematology				
n	5	5	5	
Packed cell volume (%)				
Week 13	37.3 ± 1.4	41.1 ± 1.0	41.9 ± 0.7**	
Hemoglobin (g/dL)				
Week 13	14.1 ± 0.6	15.6 ± 0.4	15.8 ± 0.3*	
Erythrocytes ($10^6/\mu L$)				
Week 13	7.35 ± 0.32	8.08 ± 0.20	8.16 ± 0.17*	
Mean cell volume (fL)				
Week 13	51.2 ± 0.2	51.0 ± 0.0	52.2 ± 0.4*	
Mean cell hemoglobin (pg)				
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
Female (continued)				
Hematology (continued)				
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 ($10^6/\mu L$)				
Week 13	0.15 ± 0.02	0.14 ± 0.01	0.09 ± 0.02*	
Leukocytes ($10^3/\mu L$)				
Week 13	2.54 ± 0.24	3.14 ± 0.22	3.38 ± 0.45	
Segmented neutrophils ($10^3/\mu L$)				
Week 13	0.63 ± 0.07	0.75 ± 0.07	0.63 ± 0.15	
Lymphocytes ($10^3/\mu L$)				
Week 13	1.87 ± 0.21	2.30 ± 0.26	2.68 ± 0.33	
Monocytes ($10^3/\mu L$)				
Week 13	0.02 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	
Eosinophils ($10^3/\mu L$)				
Week 13	0.01 ± 0.00[b]	0.04 ± 0.01	0.03 ± 0.01	
Clinical Chemistry				
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[b]	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[b]	0.77 ± 0.02	0.76 ± 0.04[b]	–
Week 13	0.79 ± 0.03[b]	0.89 ± 0.18[b]	0.70 ± 0.03[f]	–
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[b]	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[b]	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[b]	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
Female (continued)				
Clinical Chemistry (continued)				
n	5	5	5	3
Aspartate aminotransferase (IU/L)				
Day 4	86 ± 5	91 ± 6	99 ± 6	153 ± 37*
Day 16	86 ± 7	79 ± 4	76 ± 2	–
Day 46	90 ± 3[b]	90 ± 5	94 ± 7	–
Week 13	107 ± 15	100 ± 13	89 ± 6	–
Lactate dehydrogenase (IU/L)				
Day 4	563 ± 111	798 ± 102	884 ± 82	825 ± 168
Day 16	925 ± 194	767 ± 142	469 ± 52*	–
Day 46	1,009 ± 148[b]	785 ± 205	807 ± 119	–
Week 13	858 ± 187	629 ± 101	584 ± 128	–
Urinalysis				
n	5	5	5	3
Osmolality (mOsm/kg)				
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*[b]	–
Day 46	2,089 ± 148[b]	1,450 ± 158*[b]	1,533 ± 175*	–
Week 13	1,516 ± 163	1,582 ± 205	1,552 ± 154	–
Creatinine (mg/dL)				
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*[b]	–
Day 46	108.35 ± 5.20[b]	67.40 ± 10.00*[b]	67.38 ± 5.49*	–
Week 13	71.02 ± 7.45	76.26 ± 11.57	72.36 ± 7.98	–
Creatinine (mg/100 g/16 hr)				
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*[b]	–
Day 46	2.45 ± 0.14[b]	2.26 ± 0.46[b]	2.69 ± 0.34	–
Week 13	3.04 ± 0.17	2.47 ± 0.27	2.41 ± 0.27	–
Glucose (mg/dL)				
Day 4	26 ± 5	35 ± 3	38 ± 6	70 ± 0**[c]
Day 16	25 ± 3	37 ± 5	47 ± 5*[b]	–
Day 46	55 ± 7[b]	48 ± 17[b]	30 ± 3*	–
Week 13	26 ± 4	30 ± 8	28 ± 4	–
Glucose (mg/100 g/16 hr)				
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[b]	–
Day 46	1.2 ± 0.1[b]	1.5 ± 0.4[b]	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
Female (continued)				
Urinalysis (continued)				
n	5	5	5	3
Protein (mg/dL)				
Day 4	15 ± 3	17 ± 3	33 ± 16	20
Day 16	6 ± 1[b]	22 ± 9*	13 ± 3[f]	–
Day 46	19 ± 8[b]	33 ± 7[f]	23 ± 3	–
Week 13	13 ± 3[b]	22 ± 10	27 ± 7	–
Protein (mg/100 g/16 hr)				
Day 4	1 ± 0	1 ± 0	1 ± 0	0
Day 16	1 ± 0	1 ± 0	0 ± 0[f]	–
Day 46	0 ± 0[b]	3 ± 2*[b]	1 ± 0	–
Week 13	1 ± 0[b]	1 ± 0	1 ± 0	–
Volume (mL/16 hr)				
Day 4	6.6 ± 1.0	6.0 ± 1.1	3.6 ± 0.7	0.8 ± 0.2**
Day 16	8.1 ± 0.8	5.2 ± 0.6*	4.3 ± 0.7**	–
Day 46	3.5 ± 0.3[b]	6.2 ± 2.1[b]	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
** $P \leq 0.01$
[a] Mean ± standard error. No hematology data were collected for 2 ppm males and females.
[b] n=4
[c] n=2
[d] No data collected due to 100% mortality in 2 ppm males after week 2 and 2 ppm females after week 1.
[e] No standard error was calculated due to high mortality.
[f] n=3

TABLE H3
Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Male				
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*
Female				
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
[a] Mean ± standard error

TABLE H4
Hematology and Clinical Chemistry Data for Mice in the 13-Week Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.04 ppm	0.15 ppm	0.4 ppm
Male				
Hematology				
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 ($10^6/\mu L$)	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 ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	3.89 ± 0.42	3.99 ± 0.59	4.48 ± 0.39	3.80 ± 0.17
Segmented neutrophils ($10^3/\mu L$)	0.56 ± 0.09	0.77 ± 0.25	0.70 ± 0.09[b]	0.67 ± 0.12
Lymphocytes ($10^3/\mu L$)	3.24 ± 0.35	3.16 ± 0.39	3.39 ± 0.29	3.01 ± 0.09
Monocytes ($10^3/\mu L$)	0.02 ± 0.01	0.02 ± 0.01	0.05 ± 0.01	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.06 ± 0.02	0.04 ± 0.01	0.05 ± 0.01	0.11 ± 0.02
Clinical Chemistry				
n	9	7	10	4
Urea nitrogen (mg/dL)	29.2 ± 1.7	30.3 ± 1.3[c]	30.8 ± 1.5	29.6 ± 1.7[d]
Creatinine (mg/dL)	0.67 ± 0.05[c]	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[d]	138 ± 33	70 ± 10[e]	145 ± 40
Aspartate aminotransferase (IU/L)	119 ± 19[c]	113 ± 11	148 ± 49[c]	194 ± 73
Female				
Hematology				
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 ($10^6/\mu L$)	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 ($10^6/\mu L$)	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	3.65 ± 0.47	5.73 ± 0.26**	4.93 ± 0.33	4.44 ± 0.38
Segmented neutrophils ($10^3/\mu L$)	1.05 ± 0.19	0.97 ± 0.07	0.75 ± 0.18	0.84 ± 0.11
Lymphocytes ($10^3/\mu L$)	2.59 ± 0.28	4.65 ± 0.29**	4.11 ± 0.30	3.49 ± 0.34
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.05 ± 0.02	0.03 ± 0.01	0.04 ± 0.01
Eosinophils ($10^3/\mu L$)	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
Female (continued)				
Clinical Chemistry				
n	4	7	9	7
Urea nitrogen (mg/dL)	19.8 ± 0.6	17.9 ± 0.6[b]	18.7 ± 0.8	19.8 ± 1.0[c]
Creatinine (mg/dL)	0.58 ± 0.06	0.74 ± 0.04[b]	0.70 ± 0.04	0.59 ± 0.06[c]
Glucose (mg/dL)	156 ± 14	153 ± 8	150 ± 9	134 ± 2
Albumin (g/dL)	3.7 ± 0.1	4.0 ± 0.1*	3.8 ± 0.1	3.6 ± 0.0
Alanine aminotransferase (IU/L)	97 ± 27	120 ± 21[f]	149 ± 29	148 ± 29
Aspartate aminotransferase (IU/L)	160 ± 6	218 ± 50[g]	217 ± 31	273 ± 39

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
a Mean ± standard error. No data were collected for 1 and 2 ppm males and females due to 100% mortality.
b n=9
c n=8
d n=5
e n=7
f n=4
g n=6

TABLE H5
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the Special 13-Week Inhalation Study of Hexachlorocyclopentadiene[a]

	0 ppm	0.04 ppm	0.4 ppm	2 ppm
Male				
Hematology				
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 ($10^6/\mu L$)				
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 ($10^6/\mu L$)				
Week 13	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	
Leukocytes ($10^3/\mu L$)				
Week 13	6.82 ± 0.65	6.12 ± 0.74	7.93 ± 0.77	
Segmented neutrophils ($10^3/\mu L$)				
Week 13	1.54 ± 0.37	0.66 ± 0.03[b]	1.61 ± 0.28	
Lymphocytes ($10^3/\mu L$)				
Week 13	5.14 ± 0.38	5.13 ± 0.72	6.08 ± 0.74	
Monocytes ($10^3/\mu L$)				
Week 13	0.08 ± 0.03	0.08 ± 0.04	0.06 ± 0.03	
Eosinophils ($10^3/\mu L$)				
Week 13	0.05 ± 0.02	0.05 ± 0.01	0.18 ± 0.04*	
Clinical Chemistry				
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[b]	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[b]	
Week 13	0.34 ± 0.10	0.31 ± 0.10[b]	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[b]	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
Male (continued)				
Clinical Chemistry (continued)				
n	5	5	5	
Albumin (g/dL)				
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[c]	3.5 ± 0.0[b]	3.4 ± 0.1	
Alanine aminotransferase (IU/L)				
Day 4	23 ± 5	114 ± 46*	89 ± 31*	
Day 16	50 ± 11[b]	225 ± 95	116 ± 59	
Day 46	72 ± 9	33 ± 4*	38 ± 3*	
Week 13	441 ± 52	338 ± 92[b]	267 ± 88	
Aspartate aminotransferase (IU/L)				
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[b]	190 ± 47*	
Lactate dehydrogenase (IU/L)				
Day 4	404 ± 21[b]	472 ± 141	745 ± 116	
Day 16	661 ± 226	989 ± 223	998 ± 253	
Day 46	696 ± 107	427 ± 79	410 ± 55	
Urinalysis				
n	5	5	5	
Osmolality (mOsm/kg)				
Day 4	2,528 ± 293[b]	2,203 ± 118	2,517 ± 95	
Day 16	2,276 ± 270[b]	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	
Creatinine (mg/dL)				
Day 4	53.15 ± 3.86[b]	47.30 ± 2.39	49.88 ± 1.04	
Day 16	53.00 ± 4.47[b]	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	
Creatinine (mg/100 g/16 hr)				
Day 4	2.07 ± 0.48[b]	1.34 ± 0.15[b]	3.97 ± 0.52	
Day 16	2.52 ± 0.53[b]	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
Male (continued)				
Urinalysis (continued)				
n	5	5	5	
Glucose (mg/dL)				
Day 4	160 ± 49[b]	169 ± 40	44 ± 3*[b]	
Day 16	107 ± 40[b]	47 ± 8	50 ± 4	
Day 46	46 ± 5	74 ± 25	89 ± 15*	
Week 13	54 ± 3[b]	66 ± 12	95 ± 31	
Glucose (mg/100 g/16 hr)				
Day 4	6 ± 2[b]	10 ± 4	4 ± 1	
Day 16	5 ± 2[b]	3 ± 1	2 ± 0	
Day 46	2 ± 0	3 ± 1	4 ± 1*	
Week 13	2 ± 0	3 ± 0	3 ± 1	
Protein (mg/dL)				
Day 4	295 ± 42[c]	151 ± 41*[c]	115 ± 31*	
Day 16	143 ± 30[b]	148 ± 19	148 ± 37	
Day 46	200 ± 54	250 ± 70	103 ± 18	
Week 13	159 ± 30[b]	159 ± 31	114 ± 21	
Protein (mg/100 g/16 hr)				
Day 4	13 ± 2[c]	7 ± 1[c]	8 ± 1	
Day 16	6 ± 1[b]	10 ± 1	7 ± 1	
Day 46	7 ± 1	10 ± 3	5 ± 1	
Week 13	5 ± 1[b]	6 ± 1	5 ± 1	
Volume (mL/16 hr)				
Day 4	0.9 ± 0.2[b]	0.6 ± 0.1[b]	1.8 ± 0.3	
Day 16	1.1 ± 0.2[b]	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	
Female				
Hematology				
n	2	5	5	
Packed cell volume (%)				
Week 13	42.6 ± 0.4	42.2 ± 1.2	41.6 ± 0.6	
Hemoglobin (g/dL)				
Week 13	15.5 ± 0.3	16.0 ± 0.5	15.9 ± 0.1	
Erythrocytes ($10^6/\mu L$)				
Week 13	8.93 ± 0.13	9.04 ± 0.24	9.02 ± 0.08	
Mean cell volume (fL)				
Week 13	48.5 ± 0.5	47.2 ± 0.2	46.6 ± 0.2*	
Mean cell hemoglobin (pg)				
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
Female (continued)				
Hematology (continued)				
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 (10^6/μL)				
Week 13	0.1 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	
Leukocytes (10^3/μL)				
Week 13	6.55 ± 0.65	5.82 ± 0.80	6.64 ± 0.60	
Segmented neutrophils (10^3/μL)				
Week 13	1.81 ± 0.31	0.93 ± 0.14	1.22 ± 0.21	
Lymphocytes (10^3/μL)				
Week 13	4.53 ± 0.34	4.79 ± 0.65	5.32 ± 0.55	
Monocytes (10^3/μL)				
Week 13	0.13 ± 0.01	0.03 ± 0.01	0.06 ± 0.03	
Eosinophils (10^3/μL)				
Week 13	0.08 ± 0.01	0.04 ± 0.02	0.04 ± 0.02	
Clinical Chemistry				
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[d]
Day 16	18.6 ± 0.8	21.0 ± 1.5	19.6 ± 1.1	–[e]
Day 46	21.5 ± 2.1[b]	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*[b]	0.37 ± 0.00[c]	0.24
Day 16	0.39 ± 0.02	0.39 ± 0.04	0.35 ± 0.08	–
Day 46	0.54 ± 0.07[b]	0.60 ± 0.07[c]	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[b]	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[b]	3.5 ± 0.1	3.6 ± 0.0[b]	–
Week 13	3.5 ± 0.1	3.5 ± 0.0[b]	3.6 ± 0.0	–
Alanine aminotransferase (IU/L)				
Day 4	102 ± 36	79 ± 25	63 ± 20	216
Day 16	37 ± 10[b]	45 ± 7	51 ± 15	–
Day 46	43 ± 7[b]	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
Female (continued)				
Clinical Chemistry (continued)				
n	5	5	5	1
Aspartate aminotransferase (IU/L)				
Day 4	121 ± 35	85 ± 3[b]	94 ± 11	192
Day 16	90 ± 13	99 ± 15	95 ± 20	–
Day 46	160 ± 57[b]	116 ± 24	86 ± 23	–
Week 13	271 ± 35	327 ± 99	263 ± 58	–
Lactate dehydrogenase (IU/L)				
Day 4	802 ± 202	517 ± 42[b]	768 ± 158	796
Day 16	613 ± 176	602 ± 115	609 ± 97	–
Day 46	604 ± 151[b]	458 ± 96	404 ± 57	–
Urinalysis				
n	5	5	5	
Osmolality (mOsm/kg)				
Day 4	2,897 ± 309	2,125 ± 322	3,308 ± 360	
Day 16	2,442 ± 274	2,798 ± 184[b]	2,868 ± 180	
Day 46	2,844 ± 280[b]	2,426 ± 264	2,860 ± 151	
Week 13	2,296 ± 394	2,791 ± 186	2,439 ± 243	
Creatinine (mg/dL)				
Day 4	49.84 ± 4.73	41.78 ± 5.40	58.43 ± 5.25[b]	
Day 16	55.22 ± 5.72	61.93 ± 4.56[b]	59.12 ± 3.53	
Day 46	57.23 ± 4.09[b]	46.44 ± 4.32	51.38 ± 2.64	
Week 13	57.36 ± 7.63	65.28 ± 2.56	53.68 ± 5.81	
Creatinine (mg/100 g/16 hr)				
Day 4	4.28 ± 0.28	2.67 ± 0.62	2.32 ± 0.48*[b]	
Day 16	3.90 ± 0.26	3.29 ± 0.61[b]	3.43 ± 0.36	
Day 46	3.15 ± 0.10[c]	2.62 ± 0.34	3.23 ± 0.47	
Week 13	3.89 ± 0.57	3.34 ± 0.27	4.32 ± 0.51	
Glucose (mg/dL)				
Day 4	170 ± 60	290 ± 98	121 ± 36[b]	
Day 16	116 ± 31	194 ± 63[b]	87 ± 16	
Day 46	80 ± 20[b]	120 ± 39	55 ± 5	
Week 13	78 ± 30	98 ± 31	47 ± 9	
Glucose (mg/100 g/16 hr)				
Day 4	10 ± 5	16 ± 3	5 ± 1[b]	
Day 16	8 ± 2	6 ± 1[b]	5 ± 1	
Day 46	5 ± 1[c]	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
Female (continued)				
Urinalysis (continued)				
n	5	5	5	
Protein (mg/dL)				
Day 4	85 ± 13	76 ± 15[b]	73 ± 17[c]	
Day 16	86 ± 16	104 ± 19[b]	83 ± 24	
Day 46	74 ± 17[b]	90 ± 16	45 ± 3	
Week 13	56 ± 13	98 ± 7*	46 ± 8	
Protein (mg/100 g/16 hr)				
Day 4	7 ± 1	6 ± 2[b]	3 ± 0*[c]	
Day 16	6 ± 0	5 ± 1[b]	4 ± 1	
Day 46	5 ± 1[c]	5 ± 1	3 ± 0	
Week 13	4 ± 1	5 ± 0	4 ± 1	
Volume (mL/16 hr)				
Day 4	1.6 ± 0.2	1.2 ± 0.2	0.6 ± 0.2*	
Day 16	1.5 ± 0.2	1.1 ± 0.2[b]	1.2 ± 0.2	
Day 46	1.5 ± 0.2[b]	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≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] 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.
[b] n=4
[c] n=3
[d] No standard error was calculated due to high mortality in this group.
[e] 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[a]

	0 ppm	0.01 ppm	0.05 ppm	0.2 ppm
Male				
n	7	10	8	10
Urinalysis				
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*
Female				
n	10	10	10	10
Urinalysis				
Volume (mL/16 hr)	1.6 ± 0.1	1.3 ± 0.1	1.5 ± 0.2	0.9 ± 0.1**[b]
Specific gravity	1.026 ± 0.001	1.025 ± 0.002	1.029 ± 0.001	1.030 ± 0.004

* Significantly different (P≤0.05) from the control group by Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9

APPENDIX I
CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS

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 ± 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^3. 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 μg. 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.

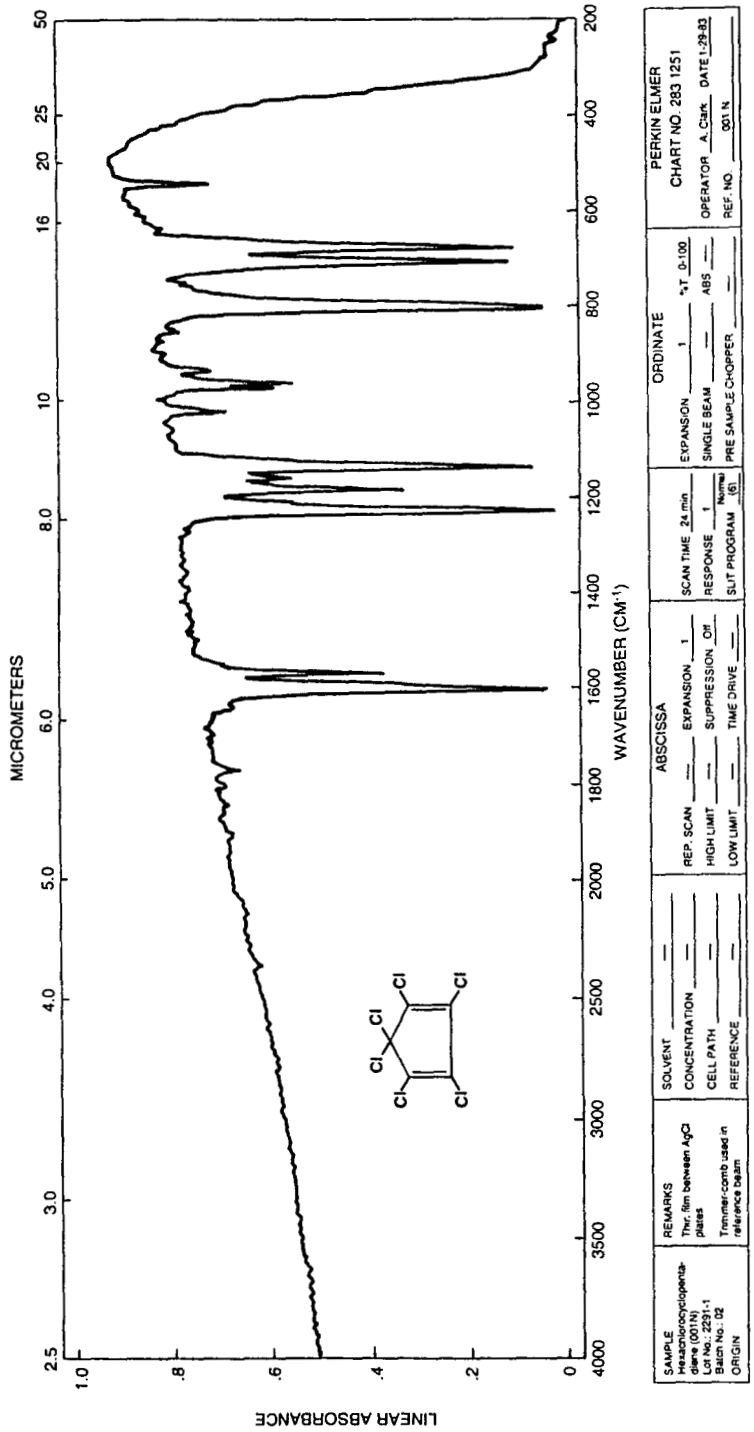

FIGURE I1
Infrared Absorption Spectrum of Hexachlorocyclopentadiene

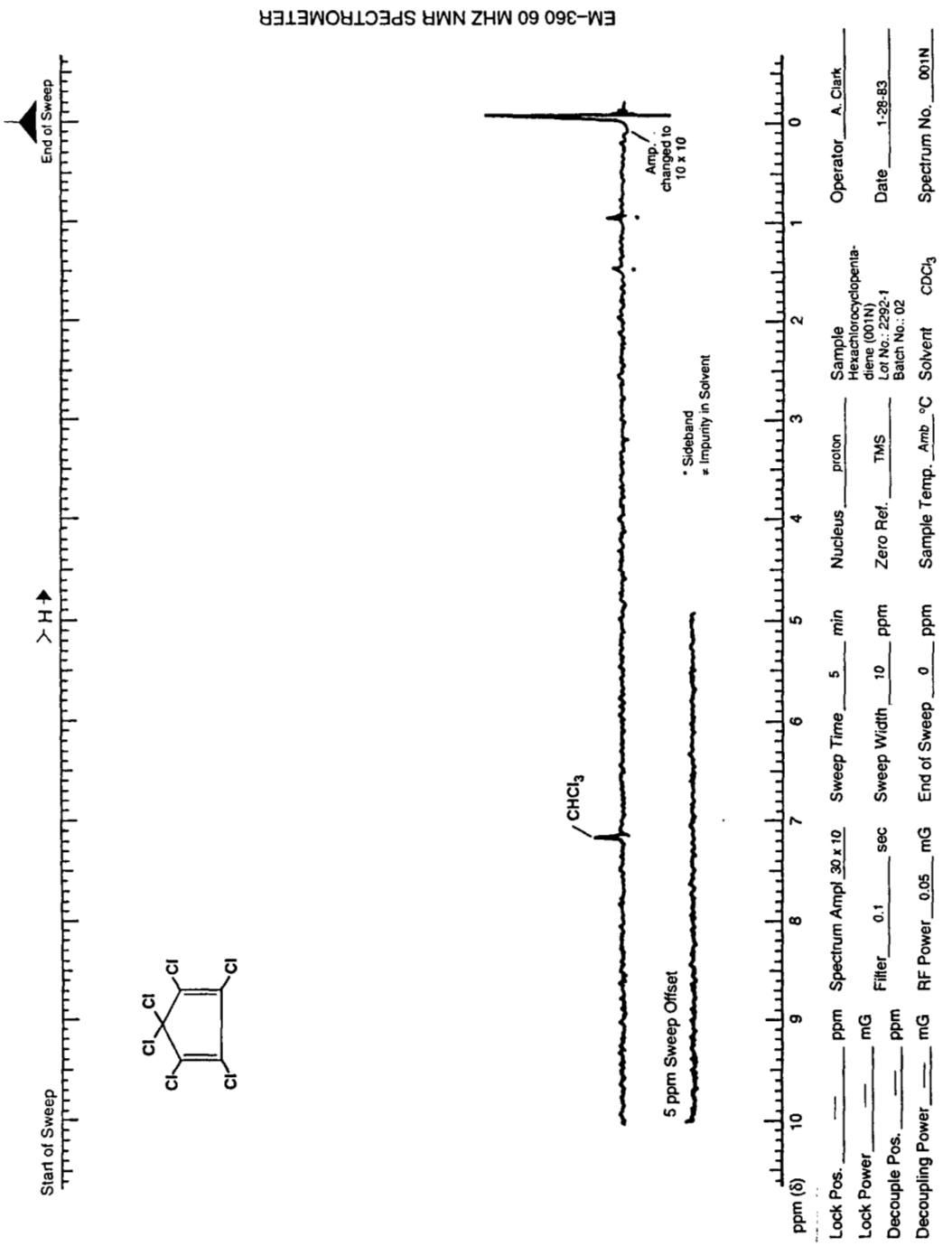

FIGURE I2
Nuclear Magnetic Resonance Spectrum of Hexachlorocyclopentadiene

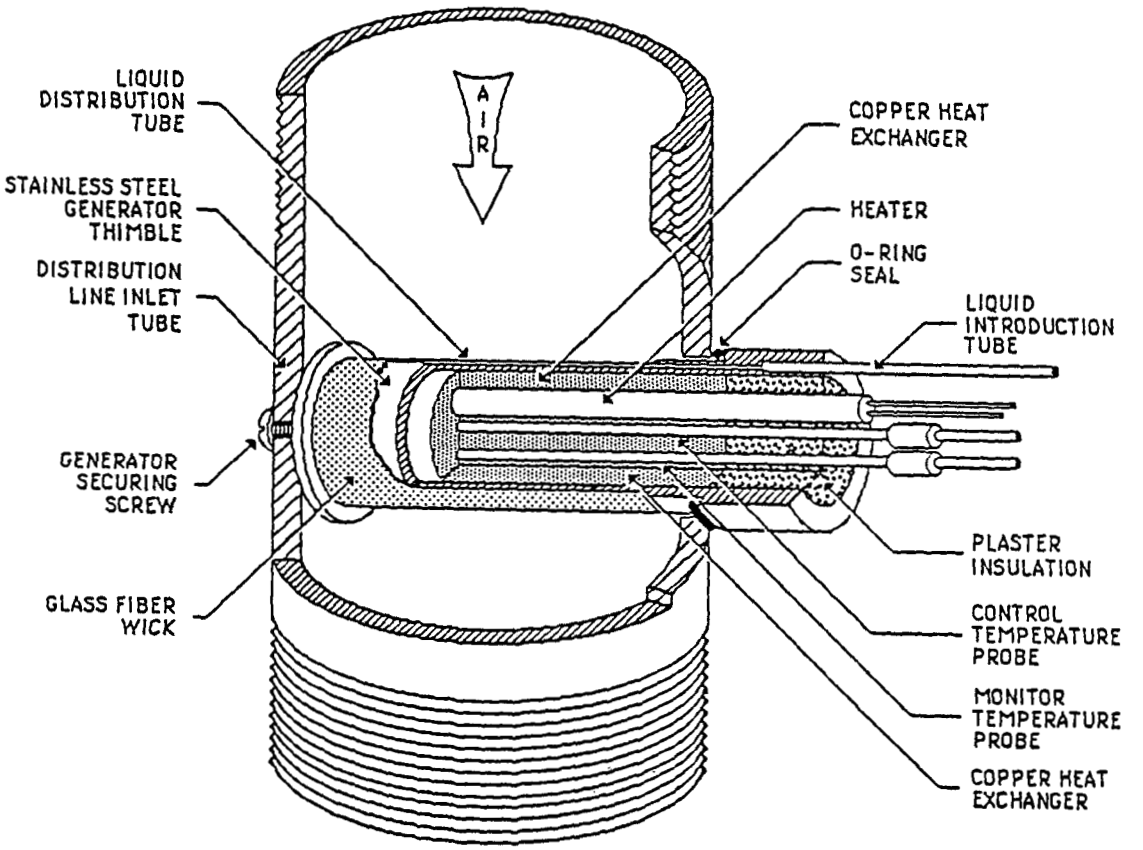

FIGURE I3a
Hexachlorocyclopentadiene Liquid Vapor Generator

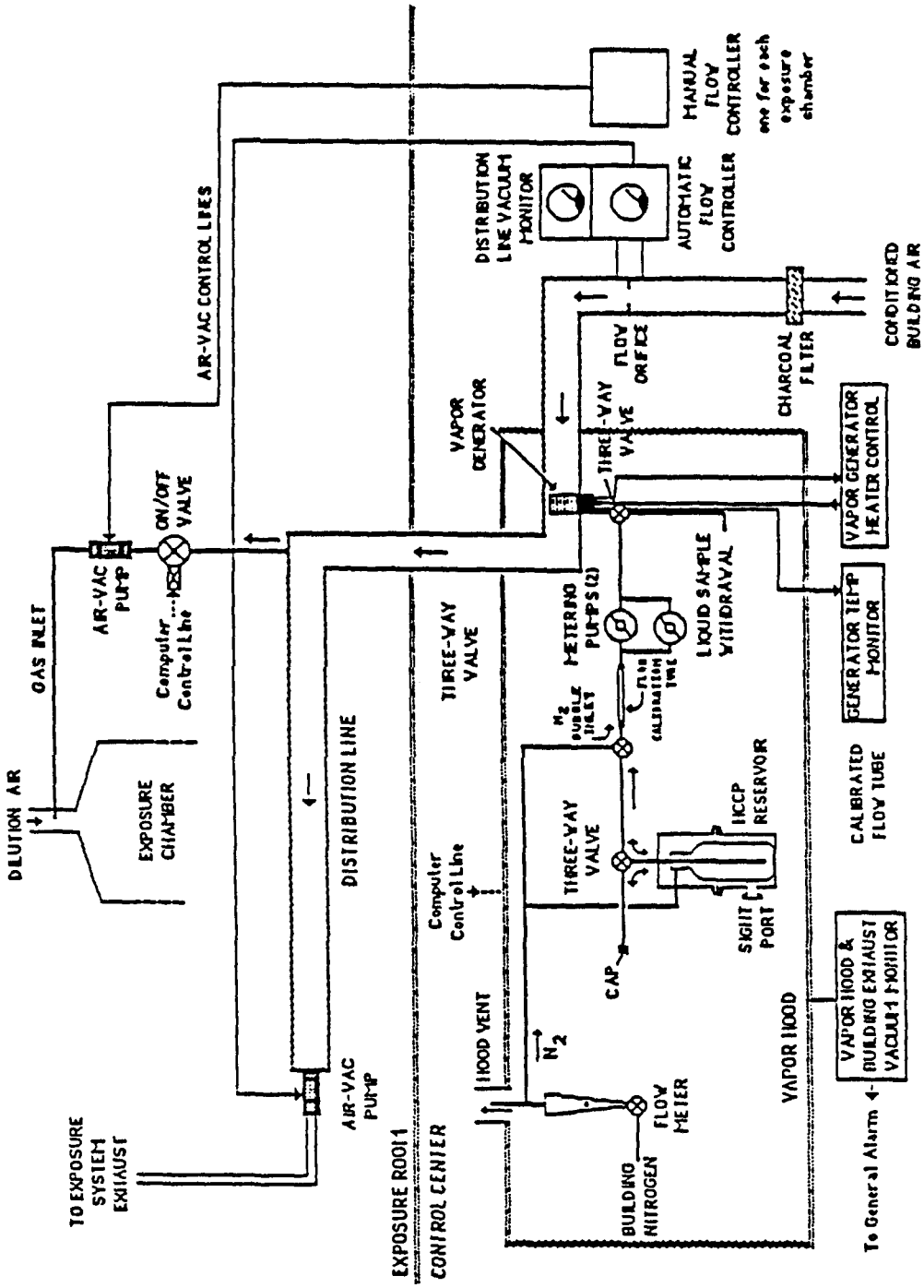

FIGURE I3b
Hexachlorocyclopentadiene Vapor Generation and Delivery System

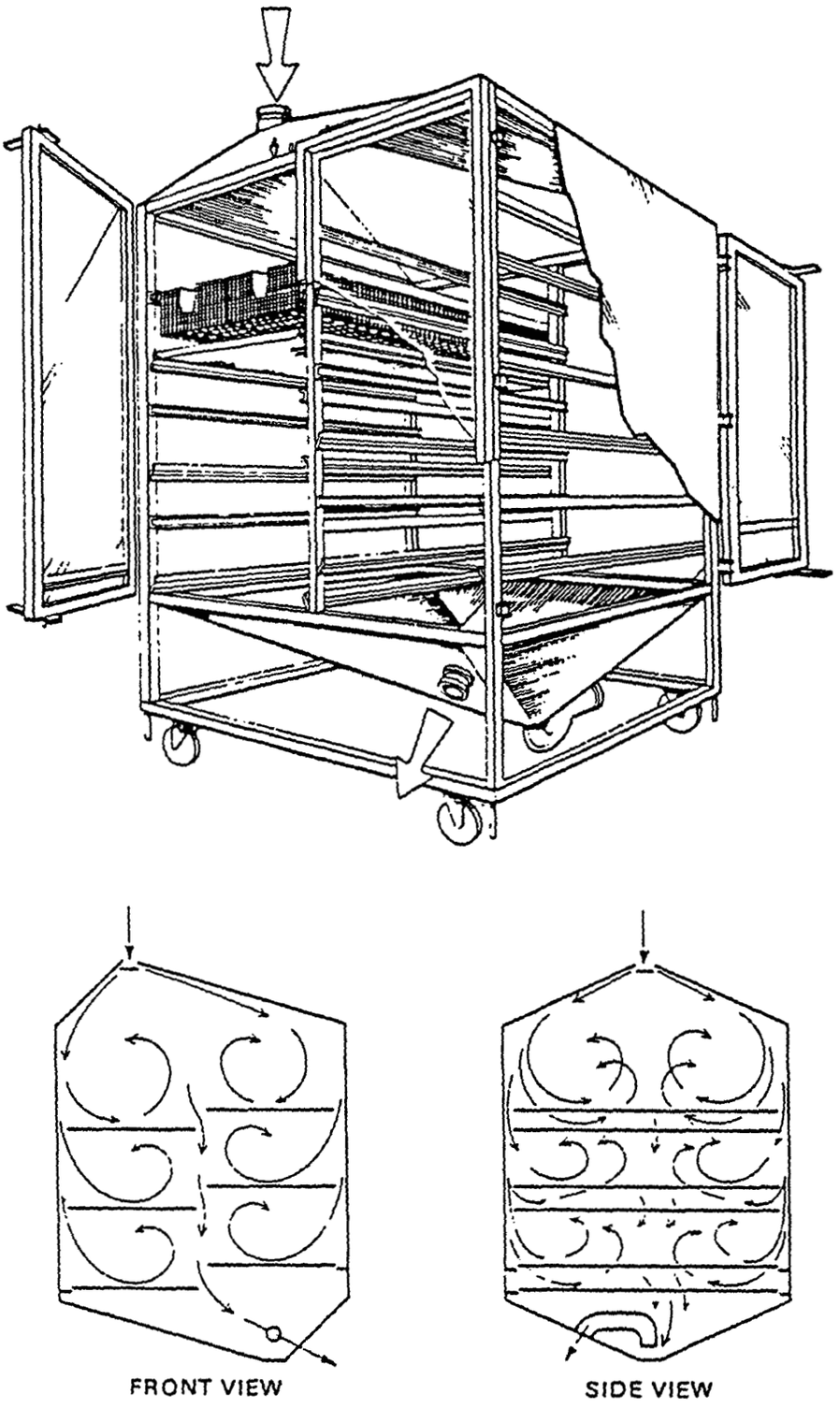

FIGURE I4
Hexachlorocyclopentadiene Inhalation Exposure Chamber

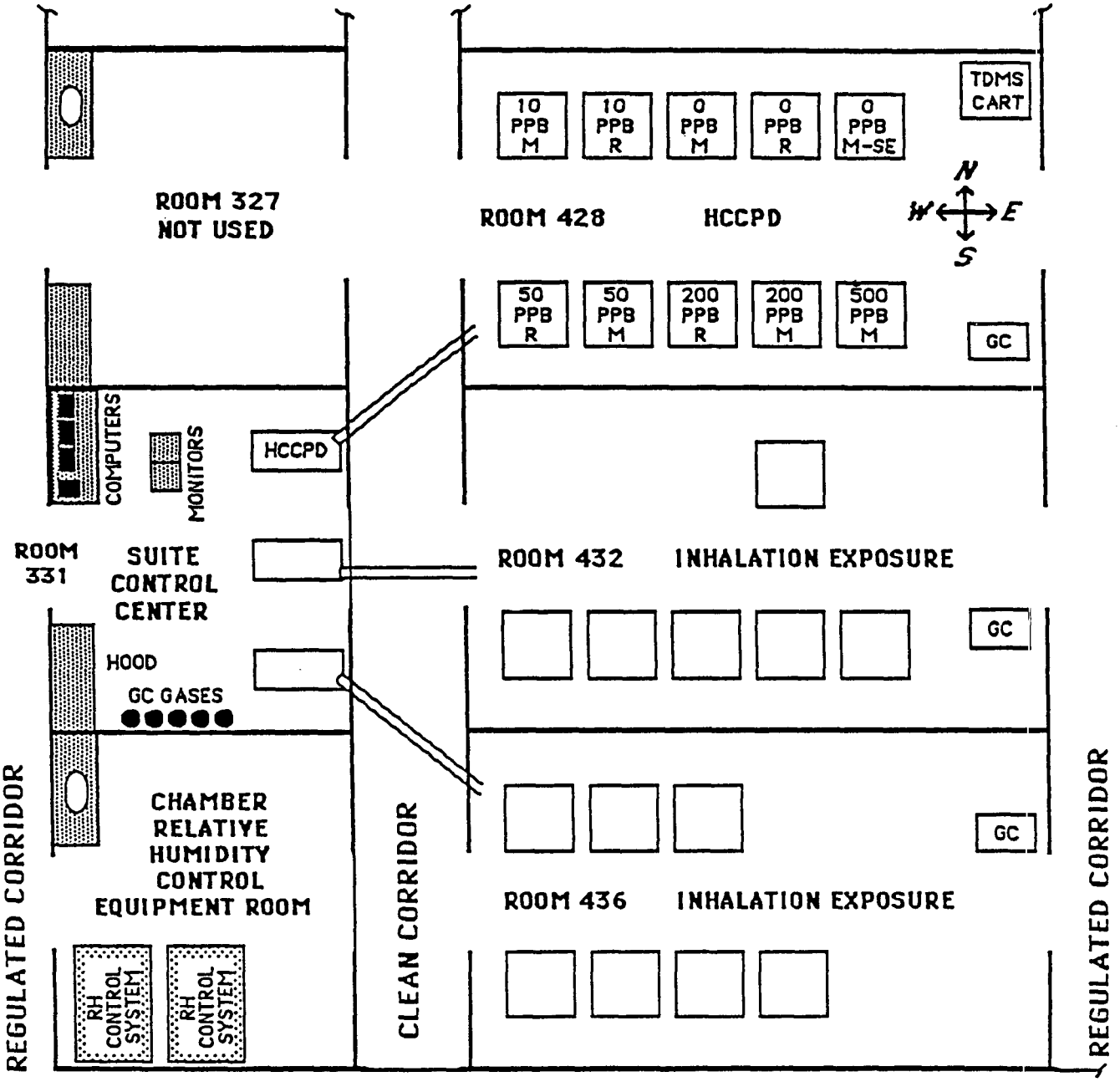

FIGURE I5
Hexachlorocyclopentadiene Exposure Suite

TABLE I1
Summary of Chamber Concentrations in the 13-Week Inhalation Studies of Hexachlorocyclopentadiene

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
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
Mouse Chambers		
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

[a] 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[a] (ppm)
Rat Chambers		
0.01	3,877	0.01 ± 0.00
0.05	4,137	0.05 ± 0.00
0.2	4,118	0.20 ± 0.01
Mouse Chambers		
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

[a] 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
Rat Chambers				
90-95	1	0	0	
95-100	6	7	7	
100-105	17	17	17	
105-110	0	0	0	
Mouse Chambers				
90-95	0	0	0	0
95-100	6	2	2	2
100-105	19	23	23	9
105-110	0	0	0	0

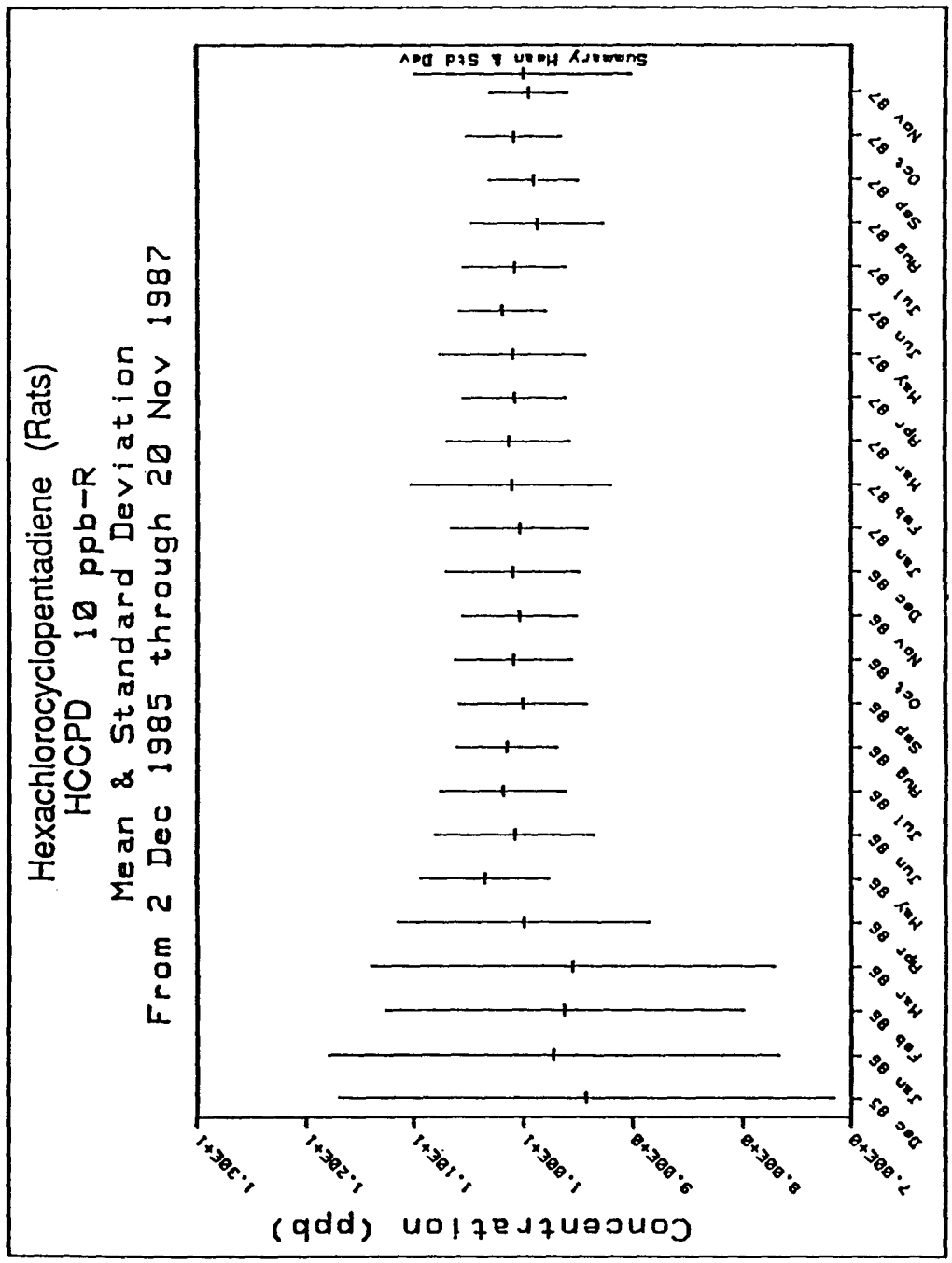

FIGURE I6
Monthly Mean Concentration and Standard Deviation in the 0.01 ppm Hexachlorocyclopentadiene Rat Exposure Chamber for the 2-Year Study

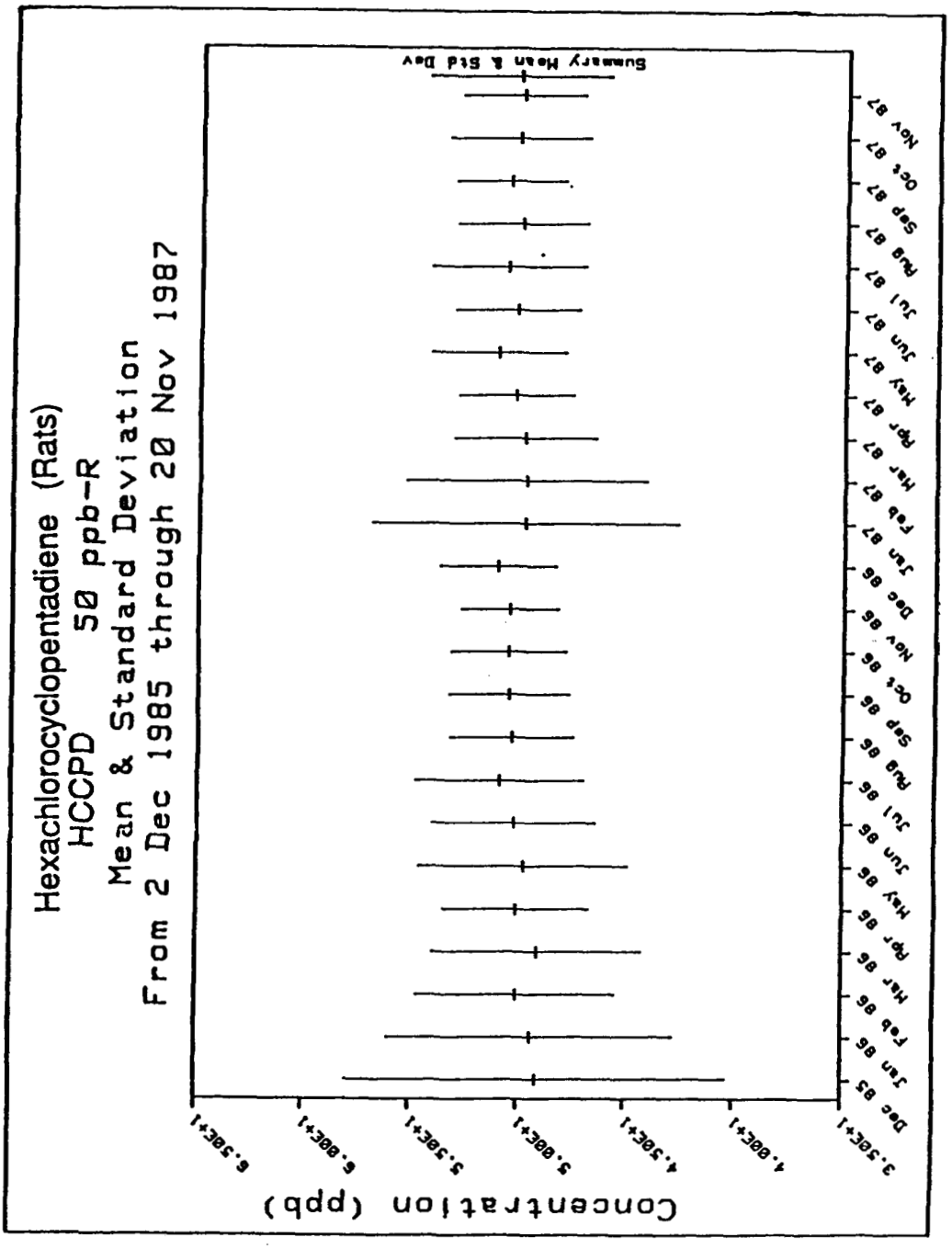

FIGURE I7
Monthly Mean Concentration and Standard Deviation in the 0.05 ppm Hexachlorocyclopentadiene Rat Exposure Chamber for the 2-Year Study

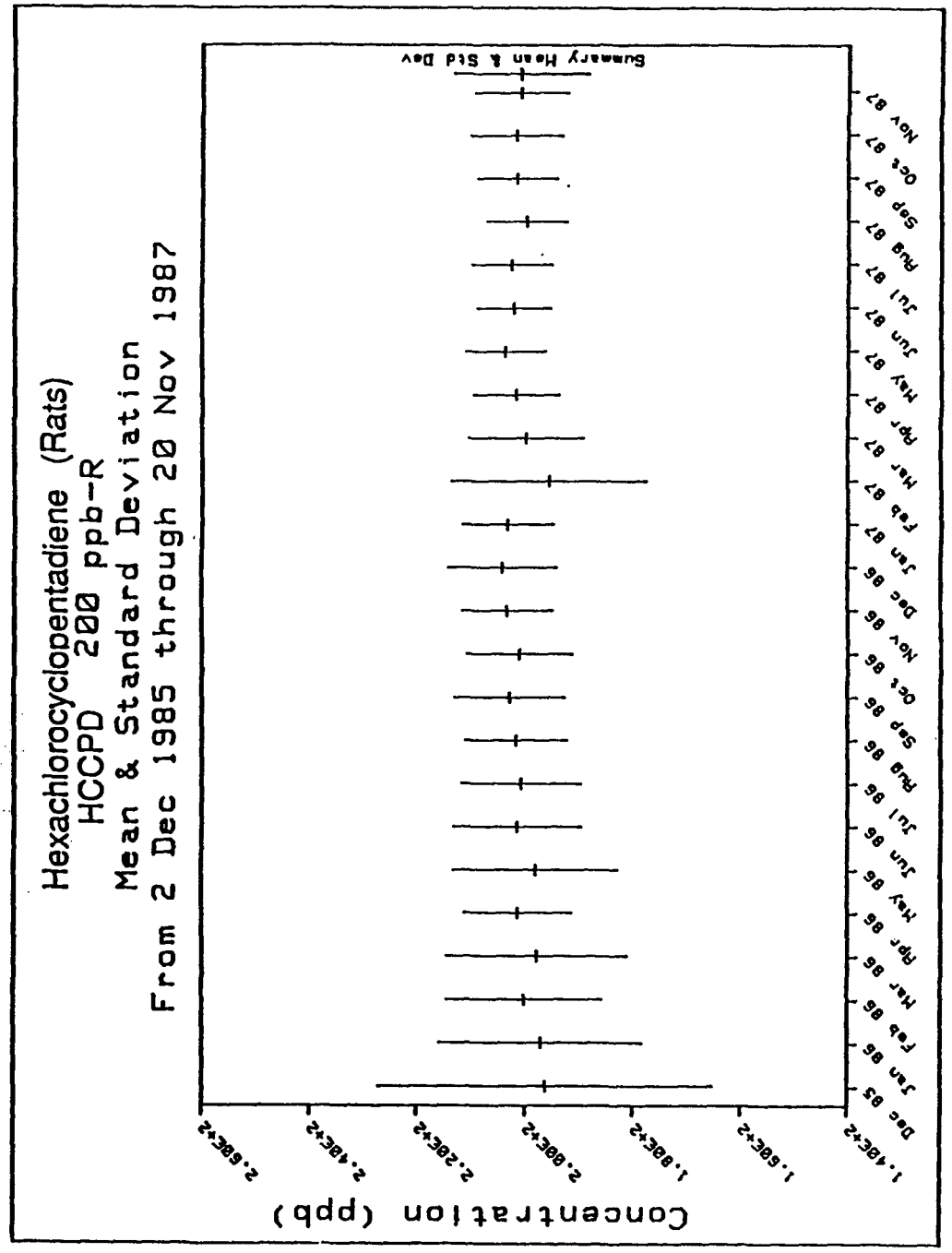

FIGURE I8
Monthly Mean Concentration and Standard Deviation in the 0.2 ppm Hexachlorocyclopentadiene Rat Exposure Chamber for the 2-Year Study

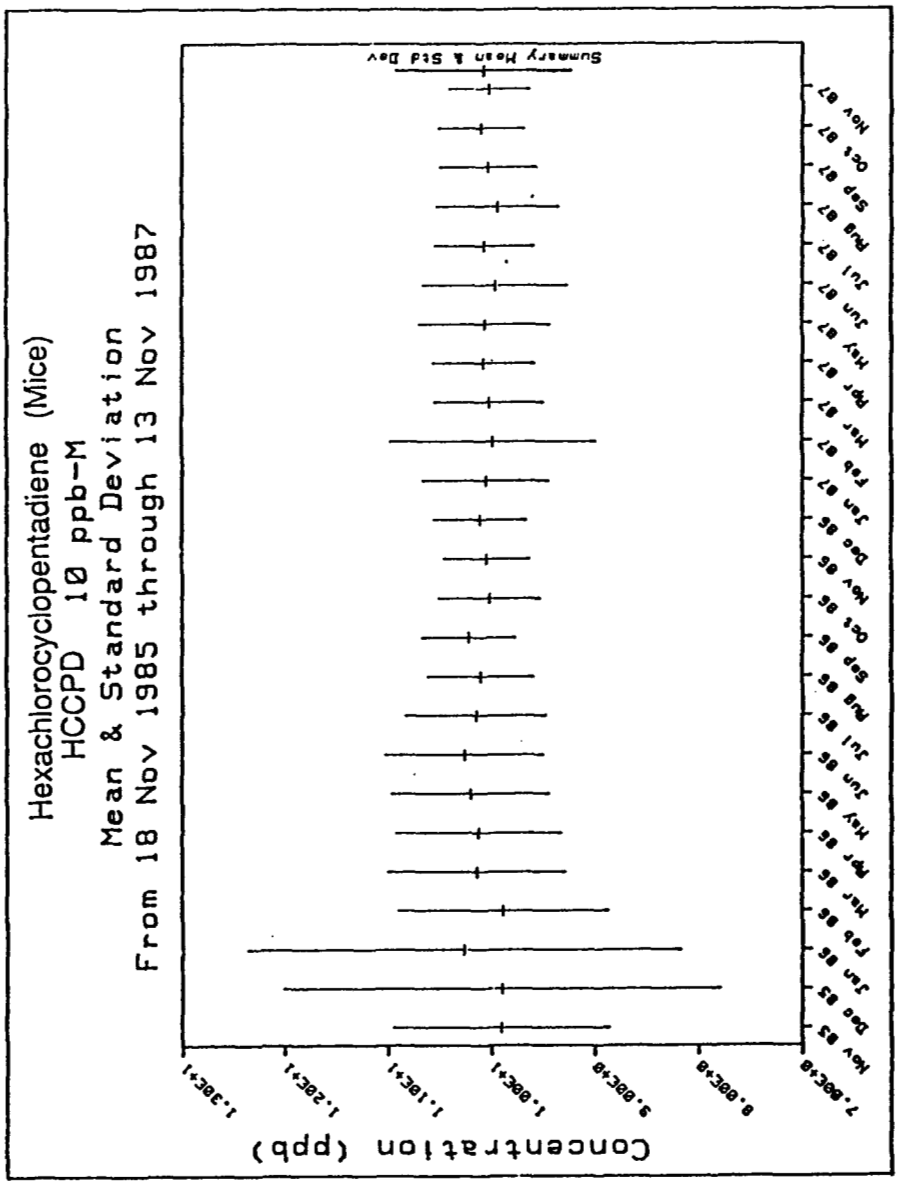

FIGURE I9
Monthly Mean Concentration and Standard Deviation in the 0.01 ppm Hexachlorocyclopentadiene Mouse Exposure Chamber for the 2-Year Study

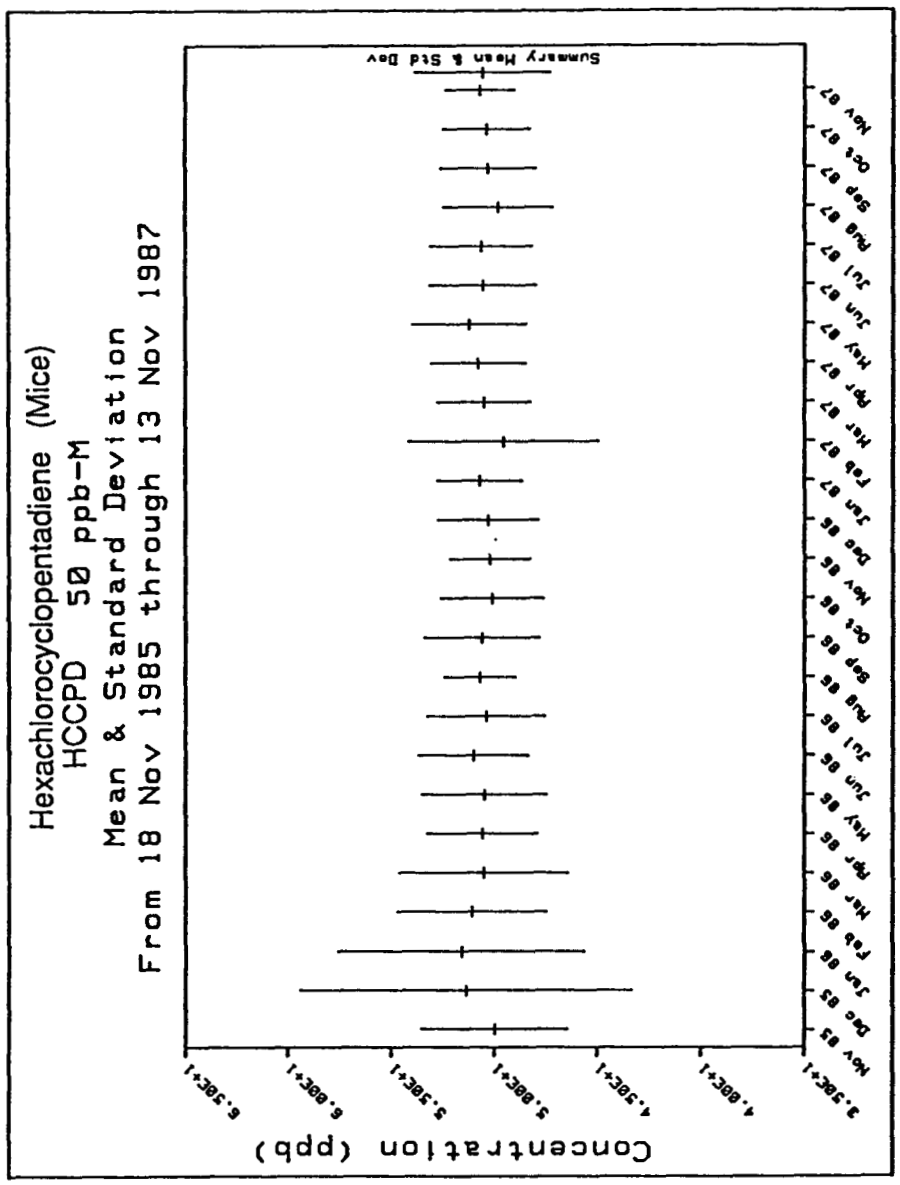

FIGURE I10
Monthly Mean Concentration and Standard Deviation in the 0.05 ppm Hexachlorocyclopentadiene Mouse Exposure Chamber for the 2-Year Study

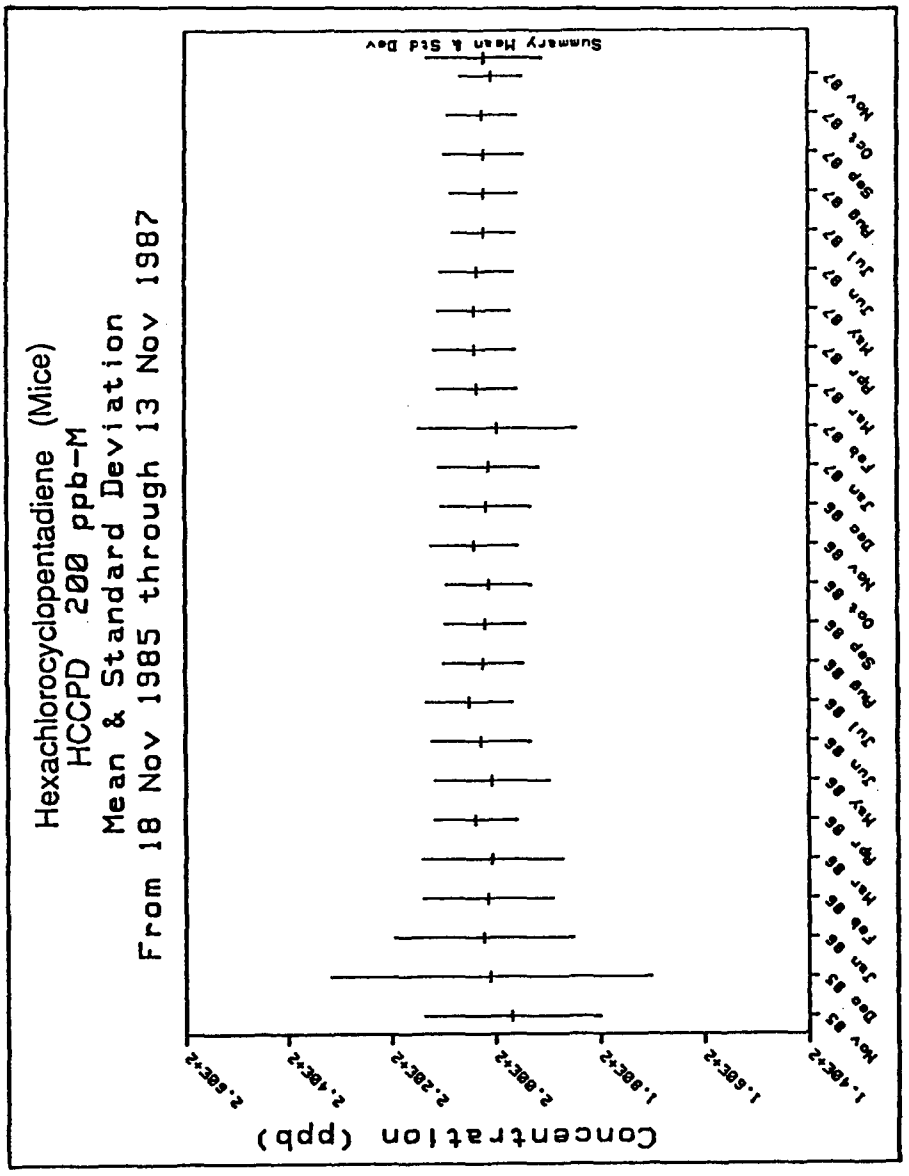

FIGURE I11
Monthly Mean Concentration and Standard Deviation in the 0.2 ppm Hexachlorocyclopentadiene Mouse Exposure Chamber for the 2-Year Study

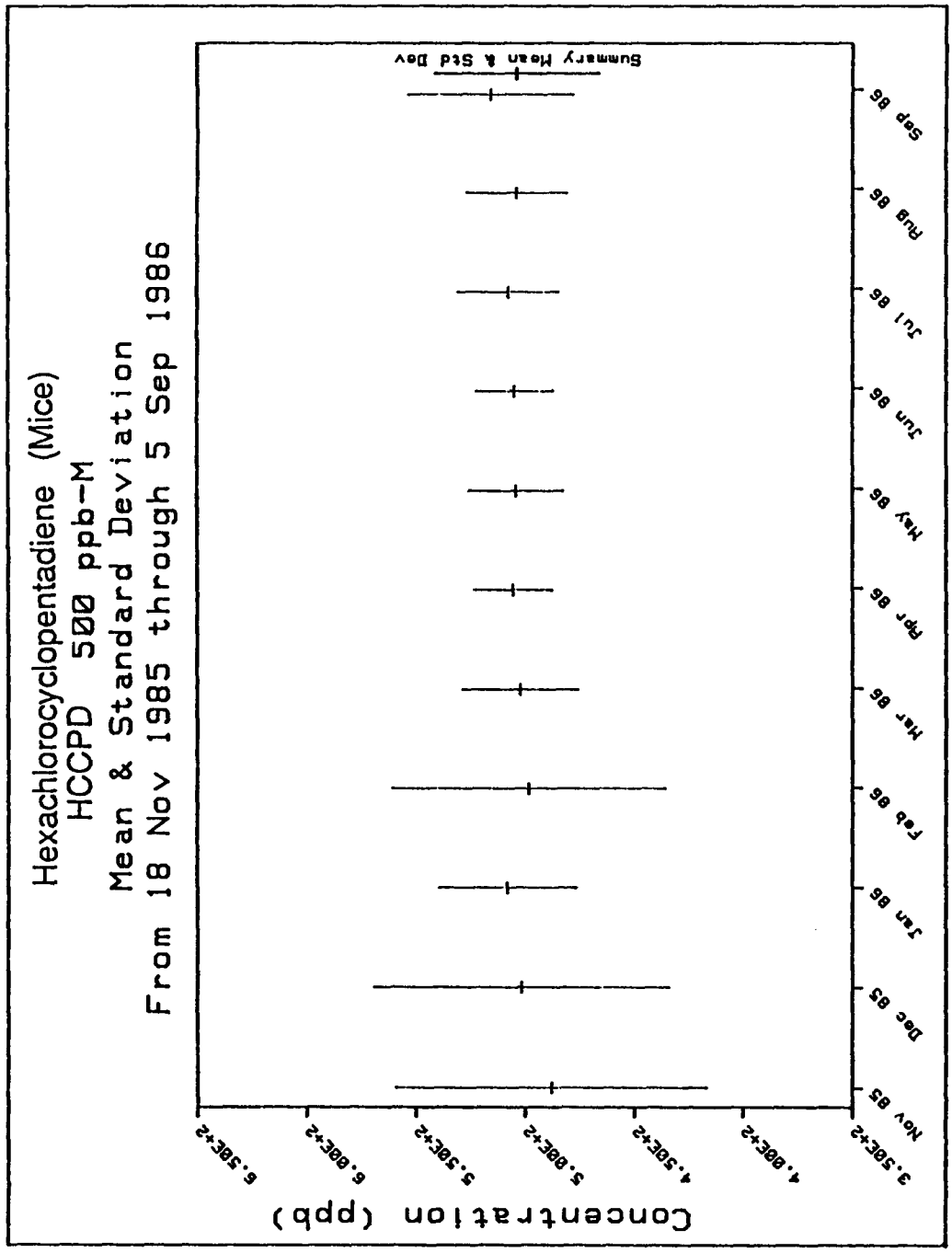

FIGURE I12
Monthly Mean Concentration and Standard Deviation in the 0.5 ppm Hexachlorocyclopentadiene Male Mouse Exposure Chamber for the Stop-Exposure Evaluation

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

TABLE J1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	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

[a] NCI, 1976; NIH, 1978
[b] 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[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
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

[a] Per ton (2,000 lb) of finished product

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

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

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

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.57 ± 0.33	0.14 – 0.98	17
Cadmium (ppm)[b]	0.10 ± 0.02	0.10 – 0.20	17
Lead (ppm)	0.37 ± 0.26	0.05 – 0.96	17
Mercury (ppm)	<0.05		17
Selenium (ppm)	0.30 ± 0.05	0.30 – 0.48	17
Aflatoxins (ppb)	<5.0		17
Nitrate nitrogen (ppm)[c]	20.29 ± 8.37	12.30 – 41.0	17
Nitrite nitrogen (ppm)[c]	0.50 ± 0.81	<0.10 – 2.60	17
BHA (ppm)[d]	2.53 ± 1.01	<2.00 – 5.00	17
BHT (ppm)[d]	1.29 ± 0.85	<1.00 – 4.00	17
Aerobic plate count (CFU/g)[e]	45,076 ± 72,968	3,400 – 300,000	17
Coliform (MPN/g)[f]	3.12 ± 0.33	<3.00 – 4.00	17
E. coli (MPN/g)	3.00		17
Total nitrosoamines (ppb)[g]	9.02 ± 4.07	3.90 – 12.00	17
N-Nitrosodimethylamine (ppb)[g]	7.68 ± 3.97	2.90 – 19.00	17
N-Nitrosopyrrolidine (ppb)[g]	1.34 ± 0.90	1.00 – 4.50	17
Pesticides			
α-BHC[h]	<0.01		17
β-BHC	<0.02		17
γ-BHC	<0.01		17
δ-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 ± 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)

[a] For values less than the limit of detection, the detection limit is given as the mean.
[b] The lot milled 30 June 1987 contained 0.20 ppm; all other lots were less than or equal to the detection limit.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] CFU = colony forming units
[f] 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.
[g] All values were corrected for percent recovery.
[h] BHC is hexachlorocyclohexane or benzene hexachloride

APPENDIX K
SENTINEL ANIMAL PROGRAM

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 weanling 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:

Method of Analysis	Time of Analysis
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:

Method of Analysis	Time of Analysis
ELISA	
Mycoplasma arthritidis	6 and 24 months
Mycoplasma pulmonis	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:

Method of Analysis	Time of Analysis
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:

Method of Analysis	Time of Analysis
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
M. arthritidis	6 and 24 months
M. pulmonis	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	Time of Analysis
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	6, 12, 15, 18, and 24 months
GDVII	18 months
LCM	12 months
MVM	18 months
Reovirus 3	18 months

All test results were negative.

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF JANUARY 1994 (CONT.)

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

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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
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_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Pariffins (C_{12}, 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

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