NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

PENTACHLOROPHENOL

(CAS NO. 87-86-5)

IN F344/N RATS

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

April 1999

NTP TR 483

NIH Publication No. 99-3973

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. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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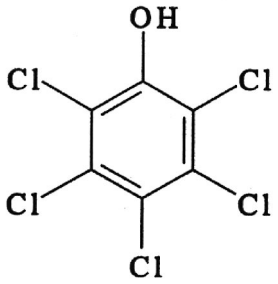
ABSTRACT



PENTACHLOROPHENOL
CAS No. 87-86-5
Chemical Formula: CHOCl Molecular Weight: 266.3

Synonyms: Chlorophen; PCP; penchlorol; penta; pentachlorofenol; pentachlorofenolo; 2,3,4,5,6-pentachlorophenol

Trade names: Acutox; Chem-Penta; Chem-Tol; Cryptogil ol; Dowicide 7; Dowicide EC-7; Dow Pentachlorophenol DP-2 Antimicrobial; Durotox; EP 30; Fungifen; Fungol; Glazd Penta; Grundier Arbezol Lauxtol; Lauxtol A; Liroprem; Moosuran; Pentacon; Penta-Kil; Pentasol; Penwar; Peratox; Permacide; Permagard; Permasan; Permatox; Priltox; Permite; Santophen; Santophen 20; Sinituho; Term-i-Trol; Thompson's Wood Fix; Weedone; Witophen P

Pentachlorophenol has been used as an herbicide, algicide, defoliant, wood preservative, germicide, fungicide, and molluscicide. Pentachlorophenol was nominated by the National Cancer Institute for carcinogenicity testing based on its widespread use as a wood preservative, potential for entering the environment (pentachlorophenol residues have been found worldwide in soil, water, and air samples; in food products; and in human and animal tissues and body fluids), and likelihood of bioaccumulation in the environment (pentachlorophenol is persistent in soil, having a half-life of up to 5 years). Technical Report No. 349 contains the results of the 2-year studies of pentachlorophenol performed by the NTP with B6C3F mice.

Male and female F344/N rats were exposed to pentachlorophenol (approximately 99% pure) in feed for 28 days or 2 years. Genetic toxicology studies were conducted in vitro in Salmonella typhimurium and cultured Chinese hamster ovary cells and in vivo in rat and mouse bone marrow cells.

28-DAY STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were given 0, 200, 400, 800, 1,600, or 3,200 ppm pentachlorophenol, equivalent to average daily doses of approximately 20, 40, 75, 150, or 270 mg pentachlorophenol/kg body weight to males and females in feed for 28 days. With the exception of one male and two females exposed to 3,200 ppm, all rats survived until the end of the study. The final mean body weights and body weight gains of male rats exposed to 1,600 or 3,200 ppm and female rats exposed to 400, 800, 1,600, or 3,200 ppm were significantly less than those of the controls; rats exposed to 3,200 ppm lost weight during the study. Feed consumption by 3,200 ppm males was less than that by the control group throughout the study. The absolute and relative

liver weights of 400, 800, and 1,600 ppm males and all exposed groups of females were significantly greater than those of the controls. Compared to the control groups, the incidences of minimal to mild hepatocyte degeneration in males and females exposed to 400 ppm or greater and the incidences of centrilobular hepatocyte hypertrophy in the 3,200 ppm groups were increased.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were fed diets containing 200, 400, or 600 ppm pentachlorophenol (equivalent to average daily doses of approximately 10, 20, and 30 mg/kg) for 105 weeks. Stop-exposure groups of 60 male and 60 female rats received 1,000 ppm (equivalent to 60 mg/kg) in feed for 52 weeks, after which animals received undosed feed for the remainder of the 2-year study; 10 male and 10 female control and 1,000 ppm rats were evaluated at 7 months.

Survival, Body Weights, and Feed Consumption

In the 2-year study, survival of 600 and 1,000 ppm males was greater than that of the controls. Mean body weights of 400 and 600 ppm males and females were generally less than those of controls. When exposure to pentachlorophenol was discontinued at week 52, mean body weights of 1,000 ppm males and females were 17% and 22% lower than those of the respective controls; however, by the end of week 87, the mean body weights were similar to those of the controls. Generally, feed consumption by exposed groups was similar to that by the controls.

Pathology Findings

At 2 years, the incidence of malignant mesothelioma originating from the tunica vaginalis was significantly greater in 1,000 ppm males than in the controls, and the incidence exceeded the historical control range. Nasal squamous cell carcinomas were present in one control male, three 200 ppm males, one 400 ppm male, and five 1,000 ppm males at 2 years, and the incidence in 1,000 ppm males exceeded the historical control range. At the 7-month interim evaluation, the incidences of centrilobular hepatocyte hypertrophy in 1,000 ppm males and females and hepatocyte cytoplasmic vacuolization in 1,000 ppm males was significantly greater than those in the controls. At 2 years, the incidences of several nonneoplastic liver lesions including hepatodiaphragmatic nodules and hepatocyte cystic degeneration in all exposed groups of males and basophilic foci in 1,000 ppm males were increased compared to the controls.

GENETIC TOXICOLOGY

Pentachlorophenol (91.6% pure) was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 at doses up to 30 μg/plate with and without induced rat or hamster liver S9; no significant increases in the number of revertant colonies were observed in any of the strain/activation combinations. When tested for cytogenetic effects in cultured Chinese hamster ovary cells, pentachlorophenol was weakly positive for induction of sister chromatid exchanges and chromosomal aberrations. In the sister chromatid exchange test, a weakly positive response was observed within a concentration range of 3 to 30 μg/mL in the absence of S9; with S9, no induction of sister chromatid exchanges was noted. In the chromosomal aberrations test, pentachlorophenol was negative without S9 but induced small but significant increases in the frequency of aberrant cells in the presence of S9 at doses of 80 and 100 μg/mL. In contrast to the positive *in vitro* results in the test for induction of chromosomal aberrations, no increase in the frequency of micronucleated erythrocytes was noted in bone marrow of male rats or mice administered pentachlorophenol by intraperitoneal injection three times at 24 hour intervals. The highest dose administered to rats (75 mg/kg) and mice (150 mg/kg) was lethal.

CONCLUSIONS

Under the conditions of this 2-year feed study, there was *no evidence of carcinogenic activity** of pentachlorophenol in male or female F344/N rats fed diets containing 200, 400, or 600 ppm. There was *some evidence of carcinogenic activity* of pentachlorophenol in male F344/N rats given feed containing 1,000 ppm for 1 year followed by control feed for 1 year (stop-exposure study), based on increased incidences of mesothelioma and nasal squamous cell carcinoma. There was *no evidence of carcinogenic activity* of pentachlorophenol in female rats given feed containing 1,000 ppm for 1 year and maintained on control feed for 1 year.

Stop-exposure males and females recovered from a transitory reduction in body weight gain by the end of the 2-year study, and males had increased survival compared to the controls.

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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 pages 11 and 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pentachlorophenol

	Male F344/N Rats		Female F344/N Rats	
	(2-Year Study)	**(Stop-Exposure Study)**	**(2-Year Study)**	**(Stop-Exposure Study)**
Doses in feed	0, 200, 400, or 600 ppm	1,000 ppm for 1 year	0, 200, 400, or 600 ppm	1,000 ppm for 1 year
Body weights	400 and 600 ppm groups less than controls	Less than controls during exposure period; similar to controls postexposure	400 and 600 ppm groups less than controls	Less than controls during exposure period; similar to controls postexposure
Survival rates	12/50, 16/50, 21/50, 31/50	27/50	28/50, 33/50, 34/50, 28/50	28/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	Malignant mesothelioma: 1/50, 9/50 Nose: squamous cell carcinoma (1/50, 5/50)	None	None
Level of evidence of carcinogenic activity	No evidence	Some evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative for TA98, TA100, TA1535, and TA1537 with and without S9			
Sister chromatid exchanges Cultured Chinese hamster ovary cells *in vitro*:	Negative with S9; weakly positive without S9			
Chromosomal aberrations Cultured Chinese hamster ovary cells *in vitro*:	Weakly positive with S9; negative without S9			
Micronucleated erythrocytes Mouse bone marrow *in vivo*:	Negative			
Rat bone marrow *in vivo*:	Negative			

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 tumors 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 tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor 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 tumor increase;
- concurrent control tumor 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 pentachlorophenol on 10 December 1997 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 the 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 10 December 1997, the draft Technical Report on the toxicology and carcinogenesis studies of pentachlorophenol received public review by the National Toxicology Program's 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. R.S. Chhabra, NIEHS, introduced the toxicology and carcinogenesis studies of pentachlorophenol by discussing the uses of the chemical and the rationale for the study, describing the experimental design, reporting on survival and body weight effects, and commenting on chemical-related neoplasms and nonneoplastic lesions in male and female rats. Dr. Chhabra also reported the findings of the earlier bioassay of two technical grades of pentachlorophenol in B6C3F$_1$ mice. The proposed conclusions for the 2-year study were *some evidence of carcinogenic activity* in male F344/N rats and *no evidence of carcinogenic activity* of pentachlorophenol in female F344/N rats.

Dr. Belinsky, a principal reviewer, did not agree with the proposed conclusion for the male rats. He found the level of evidence for nasal lesions hard to justify, noting that the incidence of neoplasms was quite variable, with none reported at 600 ppm in the 2-year study. Dr. Belinsky questioned the effects an ongoing fungal infection would have had in facilitating that type of lesion. Dr. R.R. Maronpot, NIEHS, said that the highest rate of fungal infection was in the controls, and that among the animals that had squamous cell carcinomas, only one showed any evidence of fungal infection; thus, there appeared to be little or no relationship between fungal infection and neoplasms. Dr. Belinsky asked for clarification on the rationale for the stop study. Dr. Chhabra responded by first describing the rationale for the design of the study. The chemical had been shown previously to be a mouse liver carcinogen, and this finding was supported by data from a 28-day toxicity study; hence, the 2-year study was designed on the basis of this information. The reason for the stop-exposure study was to first determine if preneoplastic liver lesions would develop after 6 months of exposure; this was to have been followed by stop exposure and observance of the progression or regression of lesions for the next 6 months. Because only mild liver toxicity was observed at the interim sacrifice, it was decided that exposure would be continued for up to a year, after which animals would be placed on control feed for the second year.

Dr. Chatman, the second principal reviewer, did not agree with the proposed conclusion regarding the male rats. She said that the incidences of nasal neoplasms in the 2-year study were not statistically significant and did not show a dose-response relationship; also, exposed groups did not show increased incidences of defined preneoplastic lesions. Dr. J.K. Haseman, NIEHS, said that internal staff discussions explored the same issues, but because nasal neoplasms are so uncommon, the conclusion was warranted. Dr. Chatman also thought that the frequency of fungal nasal infections was an additional variable interfering with the interpretation of the findings, and she wondered if the animals were immunocompromised.

Dr. Fischer, the third principal reviewer, agreed with the proposed conclusions. She said that the active fungal infection might be a confounding variable. Dr. Fischer asked about levels of pentachlorophenol in the general food supply, for purposes of making comparisons with the levels fed to the animals. Dr. Chhabra responded that information on levels in food was available and that this would be added to the report. Dr. Fischer noted that the numbers of metastatic lesions were elevated in all of the treatment groups and wanted this fact to be addressed in the discussion. Dr. Haseman responded that the numbers of metastatic lesions were misleading because most of the metastatic lesions had different cells of origin, and two neoplasms metastasized to a number of different sites, with each counted as a different metastatic neoplasm.

Dr. Bus contended that the findings on the reduction of body weight gain in the 28-day study as well as information from the previous rat bioassay suggested that 600 ppm was close to the maximum tolerated dose (MTD), and thus the 1,000 ppm dose was far in excess of the MTD; hence, the classification described for the neoplasms did not seem right. Dr. Chatman responded that the 1,000 ppm group was in reality a different study. Dr. J. Russo commented that the mesothelioma findings were quite important and that

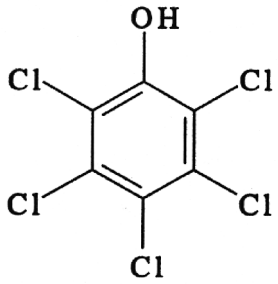
their significance should not be minimized. Dr. Goldsworthy inquired if there was any reason for males to be more sensitive than females with regard to the two neoplasm sites. Dr. Maronpot said that he would not expect any difference with respect to the nasal carcinomas; however, with regard to mesotheliomas, male Fischer rats have more spontaneous neoplasms at that site than females.

Dr. P. Lin, University of North Carolina at Chapel Hill, presented data from his research on the macromolecular binding and genotoxic effects of pentachlorophenol in tissues obtained from the interim sacrifice at 7 months in the 2-year NTP study. He said that their research with some mineral fibers indicated that free radical formation could be involved in the development of mesotheliomas. Their findings showed that in male rats exposed to 1,000 ppm, there was a twofold increase in DNA lesions in the kidney. If free radicals were involved in pentachlorophenol carcinogenesis, this would then explain the unusual dose-response relationship observed for the mesotheliomas in male rats.

Dr. B. Bernard, SRA International, representing the U.S. Pentachlorophenol Task Force, remarked that he would focus on the mesotheliomas in the epididymis and nasal neoplasms. He criticized the exposure concentrations, noting that these were based on the 28-day study and not on the 13-week studies, as is normally done. He stated that the 1,000 ppm groups were originally intended to be carried forward for 2 years, but that exposure had to be stopped after 1 year when it became obvious that survival would pose a problem. He suggested that for various reasons, including the lack of a dose response and the absence of neoplasms at the highest cumulative dose, the data supported *equivocal evidence of carcinogenic activity* at best. Dr. J.R. Bucher, NIEHS, stated that 1,000 ppm was always intended to be a stop-exposure concentration and the NTP design never included a 2-year exposure concentration at 1,000 ppm.

Dr. Belinsky moved that the Technical Report on pentachlorophenol, purified, be accepted with the revisions discussed and the conclusion as written for female rats, namely, *no evidence of carcinogenic activity*; and that the conclusion for male rats be changed to *equivocal evidence of carcinogenic activity*. Dr. Chatman seconded the motion. After some discussions suggesting that the conclusion statement for the standard 2-year study at 200, 400, and 600 ppm and the stop-exposure study at 1,000 ppm be treated separately, Dr. Belinsky made a substitute motion that "under the conditions of the study, there was *no evidence of carcinogenic activity* in male and female rats exposed for 2 years to feed containing 200, 400, or 600 ppm pentachlorophenol and that there was *some evidence of carcinogenic activity* in male rats and *no evidence of carcinogenic activity* in female rats exposed to feed containing 1,000 ppm pentachlorophenol for 1 year followed by control feed for another year." Dr. Chatman seconded the substitute motion. Dr. Bus moved to amend the second part of the motion to designate the stop-exposure study as an *inadequate study of carcinogenic activity*, based on the occurrence of significant toxicity well beyond classical MTD definitions. There being no second, the amendment was tabled. Dr. Belinsky's substitute motion was then accepted unanimously with eight votes.

INTRODUCTION



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Trade names: Acutox; Chem-Penta; Chem-Tol; Cryptogil ol; Dowicide 7; Dowicide EC-7; Dow Pentachlorophenol DP-2 Antimicrobial; Durotox; EP 30; Fungifen; Fungol; Glazd Penta; Grundier Arbezol Lauxtol; Lauxtol A; Liroprem; Moosuran; Pentacon; Penta-Kil; Pentasol; Penwar; Peratox; Permacide; Permagard; Permasan; Permatox; Priltox; Permite; Santophen; Santophen 20; Sinituho; Term-i-Trol; Thompson's Wood Fix; Weedone; Witophen P

This background information is a brief account of the toxicology literature currently available regarding pentachlorophenol. Several extensive literature reviews on the toxicology of pentachlorophenol are available (IPCS, 1987; IARC, 1991; ATSDR, 1994).

CHEMICAL AND PHYSICAL PROPERTIES

Pentachlorophenol is a colorless to light brown, noncombustible solid with a phenolic odor, a pungent taste, and the following chemical and physical properties: specific gravity, 1.978 at 20° C; melting point, 190° to 191° C; boiling point, 309° to 310° C; and vapor pressure, 0.00011 torr at 20° C. It is slightly soluble in water and petroleum ether; soluble in benzene; and very soluble in ethanol, diethyl ether, and methanol (ACGIH, 1991).

PRODUCTION, USE, AND HUMAN EXPOSURE

Pentachlorophenol is produced commercially in the United States by direct chlorination of phenol with chlorine gas in the presence of a catalyst at gradually rising temperatures up to 200° C (HSDB, 1997). In addition, a number of other chemicals such as hexachlorobenzene, pentachlorobenzene, and benzenehexachloride isomers are metabolized to pentachlorophenol (ATSDR, 1994). Contaminants formed in pentachlorophenol production are isomers of hexa-, hepta-, and octachlorodibenzo-*p*-dioxin and isomers of tetra-, penta-, hexa-, hepta-, and octachlorodibenzofuran. Technical grade pentachlorophenol typically contains 88.4% pentachlorophenol, 4.4% tetrachlorophenol, 6.2% higher-chlorinated phenoxyphenol, and traces to several parts per million

of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans.

In various products, pentachlorophenol has been used as an herbicide, algicide, defoliant, wood preservative, germicide, fungicide, and molluscicide. As a wood preservative, it is commonly applied as a 0.1% solution in mineral spirits, number 2 fuel oil, or kerosene. It is used in pressure treatment of lumber at a 5% concentration. In 1986 in the United States, approximately 97% of the pentachlorophenol usage was as a wood preservative, 1% as a general herbicide, and the remainder for miscellaneous smaller applications (IARC, 1991). Pentachlorophenol is no longer available for retail sale in the United States (HSDB, 1997). The American Conference of Governmental Industrial Hygienists (1997) has set a threshold limit value of 0.5 mg/m^3 for dermal exposure. Some 46 million pounds are produced each year in the United States (ACGIH, 1991).

Pentachlorophenol is a ubiquitous environmental contaminant, and its widespread occurrence has been reviewed (IPCS, 1987). The compound is found in all environmental media as a result of its past widespread use, but now it is regulated as a restricted-use pesticide in the United States. It has been detected in surface waters and sediments, rainwater, drinking water, aquatic organisms, and soil. Pentachlorophenol is used in large quantities as a wood preservative for utility poles, cross arms, and fenceposts. These uses may result in some environmental releases from the wood and during spills. Releases to soil can decrease in concentration due to slow biodegradation and leaching into the groundwater. If released in water, pentachlorophenol adsorbs to sediment, photodegrades (especially at higher pHs), and slowly biodegrades. Bioconcentration in fish is moderate. In air, pentachlorophenol is destroyed due to photolysis and reaction with photochemically produced hydroxyl radicals (HSDB, 1997). Pentachlorophenol has been identified in at least 247 of 1,350 hazardous waste sites in the United States (ATSDR, 1994).

Workers are exposed during the production of pentachlorophenol and the treatment of wood with pentachlorophenol (IARC, 1991). Humans are occupationally exposed to pentachlorophenol via inhalation and dermal contact primarily in situations where they use this preservative or are in contact with treated wood products. The National Occupational Exposure Survey (1981-1983) estimated that 26,800 workers are potentially exposed to pentachlorophenol annually (NIOSH, 1990). The general population is exposed primarily from ingesting food contaminated with pentachlorophenol (HSDB, 1997). Pentachlorophenol has been detected in human milk, adipose tissue, and urine. The long-term, average daily intake of pentachlorophenol is estimated to be 16 μg/day (IARC, 1991).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Pentachlorophenol is readily absorbed following inhalation, dermal, and oral exposure (IPCS, 1987) and is distributed to all tissues of the body; the concentrations in liver and kidney tissue are particularly high, whereas those in fat, brain, and muscle are relatively low (Larsen *et al.*, 1972; Braun *et al.*, 1977). Pentachlorophenol and/or its metabolites are excreted primarily in urine by rodents (62% to 83%) and monkeys (45% to 75%). The biologic half-life of pentachlorophenol is relatively short, and bioaccumulation is slight. After a single exposure of rats or mice, the initial half-life was 6 to 27 hours, but a second and slower elimination phase had a half-life of 33 to 374 hours (Larsen *et al.*, 1972; Braun *et al.*, 1977). The proposed explanation for the biphasic elimination is that a portion of pentachlorophenol and/or its metabolites escapes initial elimination and becomes involved in enterohepatic circulation or binds to plasma proteins (Braun and Sauerhoff, 1976). The half-life in monkeys is longer (41 to 92 hours) than the initial elimination phase in rodents.

The toxicokinetics of pentachlorophenol were studied by the NTP in Fischer 344 rats using intravenous and oral routes of exposure (Yuan *et al.*, 1994). Absorption of pentachlorophenol from the gastrointestinal tract after gavage doses of 9.5 or 38 mg/kg in an aqueous methylcellulose vehicle was first order with an absorption half-life of about 1.3 hours. The absorption rate constant of pentachlorophenol from dosed feed was similar to that obtained from gavage formulations; the bioavailability of pentachlorophenol administered in dosed feed was significantly lower than that of pentachlorophenol administered by gavage; and dose proportionality was established to a dosage of at least 38 mg/kg, which covers the internal

dose from dosed feed formulations up to at least a concentration of 1,000 ppm.

The kinetics of absorption, metabolism, and elimination of the impurities in pentachlorophenol are more complex and are not described here. However, some impurities, such as chlorinated dibenzo-*p*-dioxins and chlorinated dibenzofurans, may affect the rate of pentachlorophenol metabolism by stimulating mixed-function oxidase activity (Goldstein *et al.*, 1977).

In rodents, metabolism occurs via oxidation to tetrachlorohydroquinone and, to a lesser extent, to trichlorohydroquinone, as well as by glucuronidation (Jakobson and Yllner, 1971; Ahlborg and Thunberg, 1980). Dechlorination of pentachlorophenol is mediated by microsomal enzymes that can be induced by phenobarbital or by tetrachlorodibenzo-*p*-dioxin (IARC, 1979). The quinones can either be excreted in the urine or undergo conjugation with glucuronic acid to form glucuronides. More recent studies show that the metabolism of pentachlorophenol proceeds primarily through the quinols, tetrachlorohydroquinone and tetrachlorocatechol, via microsomal cytochrome P_{450} enzymes. These quinols can be oxidized to the corresponding quinones via semiquinone intermediates. Quinones and semiquinones are electrophilic and capable of binding to macromolecules (Lin *et al.*, 1997). The redox cycling associated with oxidation of tetrachlorohydroquinone and/or reduction of tetrachloro-1,4-benzoquinone generates oxygen radicals which have been shown to increase the concentration of 8-hydroxydeoxyguanosine in the livers of $B6C3F_1$ mice treated with pentachlorophenol tetrachlorohydroquinone (Dahlhaus *et al.*, 1994; Sai-Kato *et al.*, 1995, Lin *et al.*, 1997).

Humans

The elimination kinetics of pentachlorophenol in humans are less clear. After a single oral exposure of 0.1 mg sodium pentachlorophenol/kg body weight, a half-life of 30 hours (plasma) was observed, with elimination primarily of the parent compound in urine (Braun *et al.*, 1979). Over 90% was eliminated from the body within 7 days. However, the half-life depends to a great degree on the dose, vehicle, and salt used. A dose of 0.016 mg/kg sodium pentachlorophenol in 40% ethanol resulted in a substantially longer half-life in plasma of 16 days (presumably because of more complete protein binding) (Uhl *et al.*, 1986). Small amounts of pentachlorophenol may be stored for long periods in the body. Concentrations of pentachlorophenol in human adipose tissue ranged from less than 5 to 190 ppb, and urinary concentrations in healthy workers ranged from 0.003 to 32.5 ppm (ACGIH, 1991). The rat appeared to be a better model than the monkey for humans based on the similarities observed for a number of kinetic parameters such as maximum plasma concentration (C_{max}), time to C_{max}, absorption rate constant, terminal elimination rate constant, volume of distribution, simulated time to steady state (multiple doses), steady-state concentration, and amount of dose excreted as glucuronide conjugate (Braun *et al.*, 1979).

Human metabolism of tetrachlorohydroquinone has been observed (Renner and Mücke, 1986). In male volunteers, pentachlorophenol was eliminated as both the parent compound and the glucuronide; no other metabolites were observed (Braun and Sauerhoff, 1976; Braun *et al.*, 1979; Uhl *et al.*, 1986).

TOXICITY

Experimental Animals

Pentachlorophenol is moderately toxic to laboratory animals (McConnell, 1980). The oral LD_{50} values in rats range from 80 to 175 mg/kg when given in vegetable oil (Fielder *et al.*, 1982). The oral LD_{50} of pure pentachlorophenol reported by Renner *et al.* (1986) was 129 mg/kg for male mice and 134 mg/kg for female mice; Borzelleca *et al.* (1985) reported LD_{50} values of 117 mg/kg for males and 177 mg/kg for females. Signs of acute toxicity in rodents include hyperthermia (because pentachlorophenol produces an uncoupling of oxidative phosphorylation), muscle tremors and spasms, and loss of righting reflex. Death is usually due to respiratory paralysis.

Target organs of pentachlorophenol toxicity are the liver, kidney, and bone marrow. The liver appears to be a primary target organ for pentachlorophenol in rodents. Changes in the liver that are associated with exposure to pentachlorophenol include biochemical (porphyria, hepatic P_{450} enzyme activities, serum activities of enzymes of hepatic origin, and glycogen concentrations), gross (appearance and weight), and microscopic (hyperplasia, fibrosis, hepatocellular enlargement and vacuolization, pigmentation, degeneration, and necrosis). Many hepatotoxic effects of

pentachlorophenol appear to be related to the concentrations of impurities in the technical grade product (e.g., polychlorinated dibenzo-*p*-dioxins and dibenzofurans) rather than the purified chemical (ATSDR, 1994).

There is a species difference in pentachlorophenol toxicity. Pentachlorophenol induces more severe liver toxicity in mice than in rats. Mice exposed to 200 to 1,500 ppm technical or pure grades of pentachlorophenol in the diet for 6 months had severe liver toxicity (NTP, 1989). The liver lesions included hepatocellular karyomegaly, cytomegaly, and degeneration. However, the severity of the lesions was less in mice exposed to the pure grade of pentachlorophenol (98.6%) than in mice receiving similar doses of technical grade pentachlorophenol (90.4%). Mild hepatotoxicity has been observed in rats exposed to purified pentachlorophenol (Kimbrough and Linder, 1978). Rats exposed to 500 ppm pure pentachlorophenol in feed for 8 months had slightly enlarged liver cells with occasional cytoplasmic inclusions, while no alterations were noted in the livers of rats exposed to 20 or 100 ppm in feed. However, the liver toxicity was severe in rats exposed to 500 ppm technical grade pentachlorophenol in feed, as shown by lesions consisting of enlarged pleomorphic hepatocytes that had foamy cytoplasm or cytoplasm with large vacuoles. The walls of hepatic central veins of livers were thickened in male and female rats. Mild or less severe liver effects were observed in rats exposed to 20 or 100 ppm of pentachlorophenol, respectively.

Animal studies also have revealed minor effects of pentachlorophenol on the kidney. The most frequently reported toxic effect in rodent studies has been an increase in absolute kidney weight (Johnson *et al.*, 1973; Kimbrough and Linder, 1978; Schwetz *et al.*, 1978). This effect was not dose related and occurred in the absence of microscopic changes. Lactating cattle fed technical grade pentachlorophenol (0.2 to 2 mg/kg per day) for 140 days exhibited enlarged kidneys and renal microscopic changes that included diffuse interstitial nephritis, hyperemia, and swollen or atrophied glomeruli (Kinzell *et al.*, 1981).

Hematologic effects attributed to pentachlorophenol exposure include anemia in cattle (McConnell *et al.*, 1980) and depression in erythrocyte counts, hemoglobin concentrations, and hematocrit values in rats (Johnson *et al.*, 1973; Knudsen *et al.*, 1974).

The effects of pentachlorophenol on pituitary and thyroid hormone regulation were studied in female Wistar rats by Jekat *et al.* (1994). The animals were treated with 3 or 30 mg/kg pentachlorophenol per day by gavage for 28 days. A pronounced decrease in circulating thyroxine and triiodothyronine concentrations was accompanied by lower concentrations of both free thyroid hormones and thyroid-stimulating hormone. An interference of pentachlorophenol at the pituitary or hypothalamic level was assumed as a major mode of action.

Humans

According to the IARC (1991), symptoms of acute poisoning in humans include chloracne, skin rashes, central nervous system disorders, respiratory diseases, and hyperpyrexia. Hematologic disorders that have been reported in cases of human pentachlorophenol exposures include aplastic anemia, decreases in hematocrit values, and increases in hematuria (IPCS, 1987).

Human hepatic and renal abnormalities associated with occupational exposure or the misuse of pentachlorophenol include fatty infiltration, centrilobular degeneration, and elevated aspartate aminotransferase and alanine aminotransferase activity (IPCS, 1987; ATSDR, 1994).

Several extensive literature reviews on the toxicology of pentachlorophenol are available (IPCS, 1987; IARC, 1991; ATSDR, 1994).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Many studies have been conducted on pentachlorophenol to examine its reproductive toxicity or teratogenicity (IPCS, 1987). There seems to be a general agreement that pure pentachlorophenol is fetotoxic but not teratogenic (Schwetz *et al.*, 1974, 1978; Welsh *et al.*, 1987). In addition, the doses required for fetotoxicity are at or near maternally toxic doses. Pentachlorophenol does not appear to affect male fertility (Schwetz *et al.*, 1978).

Technical grade pentachlorophenol, when given to rats at 5 mg/kg per day between gestation days 6 and 15, did not cause any effects in the fetus or dam (Schwetz *et al.*, 1974). Fetal resorptions and delayed

development were observed at 15 mg/kg per day, and maternal toxicity occurred at 35 mg/kg (Cirelli, 1978). More limited fetotoxicity was observed in a similar study in rats (Courtney *et al.*, 1976). In another study, pentachlorophenol appeared to be more fetotoxic than the metabolite pentachloroanisole (Welsh *et al.*, 1987). According to one report, maternal exposure of rats to 60 mg/kg per day resulted in dwarfism, exencephaly, macrophthalmia, and absence of a tail in some fetuses (Edwards, 1968). However, these effects were attributed to hyperthermia in the dam, a well-known consequence of pentachlorophenol toxicity. Interestingly, technical grade pentachlorophenol appears to be less fetotoxic than the pure grade. The explanation for this appears to be the presence of chlorinated dibenzo-*p*-dioxins and chlorinated dibenzofurans that stimulate the liver enzymes necessary for pentachlorophenol metabolism (NRCC, 1982). However, some of these impurities are known teratogens (Courtney and Moore, 1971). It is probable that teratogenic effects have not been observed because exposure to the impurities is well below the teratogenic dose.

In summary, pure or technical grade pentachlorophenol does not appear to be a specific reproductive toxicant or teratogen.

CARCINOGENICITY

Experimental Animals

Most long-term studies of pentachlorophenol, especially those designed to evaluate carcinogenesis in mice, were confounded by various design flaws such as the presence of known carcinogenic impurities, short exposure/observation time, or use of a dose well below the maximum tolerated dose. An early long-term study of pentachlorophenol in mice did not show any carcinogenic effect in two hybrid strains (Innes *et al.*, 1969). However, the study was terminated at 18 months, which might not have been long enough to detect carcinogenic effects. The only in-depth study of pure pentachlorophenol of adequate duration (2 years) in rats did not show evidence of carcinogenicity (Schwetz *et al.*, 1978). In this study in male and female Sprague-Dawley rats, pentachlorophenol was administered in the diet at doses of 0, 1, 3, 10, or 30 mg/kg for up to 24 months. No carcinogenic activity related to pentachlorophenol exposure was observed.

The NTP conducted carcinogenesis studies of technical grade pentachlorophenol and Dowicide EC-7, a purer grade, only in mice, because at that time the studies reported by Schwetz *et al.* (1978) were considered negative and adequately designed (NTP, 1989). Groups of 50 male and 50 female B6C3F_1 mice were fed diets containing pentachlorophenol for 112 weeks. The technical grade pentachlorophenol was administered at a concentration of 100 or 200 ppm and Dowicide EC-7 at 100, 200, or 600 ppm in feed. Two groups of 35 males and 35 females were fed control diets. Significant dose-related increases in the incidences of hepatocellular adenoma or carcinoma (combined) were observed in male mice treated with either formulation of pentachlorophenol (Table 1). Dowicide EC-7 induced significant dose-related increases in the incidence of hepatocellular adenoma in female mice. Exposure to either the technical grade or Dowicide EC-7 increased the incidences of adrenal pheochromocytoma in male mice; this effect was also seen in females exposed to 600 ppm Dowicide EC-7. Also, at high concentrations, both preparations caused significantly increased incidences of hemangiosarcoma in females. Chemically related increased incidences of nonneoplastic lesions in male and female mice included hepatocellular cytomegaly, necrosis, inflammation, pigmentation, clear cell foci, intrahepatic bile duct hyperplasia, and multifocal proliferation of hematopoietic cells.

Humans

According to the IARC (1991), the data associated with pentachlorophenol exposure in humans are inadequate to evaluate carcinogenicity, but there are sufficient data to support the carcinogenicity of pentachlorophenol in experimental animals based on the NTP studies in mice (NTP, 1989). Therefore, pentachlorophenol is classified by the IARC as a possible human carcinogen (Group 2B).

TABLE 1
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Mice in the 2-Year Feed Studies of Technical-Grade Pentachlorophenol and Pentachlorophenol, Dowicide EC-7[a]

	Technical Grade			Dowicide EC-7			
	0 ppm	100 ppm	200 ppm	0 ppm	100 ppm	200 ppm	600 ppm
Male							
Liver							
Clear cell focus	0/32	11/47	6/48	0/35	19/48	21/48	19/49
Multifocal proliferation of hematopoietic cells	2/32	20/47	27/48	1/35	20/48	16/48	40/49
Diffuse chronic active inflammation	0/32	42/47	46/48	0/35	36/48	44/48	43/49
Multifocal pigmentation	0/32	45/47	46/48	0/35	40/48	37/48	45/49
Acute diffuse necrosis	0/32	41/47	45/48	0/35	47/48	47/48	46/49
Diffuse cytomegaly	0/32	47/47	48/48	0/35	48/48	48/48	47/49
Bile duct hyperplasia	0/32	22/47	37/48	1/35	3/48	5/48	32/49
Hepatocellular adenoma	5/32	20/47	33/48	5/35	13/48	17/48	32/49
Hepatocellular carcinoma	2/32	10/47	12/48	1/35	7/48	7/48	9/49
Hepatocellular adenoma or carcinoma (combined)	7/32	26/47	37/48	6/35	19/48	21/48	34/49
Adrenal Gland							
Benign pheochromocytoma	0/31	10/45	23/45	0/34	4/48	21/48	44/49
Malignant pheochromocytoma	0/31	0/45	0/45	1/34	0/48	0/48	3/49
Benign or malignant pheochromocytoma (combined)	0/31	10/45	23/45	1/34	4/48	21/48	45/49
All Organs							
Hemangiosarcoma	0/35	2/49	1/49	0/35	4/50	2/50	3/49
Female							
Liver							
Clear cell focus	1/33	3/49	17/50	1/34	2/50	13/49	26/48
Multifocal proliferation of hematopoietic cells	14/33	8/49	33/50	20/34	37/50	35/49	45/48
Diffuse chronic active inflammation	0/33	34/49	44/50	0/34	4/50	29/49	47/48
Multifocal pigmentation	0/33	37/49	47/50	0/34	4/50	32/49	48/48
Acute diffuse necrosis	0/33	44/49	47/50	0/34	21/50	49/49	48/48
Diffuse cytomegaly	0/33	48/49	48/50	0/34	37/50	49/49	48/48
Bile duct hyperplasia	0/33	1/49	2/50	0/34	0/50	1/49	40/48
Hepatocellular adenoma	3/33	8/49	8/50	1/34	3/50	6/49	30/48
Hepatocellular carcinoma	0/33	1/49	1/50	0/34	1/50	0/49	2/48
Hepatocellular adenoma or carcinoma (combined)	3/33	9/49	9/50	1/34	4/50	6/49	31/48

Incidences of Selected Neoplasms and Nonneoplastic Lesions in Mice in the 2-Year Feed Studies of Technical-Grade Pentachlorophenol and Pentachlorophenol, Dowicide EC-7

	Technical Grade			Dowicide EC-7			
	0 ppm	100 ppm	200 ppm	0 ppm	100 ppm	200 ppm	600 ppm
Female (continued)							
Adrenal Gland							
Benign pheochromocytoma	0/33	2/48	1/49	0/35	1/49	2/46	38/49
Malignant pheochromocytoma	2/33	0/48	0/49	0/35	1/49	0/46	1/49
Benign or malignant pheochromocytoma (combined)	2/33	2/48	1/49	0/35	2/49	2/46	38/49
All Organs							
Hemangiosarcoma	0/35	3/50	6/50	0/35	1/50	3/50	8/49

[a] From NTP, 1989. Incidences are given as the number of animals with neoplasms per number of animals examined microscopically (liver and adrenal gland) or necropsied (all organs).

GENETIC TOXICITY

Reviews of the mutagenicity of pentachlorophenol were presented in NTP Technical Report 349 (NTP, 1989) and more recently by Seiler (1991). Pentachlorophenol does not appear to be a strong gene mutagen, but there is some indication that it has clastogenic potential. A brief review of the published data is presented here. Results of bacterial tests for induction of gene mutations (Anderson *et al.*, 1972; Shirasu, 1975; Simmon and Kauhanen, 1978; Haworth *et al.*, 1983; Moriya *et al.*, 1983) or growth inhibition due to DNA damage (Shirasu, 1975) were negative, with the exception of a study using phenobarbital- or 5,6-benzoflavone-induced rat liver S9 (Nishimura *et al.*, 1982).

Positive results were obtained with pentachlorophenol in gene mutation assays in *Saccharomyces cerevisiae* (Fahrig, 1974; Fahrig *et al.*, 1978) but not in assays for induction of mitotic recombination (Simmon and Kauhanen, 1978). No induction of chromosome nondisjunction or sex chromosome loss was noted in *Drosophila melanogaster* (Ramel and Magnusson, 1979), and no increase in the frequency of sex-linked recessive lethal mutations occurred in germ cells of male *D. melanogaster* fed pentachlorophenol for 3 days in sucrose (Vogel and Chandler, 1974).

In cultured Chinese hamster ovary cells, pentachlorophenol (91.6% pure) induced small increases in sister chromatid exchanges in the absence of S9 and chromosomal aberrations with S9 (Galloway *et al.*, 1987; Appendix C); the increases in aberrations were noted at 80 and 100 μg/mL. Ishidate and Sofuni (1985) observed no induction of chromosomal aberrations in Chinese hamster lung fibroblasts treated for 24 or 48 hours with up to 60 μg/mL in the absence of S9, but shorter, 6-hour treatments with up to 240 μg/mL with S9 or 300 μg/mL without S9 followed by a recovery period resulted in clearly positive results at these higher doses.

Additional evidence of *in vitro* clastogenicity comes from a study in which a major rodent metabolite of pentachlorophenol, tetrachlorohydroquinone, was shown to induce significant dose-related increases in micronuclei in V79 Chinese hamster cells in the absence of S9 activation (Jansson and Jansson, 1992). Major impurities identified in the pentachlorophenol (91.6% pure) used in the NTP genetic toxicity tests were tetrachlorophenols (6.5%), octachlorodibenzo-*p*-dioxin (2%), and hexachlorobenzene (10 ppm). All these compounds were negative in the *Salmonella*

typhimurium gene mutation assay (Haworth *et al.*, 1983; Zeiger *et al.*, 1988).

Three tetrachlorophenols, the 2,3,4,5-, 2,3,4,6-, and 2,3,5,6-isomers, were tested for induction of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells (NTP, unpublished data); the results with 2,3,5,6-tetrachlorophenol for both assays were positive, whereas the other two isomers gave results that were considered equivocal for sister chromatid exchanges and positive for induction of aberrations. The positive sister chromatid exchange results with the 2,3,5,6-isomer were obtained with and without S9; the positive aberration results occurred only with S9, as was the case with the original pentachlorophenol test aliquot. The other two isomers of tetrachlorophenol also induced aberrations in the presence of S9; in addition, 2,3,4,6-tetrachlorophenol was active in this assay without S9. None of these impurities was tested *in vivo*.

In vivo, positive results were reported in a coat color spot test in which (C57BL/6JHan *X* T-stock) F_1 mouse embryos were treated transplacentally with 0 to 100 mg/kg pentachlorophenol (99% pure) (Fahrig *et al.*, 1978), but the number of pups (one or two) displaying spots was too few for statistical significance, given the small sample size (<170 offspring per experiment), even though the incidence of spots was much higher than that in the controls (control frequency was one spot in 967 offspring). Bauchinger *et al.* (1982) reported small increases ($P<0.05$) in the frequency of acentric and dicentric chromosomes in the lymphocytes of workers occupationally exposed to pentachlorophenol or its sodium salt. All the workers were smokers, so the possibility of confounding effects must be considered, although the investigators also compared their exposed worker population to a subgroup of smoking controls and found the incidence of aberrations to differ less, but still to be significantly different.

STUDY RATIONALE

Pentachlorophenol was nominated by the National Cancer Institute for carcinogenicity testing because of its widespread use as a wood preservative, its potential for entering the environment (pentachlorophenol residues have been found worldwide in soil, water, and air samples; in food products; and in human and animal tissues and body fluids), and the likelihood of bioaccumulation in the environment (pentachlorophenol is persistent in soil, having a half-life of up to 5 years).

The only in-depth study of pure pentachlorophenol of adequate duration (2 years) in rats did not show evidence of carcinogenicity (Schwetz *et al.*, 1978). The NTP (1989) conducted carcinogenesis studies of technical grade pentachlorophenol and Dowicide EC-7 only in mice, because at that time the studies reported by Schwetz *et al.* (1978) were considered negative and adequately designed. However, these studies were later considered inadequate for evaluation by the IARC (1991) because of a number of deficiencies in the design [such as fewer animals per group (25) and poor selection of exposure concentrations], and their adequacy was also questioned by the NTP Board of Scientific Counselors when considering the mouse studies in 1988 (NTP, 1989). Therefore, the NTP undertook the current studies to reevaluate the carcinogenic potential of pentachlorophenol in rats. The studies reported in this Technical Report were conducted using purified pentachlorophenol because commercial preparations contain various impurities that may produce or potentiate toxic effects. Because most human exposure to pentachlorophenol is via food, the oral route of exposure was chosen for these studies.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PENTACHLOROPHENOL

Pentachlorophenol was obtained in one lot (10412KY) from Aldrich Chemical Company (Milwaukee, WI). Identity and purity analyses were conducted by the study laboratory (Appendix F). Reports on analyses performed in support of the pentachlorophenol studies are on file at the National Institute of Environmental Health Sciences.

The chemical, an off-white powder, was identified as pentachlorophenol by infrared spectroscopy. The purity of lot 10412KY was determined by gas chromatography, which indicated one major peak area and one impurity with an area of 1.0% relative to the major peak area. The impurity was tentatively identified as tetrachlorophenol by gas chromatography/mass spectrometry. Concentrations of chlorinated dibenzodioxin, dibenzofuran, diphenylether, and hydroxydiphenylether were less than the limits of detection by gas chromatography/mass spectrometry. Based on the limits of detection, maximum concentrations of less than 0.33 ppm dibenzo-*p*-dioxins and less than 1.0 ppm dibenzofurans were present in the bulk pentachlorophenol. Results of analyses performed by the manufacturer indicated a purity of 99.9% by titration and 99.3% by gas chromatography. The overall purity of lot 10412KY was determined to be approximately 99%.

Stability studies of the bulk chemical performed by the analytical chemistry laboratory (Midwest Research Institute, Kansas City, MO) indicated that pentachlorophenol was stable for at least 2 weeks when stored at temperatures up to 60° C (MRI, 1978a). To ensure stability, the bulk chemical was stored at room temperature, protected from light, in amber glass bottles with Teflon-lined lids.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared twice during the 28-day study and approximately every 4 weeks during the 2-year study by mixing pentachlorophenol with feed (Table F1). Homogeneity of the 200, 1,000, and 3,200 ppm formulations and stability studies of the 50 and 200 ppm formulations were performed by the study laboratory using gas chromatography. Homogeneity was confirmed, and the stability of the dose formulations was confirmed for at least 25 days at −20° C or 14 days at 5° C when protected from light.

Periodic analyses of the dose formulations of pentachlorophenol were conducted at the study laboratory using gas chromatography. Dose formulations were analyzed once during the 28-day study (Table F2) and approximately every 8 weeks during the 2-year study (Table F3). All five of the dose formulations analyzed during the 28-day study and four of the five animal room samples analyzed were within 10% of the target concentrations. Of the dose formulations analyzed and used during the 2-year study, 94% (64/68) were within 10% of the target concentrations; 64% (16/25) of animal room samples were within 10% of the target concentrations.

28-DAY STUDY

Male and female F344/N rats were obtained from Taconic Laboratory Animals and Services (Germantown, NY). The rats were 4 weeks old at receipt. Animals were quarantined for 13 days and were 6 weeks old on the first day of the study. Groups of 10 male and 10 female rats were fed diets containing 0, 200, 400, 800, 1,600, or 3,200 ppm pentachlorophenol. Feed and water were available *ad libitum*. Rats were housed five per cage. Clinical findings were recorded weekly. Feed consumption

was recorded twice weekly by cage. The animals were weighed initially, weekly, and at the end of the study. Details of the study design and animal maintenance are summarized in Table 2.

A necropsy was performed on all animals. The livers of all rats were weighed. Histopathologic examinations were performed on all animals. Table 2 lists the tissues and organs examined.

2-YEAR STUDY

Study Design

Groups of 50 male and 50 female rats were fed diets containing 200, 400, or 600 ppm pentachlorophenol, and groups of 60 male and 60 female rats were fed diets containing 0 or 1,000 ppm pentachlorophenol. From week 53 until the end of the study, animals in the 1,000 ppm group were given control feed.

Source and Specification of Animals

Male and female F344/N rats were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year study. The rats were quarantined for 13 days before the beginning of the study. All animals were examined for parasite evaluation and gross observation of disease. The rats were approximately 6 weeks old at the beginning of the study. The health of the animals was monitored during the study according to the protocols of the NTP Sentinel Animal Program (Appendix I).

Animal Maintenance

The rats were housed five per cage. Feed and water were available *ad libitum*. Feed consumption was measured by cage over a 7-day period during study weeks 1, 5, 9, and 12 and once every 4 weeks thereafter (Appendix G). Cages were changed twice per week, and cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix H.

Clinical Examinations and Pathology

All animals were observed twice daily for morbidity and mortality. Clinical findings were recorded once per month. Animals were weighed initially, weekly for the first 13 weeks, monthly thereafter, and at the end of the study.

Ten male and ten female rats in the 0 and 1,000 ppm groups were designated for interim evaluation at 7 months. Blood was collected via the retroorbital plexus for clinical chemistry analyses and by cardiac puncture for harvesting erythrocytes for hemoglobin binding studies. The livers were weighed.

Blood was collected from the retroorbital plexus while rats were under carbon dioxide/oxygen anesthesia. Blood for clinical chemistry was placed in tubes with no anticoagulant. Serum samples were analyzed using a Hitachi 704 chemistry analyzer (Boehringer Mannheim, Indianapolis, IN). The clinical chemistry parameters measured are listed in Table 2. For the hemoglobin binding study, blood was mixed with heparin as the anticoagulant and then transferred to a centrifuge tube and centrifuged at 1,300 G for 25 minutes at room temperature. Plasma and buffy coat were aspirated and discarded. Packed red blood cells were then washed with isotonic saline and centrifuged at 500 G for 15 minutes at 4° C. The saline was aspirated, and the washing was repeated twice. The washed erythrocytes and portions of the liver, kidney, testes, and spleen collected at 7 months were stored at 70° C and subsequently sent to the University of North Carolina at Chapel Hill for biochemical analyses.

During study week 106 (1 to 3 days prior to necropsy while animals were still receiving dosed feed), blood samples were collected from the retroorbital sinus of 200, 400, and 600 ppm males and females. Males were bled at 6:00 a.m., 9:00 a.m., 12:00 p.m., 3:00 p.m., 6:00 p.m., or 9:00 p.m. on day 1 or 12:00 a.m. or 3:00 a.m. on day 2. Females were bled at the same time points, except on days 2 and 3. Three males or females were bled at each time point. Each animal was bled at only one time point except in groups with fewer than 24 survivors; in animals bled twice, sampling times were separated by at least 12 hours. All blood samples were collected under carbon dioxide/oxygen anesthesia into tubes containing heparin as the anticoagulant. The red cell fraction was separated from the plasma via centrifugation, and the plasma was stored at 20° C until shipped on dry ice to Midwest Research Institute for determination of plasma pentachlorophenol concentrations.

All animals were killed by carbon dioxide inhalation. A complete necropsy and microscopic examination

were performed on all study animals. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. For extended evaluation of renal proliferative lesions in male rats, kidneys were step sectioned at 1 mm intervals, and four additional sections were obtained from each kidney. Tissues examined microscopically are listed in Table 2.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The 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 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. For the 2-year study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the liver, nose, stomach, and forestomach of male rats and the liver and nose of female rats.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson 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 any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Pentachlorophenol

28-Day Study	2-Year Study
Study Laboratory Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)
Strain and Species F344/N rats	F344/N rats
Animal Source Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies 13 days	13 days
Average Age When Studies Began 6 weeks	6 weeks
Date of First Exposure Males: 1 June 1992 Females: 2 June 1992	23 November 1992
Duration of Exposure 28 days (7 days/week)	106 weeks, except 1,000 ppm group which received undosed feed from week 53 to study completion (7 days/week)
Date of Last Exposure Males: 29 June 1992 Females: 30 June 1992	28 November 1994 to 2 December 1994 (core study animals) 22 November 1993 (stop-exposure animals)
Necropsy Dates Males: 29 June 1992 Females: 30 June 1992	28 November 1994 to 2 December 1994 (core study animals) 25 May 1993 (7-month interim evaluation animals)
Average Age at Necropsy Rats: 10 weeks	7-Month interim evaluation: 33 weeks Terminal sacrifice: 112 weeks
Size of Study Groups 10 males and 10 females	50 males and 50 females (200, 400, and 600 ppm) 60 males and 60 females (0 and 1,000 ppm)
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 28-day study
Animals per Cage 5	5
Method of Animal Identification Tail tattoo	Tail tattoo
Diet NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 28-day study, changed twice weekly
Water Tap water (City of Columbus municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 28-day study

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Pentachlorophenol

28-Day Study	2-Year Study
Cages Cage type (Lab Products, Inc., Maywood, NJ), changed twice per week	Same as 28-day study
Bedding Sani-chips (P.J. Murphy Forest Products, Montville, NJ), changed twice per week	Same as 28-day study
Cage Filters DuPont 2024 spun-bonded polyester (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks	Same as 28-day study
Racks Stainless steel drawer (Lab Products, Inc., Maywood, NJ), changed every 2 weeks	Same as 28-day study
Animal Room Environment Temperature: 21.1°-23.9° C Relative humidity: 44%-64% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 20.6°-25.6° C Relative humidity: 33%-66% Room fluorescent light: 12 hours/day Room air changes: 10/hour
Exposure Concentrations 0, 200, 400, 800, 1,600, or 3,200 ppm in feed, available *ad libitum*	0, 200, 400, 600, or 1,000 ppm in feed, available *ad libitum*
Type and Frequency of Observation Observed twice daily; animals were weighed and clinical findings were recorded initially, weekly, and at the end of the study. Feed consumption was recorded twice weekly.	Observed twice daily; animals were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies. Clinical findings were recorded monthly. Feed consumption was recorded over a 7-day period during study weeks 1, 5, 9, and 12, and monthly thereafter.
Method of Sacrifice Carbon dioxide inhalation	Same as 28-day study
Necropsy Necropsy performed on all animals. The liver was weighed.	Necropsy performed on all animals. The liver was weighed at the 7-month interim evaluation.
Clinical Pathology None	Blood was collected from the retroorbital plexus of 10 males and 10 females from the control and 1,000 ppm groups at the 7-month interim evaluation for clinical chemistry. ***Clinical chemistry:*** alanine aminotransferase, alkaline phosphatase, sorbitol dehydrogenase, and bile salts

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of Pentachlorophenol

28-Day Study	2-Year Study
Histopathology	
Complete histopathology was performed on all animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland with adjacent skin, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathology was performed on all animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular, mesenteric), mammary gland with adjacent skin, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.
Plasma Pentachlorophenol Determinations	
None	At the end of the study, blood was collected from the retroorbital plexus at eight time points from rats in the 200, 400, and 600 ppm groups for plasma pentachlorophenol determinations.

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. Animals found dead of other than natural causes or missing 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 are presented in Tables A1, A5, B1, and B4 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3a, A3b, B3a, and B3b) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) 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. Tables A3a, A3b, B3a, and B3b also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived

until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344/N rats and B6C3F$_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected tests were used in the analysis of lesion incidence, and reported P values are one sided. Values of P greater than 0.5 are presented as 1–P with the letter N added to indicate a lower incidence or negative trend in neoplasm occurrence relative to the control group (e.g., P=0.99 is presented as P=0.01N). For neoplasms and nonneoplastic lesions detected at the interim evaluation, the Fisher exact test (Gart *et al.*, 1979), a procedure based on the overall proportion of affected animals, was used.

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. Liver and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Multiple comparisons of clinical chemistry data were made with Wilcoxon's test (Conover, 1971). Plasma concentrations, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). 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). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with 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 neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 2-year study was conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year study were submitted to the NTP Archives, this study was audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. 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 comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of pentachlorophenol was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and induction of micronucleated

erythrocytes in bone marrow of male rats and mice. The protocols for these studies and the results are given in Appendix C.

The genetic toxicity studies of pentachlorophenol 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 molecular structure and the effects 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 chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical mutagenesis and the somatic mutation theory of cancer (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 correlate less 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 the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are 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 appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

RESULTS

28-DAY STUDY

With the exception of one male rat and two female rats exposed to 3,200 ppm, all animals survived until the end of the study (Table 3). The final mean body weights of male rats exposed to 1,600 or 3,200 ppm and female rats exposed to 400, 800, 1,600, or 3,200 ppm were significantly less than those of the controls; males and females exposed to 3,200 ppm lost weight during the study. Mean body weight gains of males exposed to 800 ppm or greater and of all exposed groups of females were significantly less than those of the controls. Feed consumption by 1,600 and 3,200 ppm males and females on day 1 and 3,200 ppm males on day 28 was less than that by the control groups; reduced feed consumption early in the study was attributed to reduced palatability of the dosed feed. Dietary concentrations of 200, 400, 800, 1,600, and 3,200 ppm pentachlorophenol resulted in average daily doses of approximately 20, 40, 75, 150, and 270 mg pentachlorophenol/kg body weight to males and females. Clinical findings included thinness and ruffled fur in 1,600 ppm females and 3,200 ppm males and females and ruffled fur in 1,600 ppm males beginning on day 8.

The absolute liver weights of males exposed to 200, 400, 800, or 1,600 ppm and all exposed groups of females were significantly greater than those of the controls (Table E1). The absolute liver weight of males in the 3,200 ppm group was significantly less than that of the controls. Relative liver weights of males exposed to 400 ppm or greater and of all exposed groups of females were greater than those of the controls.

Increased incidences of hepatocyte degeneration occurred in males and females exposed to 400 ppm or greater compared to the controls (Table 4). Affected hepatocytes were slightly shrunken and individualized with eosinophilic, granular cytoplasm and a pale, clear nucleus or no apparent nucleus. The severity of the degeneration generally ranged from minimal to mild. Minimal centrilobular hepatocyte hypertrophy, characterized by a slight enlargement of hepatocytes, was present in the 1,600 and 3,200 ppm groups, and the incidences in the 3,200 ppm males and females were significantly greater than those in the controls. The hypertrophy was not a prominent change.

All male rats in the 3,200 ppm group had minimal to marked germinal epithelial degeneration in the seminiferous tubules (Table 4). This lesion was multifocal to diffuse and was characterized by a lack of spermatozoa and a loss of germinal epithelium. Epididymal tubules in the 3,200 ppm males contained reduced numbers of or no spermatozoa and increased numbers of sloughed degenerated germinal epithelial cells. This lesion was considered secondary to the generalized poor condition of the rats in this group. Nasal sections from males revealed minimal to mild chronic active inflammation in all groups, with a 100% incidence in the controls and lower incidences in exposed groups (control, 10/10; 200 ppm, 1/10; 400 ppm, 5/10; 800 ppm, 3/10; 1,600 ppm, 1/10; 3,200 ppm, 1/10).

TABLE 3
Survival, Body Weights, and Feed Consumption of Rats in the 28-Day Feed Study of Pentachlorophenol

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Day 1	Day 28
Male							
0	10/10	141 ± 2	231 ± 3	90 ± 4		15.6	19.0
200	10/10	142 ± 3	250 ± 2	108 ± 1	108	16.3	20.3
400	10/10	141 ± 2	242 ± 3	101 ± 2	105	16.3	20.7
800	10/10	143 ± 2	225 ± 2	83 ± 2*	98	14.8	20.9
1,600	10/10	141 ± 2	199 ± 1**	58 ± 1**	86	9.9	20.3
3,200	9/10[d]	142 ± 2	121 ± 3**	–21 ± 2**	53	6.0	12.7
Female							
0	10/10	117 ± 2	161 ± 2	44 ± 1		11.4	13.4
200	10/10	118 ± 2	156 ± 2	38 ± 1**	97	11.4	13.5
400	10/10	117 ± 1	153 ± 2**	35 ± 1**	95	10.9	13.0
800	10/10	119 ± 2	148 ± 2**	29 ± 1**	92	10.1	13.6
1,600	10/10	118 ± 2	131 ± 3**	13 ± 2**	81	4.9	13.2
3,200	8/10[e]	119 ± 2	92 ± 1**	–28 ± 2**	57	2.9	12.0

* Significantly different ($P \leq 0.05$) from the control group by Williams' test
** $P \leq 0.01$
[a] Number of animals surviving at 28 days/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.
[c] Feed consumption data are expressed as grams of feed consumed per animal per day.
[d] Day of death: 17
[e] Day of death: 7, 16

TABLE 4
Incidences of Selected Nonneoplastic Lesions in Rats in the 28-Day Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	800 ppm	1,600 ppm	3,200 ppm
Male						
Liver[a]	10	10	10	10	10	10
Hepatocyte, Degeneration[b]	0	0	4* (1.0)[c]	7** (1.7)	9** (1.9)	10** (2.4)
Hepatocyte, Centrilobular, Hypertrophy	0	0	0	0	3 (1.0)	6** (1.0)
Testes	10	10	10	10	10	10
Germinal Epithelium, Degeneration	0	0	0	0	0	10** (2.5)
Female						
Liver	10	10	10	10	10	9
Hepatocyte, Degeneration	0	0	1 (1.0)	6** (2.0)	8** (2.0)	8** (1.5)
Hepatocyte, Centrilobular, Hypertrophy	0	0	0	0	1 (1.0)	7** (1.4)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Exposure Concentration Selection Rationale: Exposure concentrations selected for the 2-year study were based on lower mean body weights and body weight gains, increased liver weights, and liver lesions observed in the 28-day study. Over a 2-year period, 400 ppm pentachlorophenol was expected to cause minimal or no adverse effects, but 800 ppm was predicted to cause serious adverse effects in the liver. Therefore, concentrations of 200, 400, and 600 ppm were selected for the 2-year pentachlorophenol studies. To test the hypothesis that some chemicals, especially halogenated hydrocarbons, are more potent carcinogens under a short-term, high-dose exposure regimen than under a low-dose, continuous exposure regimen, an additional 1,000 ppm stop-exposure group was included. Initially, exposure for the 1,000 ppm group was to be stopped after 26 weeks, and animals were to be held until the end of the 2-year study, but exposure to pentachlorophenol was extended to 12 months because no overt toxic effects were observed in the liver during the interim evaluation of animals at 7 months.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves in Figures 1 and 2. Survival of 600 and 1,000 ppm males was significantly greater than that of the controls; survival of all other exposed groups was similar to that of the control groups.

TABLE 5
Survival of Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
Male					
Animals initially in study	60	50	50	50	60
7-Month interim evaluation[a]	10	0	0	0	10
Moribund	28	28	24	11	17
Natural deaths	10	6	5	8	6
Animals surviving to study termination	12[e]	16	21	31[f]	27
Percent probability of survival at end of study[b]	24	32	42	62	54
Mean survival (days)[c]	656	647	661	693	679
Survival analysis[d]	P<0.001N[g]	P=0.810N	P=0.239N	P<0.001N	P=0.006N
Female					
Animals initially in study	60	50	50	50	60
7-Month interim evaluation[a]	10	0	0	0	10
Moribund	15	12	12	17	17
Natural deaths	7	5	4	5	5
Animals surviving to study termination	28	33	34	28	28
Percent probability of survival at end of study	56	66	68	56	56
Mean survival (days)	680	685	692	680	683
Survival analysis	P=1.000[g]	P=0.386N	P=0.319N	P=1.000	P=0.964N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[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 exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.
[e] Includes one animal that died during the last week of the study
[f] Includes two animals that died during the last week of the study
[g] Stop-exposure group not included in trend test analysis

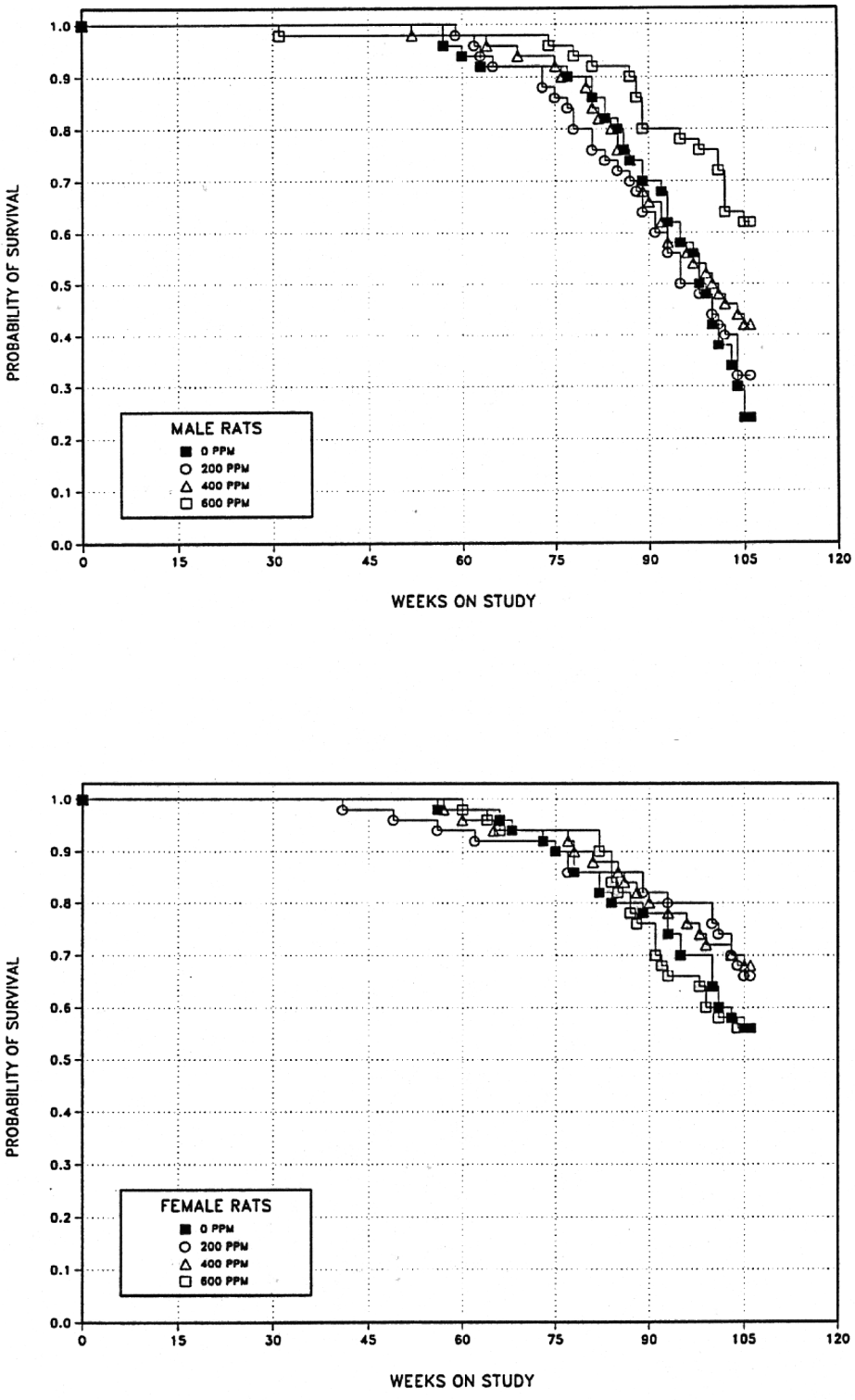

FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Pentachlorophenol for 2 Years

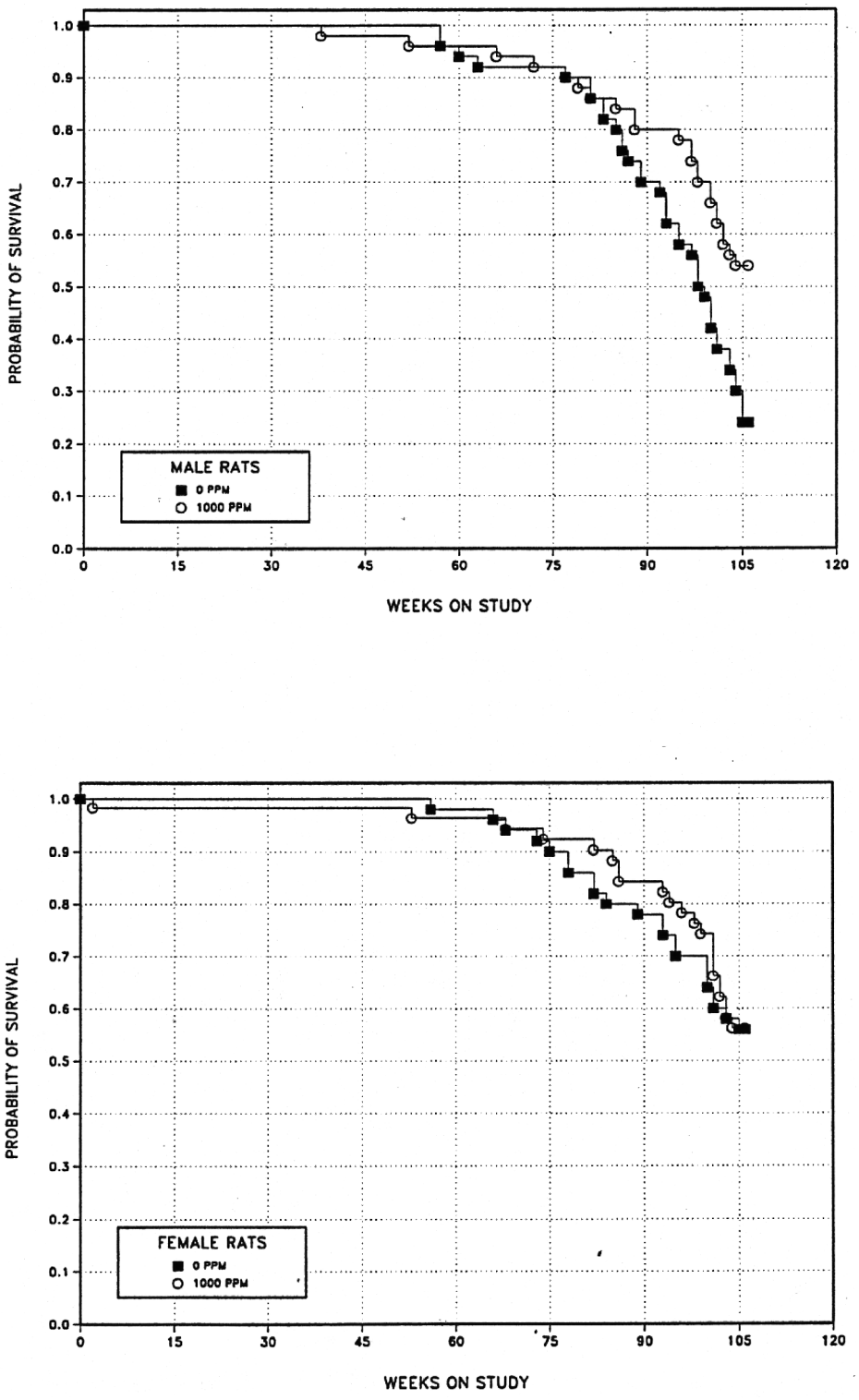

FIGURE 2
Kaplan-Meier Survival Curves for Stop-Exposure Male and Female Rats Exposed to Pentachlorophenol

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of 200 ppm males and females were generally similar to those of the controls throughout the study (Tables 6 and 7 and Figures 3 and 4). Mean body weights of 400 ppm males after week 25 and of 400 ppm females after week 37 were generally less than those of the controls until week 101. Mean body weights of 600 ppm males and females were less than those of the controls after weeks 17 and 12, respectively. When exposure to pentachlorophenol was discontinued at week 52, mean body weights of 1,000 ppm males and females were 17% and 22% less than those of the respective controls; however, by the end of week 87, the mean body weights were similar to those of the controls.

Generally, feed consumption by exposed groups was similar to that by the controls (Tables G1 and G2). The continuous exposure concentrations of 200, 400, and 600 ppm resulted in average daily doses of 10, 20, and 30 mg pentachlorophenol/kg body weight to males and females. The average daily dose for stop-exposure rats was 60 mg/kg. No chemical-related clinical findings were noted.

Clinical Chemistry

At 7 months, there was evidence of a liver effect that was demonstrated by increased serum alkaline phosphatase activity in 1,000 ppm males and increased sorbitol dehydrogenase activities in 1,000 ppm males and females (Table D1). Increased alkaline phosphatase activity typically suggests cholestasis; increased sorbitol dehydrogenase activity is an indicator of hepatocellular leakage. Alanine aminotransferase activity, another marker of hepatocellular leakage, also demonstrated a similar trend of increased values consistent with the increased sorbitol dehydrogenase activities.

Plasma Determinations of Pentachlorophenol

In general, the mean plasma concentrations were approximately proportional to pentachlorophenol concentrations in the feed. The plasma concentrations in female rats were higher than those in male rats at each exposure concentration. The average plasma concentrations for groups of males exposed to 200, 400, or 600 ppm pentachlorophenol were 17, 36, or 53 μg/mL; for the females, the average concentrations were 24, 44, or 67 μg/mL, respectively.

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Pentachlorophenol

Weeks on Study	0 ppm		200 ppm			400 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
1	137	50	139	101	50	139	101	50
2	178	50	178	100	50	178	100	50
3	215	50	214	100	50	210	98	50
4	232	50	243	105	50	233	101	50
5	261	50	264	101	50	257	98	50
6	276	50	282	102	50	274	99	50
7	297	50	299	101	50	288	97	50
8	310	50	311	100	50	297	96	50
9	327	50	325	99	50	313	96	50
10	337	50	335	100	50	325	97	50
11	344	50	342	100	50	334	97	50
12	358	50	353	99	50	342	96	50
13	366	50	361	99	50	349	95	50
17	395	50	390	99	50	377	96	50
21	416	50	413	99	50	395	95	50
25	437	50	427	98	50	412	94	50
29	452	50	449	99	50	428	95	50
33	467	50	460	98	50	441	94	50
37	476	50	470	99	50	449	94	50
41	486	50	474	98	50	451	93	50
45	494	50	483	98	50	459	93	50
49	500	50	489	98	50	463	93	50
52	500	50	491	98	50	464	93	50
57	509	50	495	97	50	472	93	49
61	508	47	493	97	49	470	93	49
65	515	46	492	96	46	474	92	48
69	514	46	492	96	46	472	92	48
73	510	46	491	96	45	470	92	47
77	504	46	485	96	43	467	93	45
81	503	44	479	95	40	461	92	43
85	498	41	473	95	37	456	92	40
89	492	36	460	94	34	448	91	36
93	483	32	453	94	30	442	92	30
97	465	29	449	97	25	436	94	28
101	449	21	434	97	22	417	93	25
105	423	14	436	103	16	417	99	21
Mean for weeks								
1-13	280		280	100		272	97	
14-52	462		455	98		434	94	
53-105	490		472	96		454	93	

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Pentachlorophenol

Weeks on Study	600 ppm			1,000 ppm (Stop-Exposure)		
	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	140	102	50	137	100	50
2	177	99	50	166	93	50
3	209	97	50	198	92	50
4	237	102	50	223	96	50
5	258	99	50	242	93	50
6	274	99	50	258	93	50
7	290	98	50	270	91	50
8	301	97	50	279	90	50
9	312	96	50	289	88	50
10	318	95	50	296	88	50
11	329	96	50	303	88	50
12	339	95	50	314	88	50
13	347	95	50	320	87	50
17	366	93	50	336	85	50
21	387	93	50	353	85	50
25	407	93	50	367	84	50
29	419	93	50	381	84	50
33	436	93	49	396	85	50
37	436	92	49	396	83	50
41	443	91	49	400	82	49
45	453	92	49	410	83	49
49	454	91	49	413	83	49
52	458	92	49	412	83	49
57	460	90	49	445	88	48
61	457	90	49	451	89	48
65	456	89	49	458	89	48
69	462	90	49	472	92	47
73	458	90	49	477	94	46
77	453	90	48	478	95	46
81	452	90	46	472	94	44
85	444	89	46	479	96	43
89	437	89	43	472	96	40
93	430	89	40	459	95	40
97	427	92	39	450	97	39
101	411	91	38	447	99	33
105	396	94	32	433	102	27
Mean for weeks						
1-13	272	97		253	90	
14-52	426	92		386	84	
52-105	442	90		461	94	

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Pentachlorophenol

Weeks on Study	0 ppm		200 ppm			400 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
1	114	50	114	100	50	113	99	50
2	132	50	133	101	50	131	99	50
3	145	50	145	100	50	143	99	50
4	153	50	156	102	50	154	101	50
5	164	50	166	101	50	164	100	50
6	171	50	172	101	50	168	99	50
7	177	50	179	101	50	174	98	50
8	180	50	182	101	50	177	98	50
9	186	50	188	101	50	183	99	50
10	191	50	191	100	50	187	98	50
11	193	50	194	100	50	189	98	50
12	197	50	196	99	50	192	97	50
13	200	50	200	100	50	196	98	50
17	210	50	207	98	50	204	97	50
21	218	50	215	99	50	209	96	50
25	223	50	219	98	50	217	97	50
29	231	50	227	98	50	221	96	50
33	237	50	233	98	50	229	97	50
37	246	50	239	97	50	231	94	50
41	256	50	249	97	50	241	94	50
45	267	50	256	96	49	243	91	50
49	275	50	263	96	48	252	92	50
52	283	50	270	95	48	260	92	50
57	300	49	288	96	47	274	91	50
61	307	49	294	96	47	283	92	48
65	315	49	303	96	46	290	92	48
69	324	47	309	95	46	298	92	47
73	326	46	307	94	46	299	92	47
77	330	45	311	94	45	304	92	47
81	330	43	315	96	43	306	93	45
85	334	40	322	96	43	308	92	44
89	336	40	320	95	43	313	93	41
93	337	38	320	95	41	314	93	40
97	339	35	326	96	40	317	94	38
101	334	32	320	96	37	323	97	36
105	335	29	322	96	34	322	96	35
Mean for weeks								
1-13	169		170	101		167	99	
14-52	245		238	97		231	94	
53-105	327		312	95		304	93	

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Pentachlorophenol

Weeks on Study	600 ppm			1,000 ppm (Stop-Exposure)		
	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	114	100	50	109	96	50
2	131	99	50	123	93	50
3	141	97	50	134	92	49
4	151	99	50	143	94	49
5	159	97	50	149	91	49
6	164	96	50	155	91	49
7	169	96	50	159	90	49
8	174	96	50	162	90	49
9	178	96	50	166	89	49
10	182	95	50	169	88	49
11	185	96	50	173	89	49
12	186	94	50	174	88	49
13	189	95	50	176	88	49
17	196	93	50	183	87	49
21	202	93	50	188	86	49
25	206	92	50	193	86	49
29	211	91	50	198	86	49
33	216	91	50	203	86	49
37	219	89	50	204	83	49
41	228	89	50	210	82	49
45	230	86	50	214	80	49
49	233	85	50	218	79	49
52	241	85	50	220	78	49
57	252	84	50	255	85	48
61	261	85	49	271	89	48
65	269	85	48	284	90	48
69	276	85	47	297	92	47
73	276	85	47	306	94	47
77	282	85	47	313	95	46
81	282	85	47	316	96	46
85	285	85	42	321	96	45
89	289	86	38	325	97	42
93	291	87	33	322	96	42
97	297	88	33	327	97	39
101	293	88	30	327	98	35
105	297	89	28	340	102	28
Mean for weeks						
1-13	163	96		153	91	
14-52	218	89		203	83	
53-105	281	86		308	94	

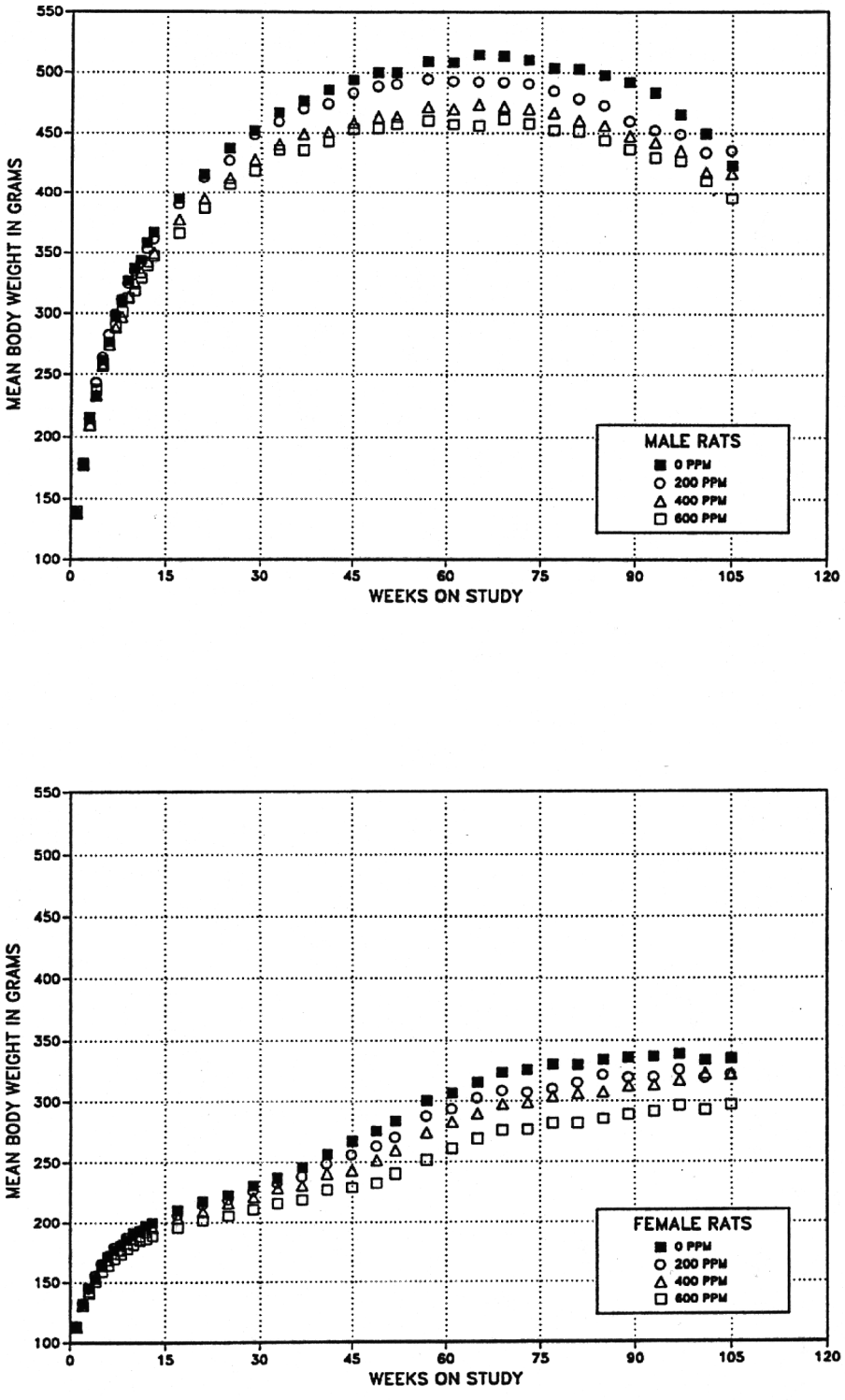

FIGURE 3
GrowthCurves for Male and Female Rats Exposed to Pentachlorophenol for 2 Years

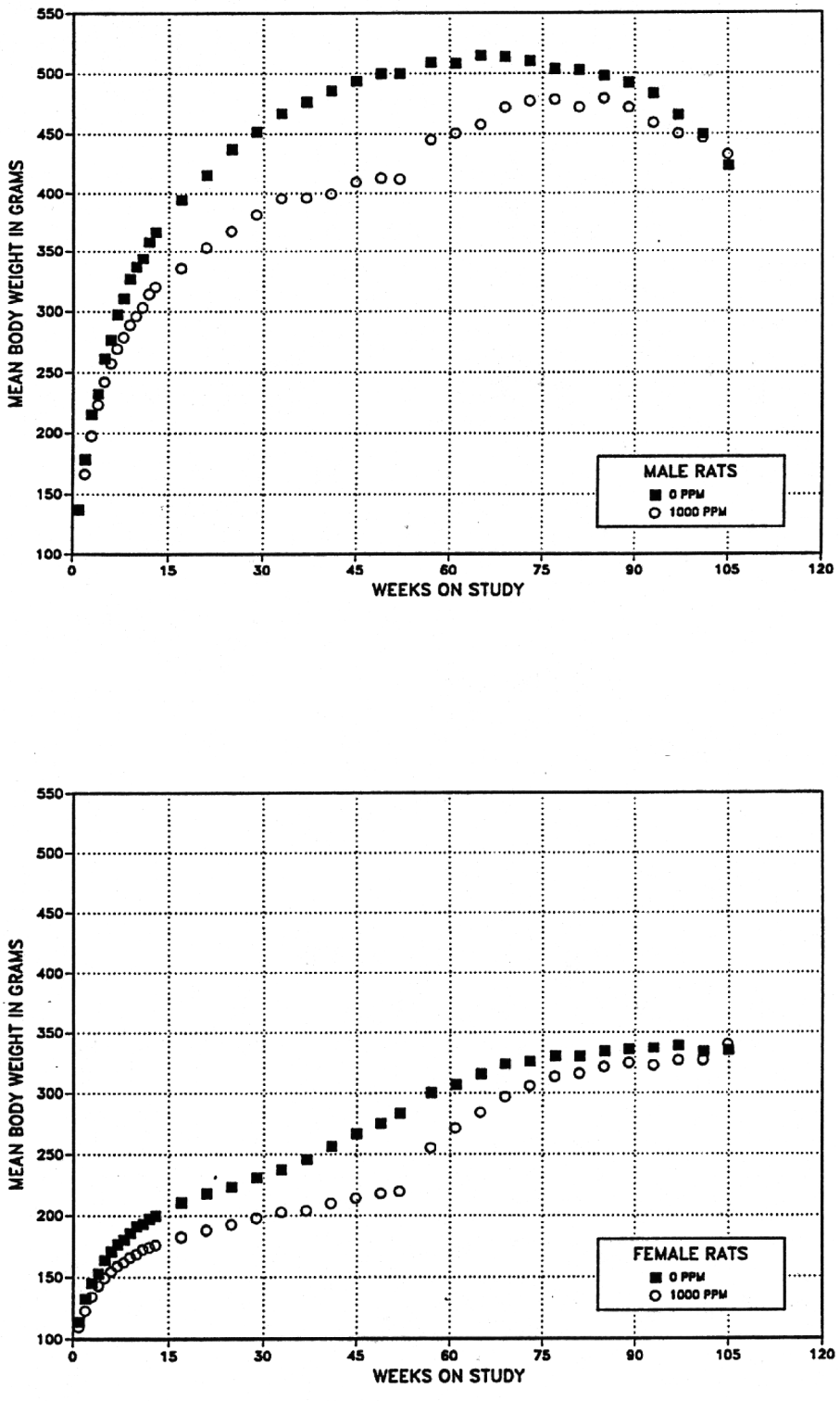

FIGURE 4
Growth Curves for Male and Female Rats Exposed to Pentachlorophenol

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mesotheliomas and incidences of neoplasms and/or nonneoplastic lesions of the nose, liver, kidney, adrenal gland, skin, and mammary 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.

Mesothelioma: A significantly increased incidence of malignant mesothelioma originating from the tunica vaginalis was present in 1,000 ppm males at the end of the study (Tables 8 and A3b). The incidence of malignant mesothelioma in 1,000 ppm males also exceeded the range for mesotheliomas in historical controls (Table A4a). In one control male and five 1,000 ppm males, these neoplasms were widely disseminated within the abdominal cavity. The mesotheliomas had the typical appearance characteristic of this lesion in F344/N rats and were composed of a highly branched, dense, fibrous stroma covered by one or more layers of basophilic cuboidal mesothelial cells. In some areas, the covering mesothelium consisted of a single layer of flattened cells. In larger neoplasms, multiple clusters or tubular structures composed of mesothelial cells were also present. Reevaluation of this anatomic site from all remaining males, including those in the core study, failed to reveal any additional neoplasms or instances of mesothelial hyperplasia.

TABLE 8
Incidences of Malignant Mesothelioma in Male Rats in the 2-Year Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-exposure)
Malignant Mesothelioma[a]					
Overall rate[b]	1/50 (2%)	0/50 (0%)	2/50 (4%)	0/50 (0%)	9/50 (18%)
Adjusted rate[c]	2.6%	0.0%	5.1%	0.0%	20.6%
Terminal rate[d]	0/12 (0%)	0/16 (0%)	0/21 (0%)	0/31 (0%)	4/27 (15%)
First incidence (days)	617	—[f]	593	—	502
Poly-3 test[e]	P=0.447N	P=0.509N	P=0.511	P=0.472N	P=0.014

[a] Historical incidence for 2-year feed studies with untreated control groups (mean ± deviation): 40/1,354 (3.0% ± 2.3%); range 0%-8%, includes data for benign, malignant, and NOS
[b] Number of neoplasm-bearing animals/number of animals examined
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test [the 1,000 ppm (stop-exposure) group was excluded from the trend test]. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[f] Not applicable; no neoplasms in animal group

Nose: Nasal squamous cell carcinomas occurred in a control male, three 200 ppm males, a 400 ppm male, and five 1,000 ppm males at 2 years (Tables 9 and A1), and the incidence in the 1,000 ppm group exceeded the historical control range (Table A4b). This neoplasm was not observed in females. Squamous cell carcinomas had the typical morphologic appearance associated with these neoplasms. They were composed of multiple layers of clusters, moderately to highly pleomorphic stratified squamous epithelium with varying degrees of keratin formation, and, in many neoplasms, a mild to marked scirrhous reaction. Two of these neoplasms had the appearance of arboriform masses consisting of a dense fibrous tissue core covered by a thick layer of stratified squamous epithelium with areas of invasion of the fibrous stroma along the base of the neoplasm. At 2 years, one nasal squamous cell carcinoma had spread to the oral cavity in a 1,000 ppm male (Table A1). Nasal squamous cell carcinomas are rare; none have been observed in 353 male controls from previous feed studies at the study laboratory. The overall historical control rate in male rats from feed studies was only 0.4% (Tables 9 and A4b). Hence, the increase seen in the 2-year study was considered to be chemical related.

At 2 years, evidence of a fungal infection was present in males and to a lesser extent in females. The incidences of nasal fungus in 400, 600, and 1,000 ppm males and 600 ppm females were significantly decreased relative to the controls (Tables 9, A5, and B4). The incidences of hyperplasia of the respiratory epithelium were significantly decreased in 600 and 1,000 ppm males and 200, 400, and 1,000 ppm females relative to the controls. The incidences of squamous metaplasia of the respiratory epithelium in 1,000 ppm males and females were less than those in the controls. Incidences of inflammation in exposed animals were slightly, but not significantly, less than those in the controls. Except for minimal inflammation in a few rats, these changes were not observed in animals at the 7-month interim evaluation. The inflammatory reaction in animals in the core-study and stop-exposure groups consisted of large aggregates of mixed inflammatory cells, mainly neutrophils in the nasal cavity. Often these inflammatory cells surrounded a large mat of fungal mycelia. The respiratory epithelium adjacent to the inflammation was thickened and, in some areas, had undergone metaplasia to stratified squamous epithelium. There did not appear to be a direct correlation between hyperplasia or squamous metaplasia and squamous cell carcinoma: higher incidences of squamous cell carcinoma occurred in exposed groups, which had lower incidences of hyperplasia and squamous metaplasia than the controls. In the evaluation of three nasal sections at a single time point, only one of the five animals with nasal squamous cell carcinomas from the stop-exposure group also had a diagnosis of fungus and/or lesions (inflammation or squamous metaplasia) possibly associated with fungus.

Nasal tissues from four controls which had mycelial growths with conidiophores were stained with periodic acid-Schiff and Gomori-methanamine-silver stains, and examination of these stained slides revealed filamentous fungal organisms with regular septate hyphae and dichotomous branching, prominent conidiophores, and numerous round conidia. These morphologic features are consistent with *Aspergillus* species.

TABLE 9
Incidences of Selected Neoplasms and Nonneoplastic Lesions of the Nose in Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm		200 ppm		400 ppm		600 ppm		1,000 ppm (Stop-Exposure)	
Male										
7-Month Interim Evaluation										
Number Examined Microscopically	10								10	
Inflammation, Chronic Active[a]	3	(2.3)[b]							1	(3.0)
2-Year Study										
Number Examined Microscopically	50		50		50		50		50	
Fungus	21		15		10**		11**		7**	
Respiratory Epithelium, Hyperplasia	24	(2.4)	16	(2.6)	17	(2.4)	13*	(2.5)	11**	(2.5)
Respiratory Epithelium, Metaplasia, Squamous	12	(2.1)	9	(2.6)	8	(2.3)	7	(2.1)	5*	(2.0)
Squamous Cell Carcinoma[c]										
Overall rate[d]	1/50 (2%)		3/50 (6%)		1/50 (2%)		0/50 (0%)		5/50 (10%)	
Adjusted rate[e]	2.7%		8.1%		2.6%		0.0%		11.65%	
Terminal rate[f]	0/12 (0%)		0/16 (0%)		0/21 (0%)		0/31 (0%)		2/27 (7%)	
First incidence (days)	643		505		593		—[h]		460	
Poly-3 test[g]	P=0.171N		P=0.299		P=0.756N		P=0.471N		P=0.128	
Female										
7-Month Interim Evaluation										
Number Examined Microscopically	10								10	
Inflammation, chronic active	4	(2.3)							1	(2.0)
2-Year Study										
Number Examined Microscopically	50		50		50		50		50	
Fungus	6		2		1		0*		2	
Inflammation, Chronic Active	13	(2.0)	13	(1.2)	7	(1.3)	6	(1.3)	7	(1.6)
Respiratory Epithelium, Hyperplasia	10	(2.5)	3*	(2.0)	2*	(1.5)	4	(2.0)	2*	(2.5)
Respiratory Epithelium, Metaplasia, Squamous	3	(2.7)	3	(2.0)	0		1	(1.0)	0	

* Significantly different (P≤0.05) from the control group by the Poly-3 test
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year feed studies with untreated control groups (mean ± deviation): 5/1,341 (0.4% ± 1.0%); range, 0%-4%
[d] Number of animals with neoplasm per number of animals with nose examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence are the P values associated with the trend test [the 1,000 ppm (stop-exposure) group was excluded from the trend test]. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.
[h] Not applicable; no neoplasms in animal group.

Liver: At the 7-month interim evaluation, the incidences of centrilobular hepatocyte hypertrophy in 1,000 ppm males and females and hepatocyte cytoplasmic vacuolization in males significantly exceeded those in the controls. Hepatocyte hypertrophy was not observed at 2 years, and incidences of cytoplasmic vacuolization in exposed rats were generally similar to or lower than those in the controls. At 2 years, the

incidence of basophilic foci in 1,000 ppm male rats, but not in the other exposed male groups, was significantly greater than that in the controls (Tables 10 and A5). The incidence of eosinophilic foci in 600 ppm males was marginally more significant than that in the controls, while incidences of clear cell and mixed cell foci occurred with negative trends in core-study females. Incidences of hepatodiaphragmatic nodules in males in all exposed groups and hepatocyte cystic degeneration in males exposed to 400 ppm or greater were significantly greater than those in the controls. Hepatodiaphragmatic nodules are developmental anomalies commonly observed in F344/N rats; the increased incidences observed were not related to exposure concentration. Cystic degeneration, which appeared to be treatment related, was of uncertain biological relevance. At 2 years, the incidence of minimal to mild chronic inflammation in 1,000 ppm males was increased, but this lesion was of similar severity to that observed in the controls and other exposed groups. These changes were not associated with any treatment-related increases in the incidences of hepatocellular neoplasms.

Kidney: Renal tubule adenomas occurred in one control male, one 200 ppm male, and two 1,000 ppm males at 2 years. Renal tubule carcinomas occurred in two 600 ppm males, and benign renal tubule oncocytoma occurred in one 1,000 ppm male (Table A1). Additional step sections of kidneys were prepared from the remaining formalin-fixed tissues. Although additional neoplasms were found when the standard and extended evaluations were combined, the incidences of renal tubule adenoma or carcinoma (combined) in exposed groups were not significantly different from that in the controls (Tables A3a and A3b).

There was an undefined pigment in the renal tubule epithelium of all 1,000 ppm males and females, but not in the controls, at the 7-month interim evaluation. Renal tubule pigmentation similar to, but more severe than, that observed at the 7-month interim evaluation was present in nearly all rats at 2 years (males: 49/50; 48/50; 49/50; 50/50, 47/50; females: 48/50, 48/50, 50/50, 50/50, 49/50; Tables A5 and B4). The pigmentation was slightly more severe in exposed rats than in the controls (males: 1.1, 1.4, 1.4, 1.6, 1.2; females: 1.1, 1.1, 1.2, 1.4, 1.2). Kidney sections from three 600 ppm males with evidence of pigment in renal tubule epithelium were stained in an attempt to identify the pigment. Spleen sections provided a positive control for hemosiderin pigment and for comparison to the pigment reported by the study pathologist in kidneys. Prussian blue-positive pigment consistent with hemosiderin was present in the spleen with only a small amount of the renal pigment staining positive for hemosiderin. Unstained, coarse, brown particulate pigment was present in renal tubule cells. Renal and splenic pigment was negative for lipofuscin based upon periodic acid-Schiff and Ziel-Nielsson acid-fast staining but positive by Schmorl's staining for lipofuscin. Renal tubule pigment was not present in the 28-day study.

Adrenal Gland: The incidences of adrenal medullary hyperplasia were slightly increased in exposed groups of males compared to the controls at 2 years (control, 18/50; 200 ppm, 27/50; 400 ppm, 22/50; 600 ppm, 25/50; 1,000 ppm, 28/50; Table A5). At 2 years, the incidences of adrenal cortical hyperplasia in exposed females (7/50, 12/50, 23/50, 12/50, 17/50) and adrenal cortical hypertrophy in 400 and 600 ppm females (1/50, 6/50, 8/50, 7/50, 3/50; Table B4) were increased.

Skin: At 2 years, the incidence of keratoacanthoma in the 1,000 ppm males was increased compared to the controls (control, 0/50; 1,000 ppm, 7/50; Table A3b). However, the incidence in the 1,000 ppm group was within the historical control range from the NTP feed studies (Table A4c), and when viewed within the context of the combined related epidermal neoplasms, this effect was not considered to be biologically significant.

Mammary Gland: At 2 years, the incidences of fibroadenoma of the mammary gland in 600 and 1,000 ppm females were significantly less than that in the control group (control, 25/50; 200 ppm, 20/50; 400 ppm, 19/50; 600 ppm, 12/50; 1,000 ppm, 15/50; Tables B3a and B3b). This neoplasm occurred with a significant negative trend and was probably associated with low body weight gain.

TABLE 10
Incidences of Selected Nonneoplastic Lesions of the Liver in Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm		200 ppm		400 ppm		600 ppm		1,000 ppm (Stop-Exposure)	
Male										
7-Month Interim Evaluation										
Number Examined Microscopically	10								10	
Hepatocyte, Centrilobular, Hypertrophy[a]	0								6**	(1.7)[b]
Hepatocyte, Vacuolization, Cytoplasmic	0								8**	(1.3)
2-Year Study										
Number Examined Microscopically	50		50		50		50		50	
Basophilic Focus	17		14		20		16		31**	
Eosinophilic Focus	2		2		1		9*		7	
Hepatodiaphragmatic Nodule	0		7**		6*		8**		5*	
Inflammation, Chronic	22	(1.2)	16	(1.2)	22	(1.3)	22	(1.3)	34*	(1.3)
Hepatocyte, Vacuolization Cytoplasmic	10	(1.4)	3*	(1.7)	5	(1.2)	7	(1.3)	13	(1.5)
Hepatocyte, Degeneration, Cystic	16	(1.8)	22	(1.3)	28*	(1.5)	39**	(1.7)	28*	(1.5)
Female										
7-Month Interim Evaluation										
Number Examined Microscopically	10								10	
Hepatocyte, Centrilobular, Hypertrophy	0								6**	(1.5)
2-Year Study										
Number Examined Microscopically	50		50		50		50		50	
Clear Cell Focus	11		10		8		3*		16	
Mixed Cell Focus	7		7		5		2		5	
Hepatocyte, Degeneration, Cystic	0		0		0		1	(2.0)	0	
Hepatocyte, Vacuolization Cytoplasmic	7	(1.9)	2	(2.5)	1*	(1.0)	3	(1.0)	9	(1.4)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluation) or the Poly-3 test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

GENETIC TOXICOLOGY

Pentachlorophenol (91.6% pure) was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 at doses up to 30 μg/plate with and without induced rat or hamster liver S9; no significant increases in the number of revertant colonies were observed in any of the strain/activation combinations (Haworth *et al.*, 1983; Table C1). When tested for cytogenetic effects in cultured Chinese hamster ovary cells (Galloway *et al.*, 1987), pentachlorophenol was weakly positive for induction of sister chromatid exchanges (Table C2) and chromosomal aberrations (Table C3). In the sister chromatid exchange test, a weakly positive response was observed within a concentration range of 3 to 30 μg/mL in the absence of S9; with S9, no induction of sister chromatid exchanges was noted. In the chromosomal aberrations test, pentachlorophenol was negative without S9 but induced small but significant increases in the frequency of aberrant cells in the presence of S9 at concentrations of 80 and 100 μg/mL. In contrast to the positive *in vitro* results in the test for induction of chromosomal aberrations, no increase in the frequency of micronucleated erythrocytes was noted in the bone marrow of male rats (Table C4) or mice (Table C5) administered pentachlorophenol by intraperitoneal injection three times at 24-hour intervals. The highest doses administered to rats (75 mg/kg) and mice (150 mg/kg) were lethal.

DISCUSSION AND CONCLUSIONS

The National Cancer Institute nominated pentachlorophenol to the NTP for carcinogenicity testing based upon its widespread use as a wood preservative, its potential for entering the environment (pentachlorophenol residues have been found worldwide in soil, water, and air samples; in food products; and in human and animal tissues and body fluids), and the likelihood of bioaccumulation in the environment (the half-life of pentachlorophenol in soil is up to 5 years). The only in-depth study of pure pentachlorophenol of adequate duration (2 years) in rats did not show evidence of carcinogenicity (Schwetz *et al.*, 1978). The NTP (1989) conducted carcinogenesis studies of technical grade pentachlorophenol and Dowicide EC-7 only in mice because, at that time, the studies reported by Schwetz *et al.* (1978) were considered to be negative and adequately designed. However, these studies of pure pentachlorophenol were later considered to be inadequate for evaluation by the IARC (1991). Based on this evaluation and the positive findings in the mouse studies, the NTP undertook the current studies to reevaluate the carcinogenic potential of pentachlorophenol in rats.

A 28-day toxicity study of pentachlorophenol in male and female F344/N rats was conducted to select the exposure concentrations for the carcinogenicity study. The mean body weight gains of male rats exposed to 800 ppm or greater and of all exposed female groups were significantly less than those of the controls. The liver was the only major target of pentachlorophenol toxicity. The absolute and relative liver weights of 400, 800, and 1,600 ppm males and all exposed groups of females were significantly greater than those of the controls. Exposure concentration-related increases in the incidences of minimal to mild hepatocyte degeneration occurred in males and females exposed to 400 ppm or greater. For the 2-year exposure concentration selection, 400 ppm was expected to cause minimal or no adverse effects, but 800 ppm was predicted to cause serious adverse effects in the liver. Therefore, exposure concentrations of 200, 400, and 600 ppm were selected for the 2-year pentachlorophenol study. To test the hypothesis that some chemicals, especially halogenated hydrocarbons, appear to be more potent as carcinogens in a short-term, high-exposure regimen, a 1,000 ppm stop-exposure group was included. Initially, the pentachlorophenol exposure of the 1,000 ppm group was to be stopped after 26 weeks, and animals were to be held until the end of the 2-year study, but exposure to pentachlorophenol was extended to 12 months because no overt toxic effects were observed in the liver during the interim evaluation at 7 months. Based on the NTP pentachlorophenol toxicokinetic studies (Yuan *et al.*, 1994), the absorption and elimination of pentachlorophenol at the exposure concentrations selected (including the stop-exposure group) were expected to follow first-order kinetics.

In the 2-year study, survival of 600 and 1,000 ppm groups was greater than that of the controls; survival of all other exposed groups was similar to that of the controls. Mean body weights of the 400 and 600 ppm groups were generally less than those of the controls. The mean body weights of 1,000 ppm males and females were 17% and 22% less than those of the controls, respectively, when pentachlorophenol exposure was stopped at week 52. However, by the end of week 87, the mean body weights were similar to those of the controls. Generally, feed consumption by the exposed groups was similar to that by the controls. The increased survival in the 600 and 1,000 ppm groups may have been related to decreases in the body weights of these animals (Rao *et al.*, 1990).

In the 2-year study, a marginally significant increase in the incidence of hepatic eosinophilic foci occurred in males exposed to 600 ppm. In the absence of hepatocellular neoplasms, these foci are not considered to be biologically significant. In contrast to the 28-day study and the 7-month interim evaluation rats in the 1,000 ppm group, centrilobular hypertrophy was not observed in rats at 2 years. Mild hepatotoxicity has been observed in other studies using purified pentachlorophenol (Kimbrough and Linder, 1978). In those studies, rats that received 500 ppm pure pentachlorophenol in feed for 8 months had slightly enlarged liver cells with occasional cytoplasmic inclusions; no alterations were noted in the livers of rats

exposed to 20 or 100 ppm. However, liver toxicity was severe in rats exposed to 500 ppm technical grade pentachlorophenol in feed, as shown by lesions consisting of enlarged pleomorphic hepatocytes that had foamy cytoplasm or cytoplasm with large vacuoles. The walls of hepatic central veins of livers in exposed males and females were thickened. Mild and less severe liver effects were observed at 20 and 100 ppm.

Pentachlorophenol toxicity varies for different species. Pentachlorophenol induces much more severe liver toxicity in mice than in rats. The NTP conducted carcinogenesis studies of technical grade pentachlorophenol and Dowicide EC-7, a somewhat purer grade, in mice (NTP, 1989). Significant dose-related increases in the incidences of hepatocellular adenoma or carcinoma (combined) were observed in male mice treated with either formulation of pentachlorophenol. Dowicide EC-7 induced significant dose-related increases in the incidences of hepatocellular adenoma in female mice. Exposure to either the technical grade or Dowicide EC-7 caused increased incidences of adrenal pheochromocytoma in male mice; this effect was also seen in females exposed to 600 ppm Dowicide EC-7. Both preparations caused significant increases in the incidences of hemangiosarcoma. Chemical-related increases in the incidences of nonneoplastic liver lesions in male and female mice included hepatocellular cytomegaly, necrosis, inflammation, pigmentation, clear cell foci, and intrahepatic bile duct hyperplasia. However, the lesions were less severe in the livers of mice exposed to pure (98.6%) pentachlorophenol than in comparable groups exposed to technical grade (90.4%) pentachlorophenol.

Studies have also revealed minor effects of pentachlorophenol on the kidney. The most frequently reported toxic effect in rodent studies has been increased absolute kidney weight (Johnson *et al.*, 1973; Kimbrough and Linder, 1978; Schwetz *et al.*, 1978). This effect was not dose related and occurred in the absence of microscopic changes. In the current study, no renal effects were observed except for an undefined pigment present in the renal tubular epithelium of all groups of rats; this pigmentation was slightly more severe in exposed groups than in the controls. Brown granular pigment within the tubular epithelial cells in female rats exposed to 10 or 30 mg of pentachlorophenol/kg body weight was observed in previous carcinogenicity studies reported by Schwetz *et al.* (1978). The significance of these pigments is unknown.

In the previous carcinogenicity studies in male and female Sprague-Dawley rats (Schwetz *et al.*, 1978), pentachlorophenol was administered in feed at concentrations of 0, 1, 3, 10, or 30 mg/kg body weight for up to 2 years. No carcinogenic activity related to pentachlorophenol administration was observed. In the current studies, the continuous exposure concentrations of 200, 400, and 600 ppm resulted in average daily doses of 10, 20, and 30 mg pentachlorophenol per kilogram body weight to males and females. At these exposure concentrations, which are similar to those in the previous studies, no pentachlorophenol-induced increases in neoplasm incidences were observed. However, the 1,000 ppm stop-exposure male rats (which received an average daily dose of about 60 mg/kg for 12 months and were held for 1 year on the control diet) had an increased incidence of mesothelioma. Mesotheliomas originating from the tunica vaginalis were present in nine treated males and one control male. In five exposed males and in the control male, these neoplasms were widely disseminated within the abdominal cavity.

The cytologic features and growth patterns of the mesotheliomas in this pentachlorophenol study were compared with those diagnosed in 263 exposed and 12 control males in eight previously conducted bioassays. The ranges of severity of the tunica vaginalis and abdominal cavity involvement, the spectra of growth patterns, and the ranges of cytological differentiation were similar between the mesotheliomas in the pentachlorophenol study and those in the other eight studies, including those in control males. Thus, there was no obvious cytomorphological difference between the pentachlorophenol-induced mesotheliomas and those commonly observed in F344/N male rats.

Although rather rare in control rats, mesotheliomas are the most common spontaneous neoplasms of the peritoneal cavity of male F344/N rats and have a historical control range of 0% to 8%. The incidence of spontaneous mesothelioma in female F344/N rats is 4 of 1,351. Others have also noted this difference between male and female rats. In a survey of mesothelioma incidences in 395 untreated male and female F344/N rats, 17 males but no females had this neoplasm (Tanigawa *et al.*, 1987).

The occurrence of nine mesotheliomas in 1,000 ppm males is clearly in excess of the historical control

incidence. Mesothelioma was first observed in the 1,000 ppm males on day 502 of the study. The mesotheliomas with the most extensive abdominal cavity involvement generally occurred before the end of the study. The single control rat with mesothelioma died on day 617. The etiopathogenesis and toxicological significance of mesotheliomas of the scrotal sac in rats are obscure. These neoplasms are morphologically similar to some phenotypic forms of asbestos-induced mesotheliomas in the pleural cavity of rats as well as humans. Furthermore, mesothelial proliferations are not uncommon in human males and may be the result of intrascrotal inflammation, and rare malignant mesotheliomas have been reported to occur within the scrotum of humans (Petersen, 1988). Mesotheliomas of the abdominal cavity of rats are generally considered malignant.

Mesotheliomas became well known in the 1960s, and their occurrence has been closely related to asbestos exposure in humans. However, it has since been reported that mesotheliomas are caused by substances other than asbestos in humans and laboratory animals (Ilgren and Wagner, 1991). In the NTP database, the chemicals associated with induction of mesotheliomas of the abdominal cavity/tunica vaginalis following intraperitoneal injection showed no structural similarities, and mesotheliomas were induced by aromatic amine/nitro compounds or brominated ethane/propane in feed and dermal studies (Table 11). All of the chemicals that were clearly carcinogenic and for which *Salmonella typhimurium* data existed were positive in the *Salmonella* assay. Pentachlorophenol is not structurally related to any of the chemicals listed in Table 11. Furthermore, the chemicals that are structurally related to pentachlorophenol and that have amine/nitro groups, such as pentachloroanisole, nitroanisole, and pentachloronitrobenzene, did not induce mesotheliomas in the studies reported by the NTP (1987, 1993a,b).

Nasal squamous cell carcinomas were present in one control male, three 200 ppm males, one 400 ppm male, and five 1,000 ppm males at 2 years; none were observed in females. Even though the incidences of these neoplasms were not statistically significant, the incidences were much higher than the historical control rate. Therefore, the increased incidences of these neoplasms were considered related to pentachlorophenol exposure. Morphologically, the squamous cell carcinomas had the typical appearance associated with these neoplasms. They were composed of multiple layers of clusters, moderately to highly pleomorphic stratified squamous epithelium with varying degrees of keratin formation, and, in many neoplasms, a mild to marked scirrhous reaction. Two of these neoplasms had the appearance of arboriform masses consisting of a dense fibrous tissue core covered by a thick layer of stratified squamous epithelium with areas of invasion of the fibrous stroma along the base of the neoplasm. The nasal effects in exposed animals in these studies could be due to systemic exposure to pentachlorophenol, to direct contact of nasal mucous membrane to pentachlorophenol vapor during ingestion of the feed formulations, or to the feed dust containing pentachlorophenol. In the NTP mouse studies on pentachlorophenol, no nasal neoplasms were observed, but nasal mucosal metaplasia incidences related to pentachlorophenol exposure in the diet for 6 months or 2 years did occur (NTP, 1989). There are only two other dosed-feed carcinogenicity studies in the NTP database that had increased incidences of nasal neoplasms. Exposure of rats to *p*-cresidine caused increased incidences of olfactory neuroblastomas (NCI, 1979a), and exposure to 2,6-xylidine caused adenomas, carcinomas, and rhabdomyosarcomas in male and female rats (NTP, 1990a). Nasal cavity neoplasms have been associated with occupational exposure of humans and chemical administration to laboratory animals. Occupations associated with increased incidences of nasal neoplasms include the furniture industry, the shoe industry, and the nickel-refining industry. In experimental animals, nasal cavity neoplasms have been associated with chemical administration in the diet, in drinking water, or by intraperitoneal injection (NTP, 1990a,b,c). In humans, pentachlorophenol in dust has been reported to cause eye and nasal irritation at concentrations as low as 0.3 mg/m^3 (HSDB, 1997).

Chlorinated phenols are very effective at uncoupling oxidative phosphorylation in mitochondria. The incorporation of inorganic phosphate into adenosine triphosphate is prevented without blocking the electron transport chain. As a result of this action, cells continue to respire but soon are depleted of the adenosine triphosphate necessary for energy utilization. Pentachlorophenol causes significant uncoupling of oxidation and phosphorylation cycles in tissues (HSDB, 1997). Decreases in mean body weights of

TABLE 11
Chemicals Associated with Neoplasm Induction in the Mesothelium (Abdominal Cavity/Tunica Vaginalis)

Chemical	Route	Levels of Evidence of Carcinogenicity[a]				Multiple Tumor Site	*Salmonella typhimurium*[b]	Reference
		Male Rats	Female Rats	Male Mice	Female Mice			
Acronycine	Intraperitoneal injection	C*	C*	I	I	Yes	—[c]	NCI, 1978a
Cytembena	Intraperitoneal injection	C*	C	N	N	Yes	+	NTP, 1981
1,2-Dibromoethane	Inhalation	C*	C	C	C	Yes	+	NTP, 1982
2,3-Dibromo-1-propanol	Dermal	C*	C	C	C	Yes	+	NTP, 1993c
3,3'-Dimethylbenzidine Dihydrochloride	Drinking water	C*	C	—	—	Yes	+	NTP, 1991
3,3'-Dimethoxybenzidine Dihydrochloride	Drinking water	C*	C	—	—	Yes	—	NTP, 1990b
Ethyl Tellurac	Feed	E*	N	E	E	Yes	-,-	NCI, 1979b
Glycidol	Gavage	C*	C	C	C	Yes	+,+	NTP, 1990c
3,3'-Iminobis-1-propanol Dimethanesulfonate (ester) Hydrochloride	Intraperitoneal injection	E*	E*	E	E	Yes	—	NCI, 1978b
Nitrofurazone	Feed	E*	C	N	C	Yes	+	NTP, 1988
Phenoxybenzamine Hydrochloride	Intraperitoneal injection	C*	C*	C*	C*	No	+	NCI, 1978c
o-Toluidine Hydrochloride	Feed	C*	C	C	C	Yes	-,+	NCI, 1979c
	Totals[d]	12	3	1	1			

* Indicates the animal group in which neoplasms in the mesothelium are abdominal cavity/tunica vaginalis in origin
[a] C=Clear Evidence, E=Equivocal Evidence, N=No Evidence, I=Inadequate Experiment
[b] *Salmonella typhimurium* results: +=Positive, -=Negative
[c] No study conducted
[d] Number of chemicals causing neoplasms in the mesothelium (abdominal cavity/tunica vaginalis)

animals exposed to pentachlorophenol may have been due to uncoupling of oxidative phosphorylation. By the end of the study, the mean body weights of animals in the stop-exposure groups were similar to those of the control rats, suggesting the lack of a persistent uncoupling of oxidative phosphorylation by pentachlorophenol.

Pentachlorophenol is not mutagenic in bacterial systems, but one of its major metabolites, tetrachloro-*p*-hydroquinone, has been shown to be genotoxic. It induces DNA strand breaks in isolated DNA and in human fibroblasts (Carstens *et al.*, 1990). Two possible mechanisms of DNA damage by tetrachloro-*p*-hydroquinone have been proposed. One is by the covalent binding of tetrachloro-*p*-hydroquinone to protein and DNA. The other is by oxidative damage of DNA. Tetrachloro-*p*-hydroquinone easily oxidizes to its semiquinone radical, producing reactive oxygen species that may damage cellular DNA (Naito *et al.*, 1994; Dahlhaus *et al.*, 1995). A close relationship between 8-hydroxyguanosine formation and carcinogenesis resulting from the administration of other chemicals has been shown (Sai-Kato *et al.*, 1995). Using 8-hydroxyguanosine as a marker of oxidative damage, a number of laboratories have proposed that pentachlorophenol-induced mouse liver carcinogenesis may be related to oxidative damage of DNA in the liver by reactive oxygen species generated by tetrachloro-*p*-hydroquinone (Dahlhaus *et al.*, 1994, 1995; Sai-Kato *et al.*, 1995). In the livers of $B6C3F_1$ mice fed pentachlorophenol at a concentration of 0.03%, 0.06%, or 0.12% for up to 4 weeks, a 2.4- to 2.8-fold increase in the concentration of 8-hydroxyguanosine was observed (Umemera *et al.*, 1996).

The production of protein adducts of chlorinated quinones and semiquinones and the oxidative damage of hepatic DNA in tissue samples collected at the 7-month interim evaluation of the stop-exposure group was investigated (J. Swenberg, personal communication). The results showed an elevation of hemoglobin adducts in males and females. Pentachlorophenol metabolites including tetrachloro-1,4-benzoquinone, tetrachloro-1,2-benzosemiquinone, and tetrachloro-1,4-benzosemiquinone were formed and bound to liver proteins in males, and a twofold greater 8-hydroxyguanosine concentration occurred in male liver DNA digests than in control samples.

It is possible that the mesotheliomas seen in male rats exposed to pentachlorophenol in the current study were due to oxidative damage of the mesothelial cells of the tunica vaginalis. Oxidative injury is also one possible mechanism in asbestos-induced mesotheliomas. Effects induced by asbestos on pleural mesothelial cells do not represent a direct effect of fiber in contact with mesothelial cells, but may be due to fiber-induced release of reactive oxygen species (Adachi *et al.*, 1994). This is supported by studies of another oxidant chemical, potassium bromate, in which male rats exposed to 250 or 500 ppm in feed for 110 weeks had significantly increased incidences of mesothelioma of the peritoneum compared to the controls (Kurokawa *et al.*, 1986). Mesotheliomas were not induced in female rats by pentachlorophenol. The rare presence of spontaneous or chemically induced mesotheliomas in female rats suggests that females are protected by their hormonal status or by some other endogenous protective mechanism(s) specific to female rats. Further mechanistic studies are needed to fully explain the molecular events leading to the formation of mesotheliomas by pentachlorophenol and other chemicals.

CONCLUSIONS

Under the conditions of this 2-year feed study, there was *no evidence of carcinogenic activity** of pentachlorophenol in male or female F344/N rats fed diets containing 200, 400, or 600 ppm. There was *some evidence of carcinogenic activity* of pentachlorophenol in male F344/N rats given feed containing 1,000 ppm for 1 year followed by control feed for 1 year (stop-exposure study), based on increased incidences of mesothelioma and nasal squamous cell carcinoma. There was *no evidence of carcinogenic activity* of pentachlorophenol in female rats given feed containing 1,000 ppm for 1 year and maintained on control feed for 1 year.

Stop-exposure males and females recovered from a transitory reduction in body weight gain by the end of the 2-year study, and males had increased survival compared to the controls.

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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 pages 11 and 12.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF PENTACHLOROPHENOL

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

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	60	50	50	50	60
7-Month interim evaluation	10				10
Early deaths					
Moribund	28	28	24	11	17
Natural deaths	10	6	5	8	6
Survivors					
Died last week of study	1			2	
Terminal sacrifice	11	16	21	29	27
Animals examined microscopically	60	50	50	50	60
7-Month Interim Evaluation					
Nervous System					
Brain	(10)				(10)
Astrocytoma malignant					1 (10%)
Systems Examined with No Neoplasms Observed					
Alimentary System					
Cardiovascular System					
Endocrine System					
General Body System					
Genital System					
Hematopoietic System					
Integumentary System					
Musculoskeletal System					
Respiratory System					
Special Senses System					
Urinary System					
2-Year Study					
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(49)	(49)
Leiomyoma					1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(49)	
Polyp adenomatous		1 (2%)			
Intestine large, cecum	(50)	(50)	(50)	(50)	(49)
Polyp adenomatous		1 (2%)			1 (2%)
Intestine small, duodenum	(50)	(50)	(50)	(49)	(50)
Intestine small, jejunum	(49)	(50)	(50)	(50)	(50)
Carcinoma					1 (2%)
Intestine small, ileum	(49)	(50)	(50)	(49)	(49)
Carcinoma					1 (2%)
Carcinoma, metastatic, intestine jejunum					1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Alimentary System (continued)					
Liver	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma			1 (2%)		
Hepatocellular carcinoma		1 (2%)			
Hepatocellular adenoma			1 (2%)		
Osteosarcoma, metastatic, spleen				1 (2%)	
Mesentery	(15)	(12)	(15)	(11)	(15)
Lipoma		1 (8%)			
Fat, osteosarcoma, metastatic, spleen				1 (9%)	
Fat, sarcoma	1 (7%)				
Oral mucosa	(1)	(1)	(1)		(2)
Squamous cell papilloma					1 (50%)
Gingival, squamous cell carcinoma, metastatic, nose					1 (50%)
Pharyngeal, squamous cell papilloma	1 (100%)				
Pancreas	(50)	(50)	(50)	(48)	(50)
Acinus, adenoma	2 (4%)		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)	
Osteosarcoma, metastatic, spleen				1 (2%)	
Squamous cell carcinoma			1 (2%)		
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, spleen				1 (2%)	
Tongue	(1)		(1)	(1)	(1)
Squamous cell carcinoma				1 (100%)	
Squamous cell papilloma	1 (100%)		1 (100%)		1 (100%)
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	
Heart	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, liver			1 (2%)		
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Adenoma					1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Pheochromocytoma complex	1 (2%)	1 (2%)			
Pheochromocytoma benign	7 (14%)	17 (34%)	17 (34%)	12 (24%)	12 (24%)
Bilateral, pheochromocytoma benign	7 (14%)	4 (8%)	3 (6%)	11 (22%)	4 (8%)
Islets, pancreatic	(50)	(50)	(50)	(48)	(50)
Adenoma				1 (2%)	1 (2%)
Carcinoma				1 (2%)	
Parathyroid gland	(47)	(45)	(47)	(46)	(47)
Adenoma	1 (2%)		1 (2%)	1 (2%)	
Pituitary gland	(50)	(50)	(49)	(50)	(50)
Pars distalis, adenoma	18 (36%)	16 (32%)	13 (27%)	13 (26%)	16 (32%)
Pars distalis, adenoma, multiple			1 (2%)		
Pars distalis, carcinoma				1 (2%)	
Pars intermedia, adenoma		1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Endocrine System (continued)					
Thyroid gland	(50)	(50)	(50)	(50)	(50)
C-cell, adenoma	5 (10%)	8 (16%)	7 (14%)	6 (12%)	4 (8%)
C-cell, carcinoma		2 (4%)	2 (4%)	2 (4%)	
Follicular cell, adenoma			1 (2%)		2 (4%)
Follicular cell, carcinoma		1 (2%)		1 (2%)	1 (2%)
General Body System					
Peritoneum					(2)
Genital System					
Epididymis	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Preputial gland	(50)	(50)	(50)	(50)	(49)
Adenoma	4 (8%)		3 (6%)	1 (2%)	4 (8%)
Carcinoma	1 (2%)	7 (14%)	1 (2%)		2 (4%)
Bilateral, adenoma		1 (2%)			
Prostate	(50)	(50)	(50)	(49)	(50)
Carcinoma			1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(49)	(50)
Testes	(50)	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	34 (68%)	35 (70%)	42 (84%)	42 (84%)	38 (76%)
Interstitial cell, adenoma	8 (16%)	12 (24%)	3 (6%)	4 (8%)	7 (14%)
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, liver			1 (2%)		
Lymph node	(34)	(34)	(35)	(41)	(28)
Deep cervical, carcinoma, metastatic, thyroid gland				1 (2%)	
Mediastinal, fibrous histiocytoma, metastatic, liver			1 (3%)		
Mediastinal, osteosarcoma, metastatic, spleen				1 (2%)	
Mediastinal, sarcoma, metastatic, mesentery	1 (3%)				
Renal, pheochromocytoma malignant, metastatic, adrenal medulla			1 (3%)		
Lymph node, mandibular	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, liver			1 (2%)		
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(50)
Fibrous histiocytoma, metastatic, liver			1 (2%)		
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Osteosarcoma, metastatic, spleen				1 (2%)	
Spleen	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, liver			1 (2%)		
Osteosarcoma				1 (2%)	
Thymus	(49)	(46)	(49)	(47)	(48)
Fibrous histiocytoma, metastatic, liver			1 (2%)		
Thymoma malignant			1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Integumentary System					
Mammary gland	(49)	(47)	(50)	(49)	(49)
Carcinoma		1 (2%)			
Fibroadenoma	5 (10%)	5 (11%)	4 (8%)	2 (4%)	2 (4%)
Skin	(50)	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)				2 (4%)
Basal cell carcinoma			1 (2%)		
Fibrous histiocytoma, metastatic, liver			1 (2%)		
Keratoacanthoma		2 (4%)	1 (2%)	3 (6%)	6 (12%)
Keratoacanthoma, multiple					1 (2%)
Squamous cell papilloma	2 (4%)	1 (2%)		3 (6%)	
Trichoepithelioma					2 (4%)
Subcutaneous tissue, fibroma	1 (2%)	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Subcutaneous tissue, fibroma, multiple	1 (2%)				
Subcutaneous tissue, fibrosarcoma	2 (4%)			2 (4%)	1 (2%)
Subcutaneous tissue, fibrous histiocytoma	1 (2%)	1 (2%)			
Subcutaneous tissue, schwannoma malignant					1 (2%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Vertebra, chordoma			1 (2%)		
Vertebra, hemangiosarcoma	1 (2%)				
Skeletal muscle		(1)		(1)	(1)
Osteosarcoma, metastatic, spleen				1 (100%)	
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	1 (2%)	1 (2%)
Carcinoma, metastatic, pituitary gland				1 (2%)	
Oligodendroglioma, malignant					1 (2%)
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		2 (4%)			
Alveolar/bronchiolar carcinoma			1 (2%)		
Carcinoma, metastatic, harderian gland					1 (2%)
Carcinoma, metastatic, thyroid gland		1 (2%)			
Chordoma, metastatic, bone			1 (2%)		
Fibrous histiocytoma, metastatic, liver			1 (2%)		
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)		
Squamous cell carcinoma				1 (2%)	
Mediastinum, hemangiosarcoma		1 (2%)			
Mediastinum, squamous cell carcinoma, metastatic, lung				1 (2%)	
Nose	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)	3 (6%)	1 (2%)		5 (10%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Special Senses System					
Harderian gland					(1)
Carcinoma					1 (100%)
Zymbal's gland			(1)	(2)	
Adenoma				1 (50%)	
Carcinoma			1 (100%)	1 (50%)	
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, liver			1 (2%)		
Fibrous histiocytoma, metastatic, skin		1 (2%)			
Renal tubule, adenoma	1 (2%)	1 (2%)			2 (4%)
Renal tubule, carcinoma				2 (4%)	
Renal tubule, oncocytoma benign					1 (2%)
Urinary bladder	(48)	(50)	(50)	(49)	(49)
Transitional epithelium, papilloma	1 (2%)			1 (2%)	
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Leukemia mononuclear	25 (50%)	26 (52%)	26 (52%)	23 (46%)	15 (30%)
Mesothelioma malignant	1 (2%)		2 (4%)		9 (18%)
Neoplasm Summary					
Total animals with primary neoplasms[c]					
7-Month interim evaluation					1
2-Year study	50	50	50	48	49
Total primary neoplasms					
7-Month interim evaluation					1
2-Year study	135	155	145	141	152
Total animals with benign neoplasms					
2-Year study	48	50	48	48	47
Total benign neoplasms					
2-Year study	100	110	101	103	110
Total animals with malignant neoplasms					
7-Month interim evaluation					1
2-Year study	32	37	36	32	29
Total malignant neoplasms					
7-Month interim evaluation					1
2-Year study	35	45	44	38	42
Total animals with metastatic neoplasms					
2-Year study	1	2	4	4	3
Total metastatic neoplasms					
2-Year study	1	5	13	10	3

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[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 Feed Study of Pentachlorophenol: 0 ppm

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

+: 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 Feed Study of Pentachlorophenol: 0 ppm

Number of Days on Study	6 9 0	6 9 5	6 9 8	6 9 8	7 0 2	7 0 3	7 1 5	7 1 5	7 2 2	7 2 4	7 2 9	7 3 3	7 3 3	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 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 5 3	0 1 6	0 3 6	0 4 5	0 2 5	0 1 4	0 1 4	0 1 9	0 5 8	0 2 4	0 4 2	0 0 6	0 3 8	0 1 0	0 1 2	0 1 8	0 2 3	0 2 7	0 2 8	0 3 2	0 3 5	0 4 1	0 4 4	0 4 6	0 5 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+								+		+				+					+		+				15
Fat, sarcoma																										1
Oral mucosa																		+								1
Pharyngeal, squamous cell papilloma																		X								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																						X				2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue					+																					1
Squamous cell papilloma					X																					1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																X										1
Pheochromocytoma complex								X																		1
Pheochromocytoma benign				X															X				X	X		7
Bilateral, pheochromocytoma benign						X								X								X				7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X					X											X	X		X		X		18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X													X												5
General Body System																										
None																										
Genital System																										
Coagulating gland								+				+														2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X											X												4
Carcinoma																										1

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

Number of Days on Study	3 9 6	3 9 6	4 2 0	4 3 5	5 3 5	5 6 1	5 6 4	5 7 6	5 7 9	5 9 3	6 0 0	6 0 0	6 0 3	6 1 7	6 1 9	6 4 3	6 4 5	6 4 6	6 4 7	6 6 0	6 6 3	6 7 5	6 8 1	6 8 4	6 8 4
Carcass ID Number	0 1 7	0 5 6	0 4 3	0 3 7	0 1 5	0 0 3	0 0 5	0 0 8	0 2 0	0 2 9	0 2 0	0 5 4	0 6 0	0 5 5	0 0 7	0 5 0	0 0 9	0 0 1	0 4 8	0 4 0	0 2 1	0 5 9	0 3 0	0 2 2	0 3 1
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X	X			X				X	X	X			X	X	X	X	X	X	X
Interstitial cell, adenoma								X			X		X					X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+						+		+	+	+	+	+	+		+	+	+	+	+	+	+
Mediastinal, sarcoma, metastatic, mesentery																						X			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Fibroadenoma															X				X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									X
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																				X					
Subcutaneous tissue, fibroma, multiple													X												
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, fibrous histiocytoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, hemangiosarcoma				X																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																X									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Transitional epithelium, papilloma																						X			
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X			X	X		X		X	X			X		X			X	X
Mesothelioma malignant														X											

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

Number of Days on Study	6 9 0	6 9 5	6 9 8	6 9 8	7 0 2	7 0 3	7 1 5	7 1 5	7 2 2	7 2 4	7 2 9	7 3 3	7 3 3	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 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 5 3	0 1 6	0 3 6	0 4 5	0 2 5	0 1 4	0 0 4	0 1 9	0 5 8	0 2 4	0 4 2	0 0 6	0 3 8	0 1 0	0 1 2	0 1 8	0 2 3	0 2 7	0 2 8	0 3 2	0 3 5	0 4 1	0 4 4	0 4 6	0 5 1	Total Tissues/ Tumors
Genital System (continued)																										
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	X	X		X	X	X	X	X	34
Interstitial cell, adenoma						X						X			X					X						8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+		+	+		+	+	+			+	+			+	+	+	+		+	34
Mediastinal, sarcoma, metastatic, mesentery																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma			X					X																	X	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Squamous cell papilloma														X				X								2
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibroma, multiple																										1
Subcutaneous tissue, fibrosarcoma																								X	X	2
Subcutaneous tissue, fibrous histiocytoma		X																								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma		X																								1
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X		X	X		X			X	X		X			X		X		X		X		25
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 200 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 200 ppm

Number of Days on Study	6 8 4	6 9 8	6 9 8	7 0 2	7 0 8	7 2 2	7 2 3	7 2 3	7 2 6	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 6 9	1 0 9	1 1 0	1 0 5	0 8 5	0 6 5	0 7 8	0 9 0	0 8 2	0 6 1	0 6 3	0 6 7	0 7 0	0 7 8	0 8 7	0 9 2	0 9 4	0 9 5	0 9 8	0 9 9	1 0 0	1 0 1	1 0 3	1 0 4	1 0 7	1 0 8	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous											X																1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																X											1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																											1
Mesentery	+	+	+						+																+		12
Lipoma																									X		1
Oral mucosa																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																							X				1
Pheochromocytoma complex																											1
Pheochromocytoma benign		X			X		X		X		X	X	X		X	X	X		X				X		X		17
Bilateral, pheochromocytoma benign																						X				X	4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma						X		X				X	X		X			X						X	X		16
Pars intermedia, adenoma																					X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X		X							X			X	X										X	X		8
C-cell, carcinoma															X												2
Follicular cell, carcinoma											X																1
General Body System																											
None																											
Genital System																											
Coagulating gland																								+			1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma							X		X				X	X										X			7
Bilateral, adenoma																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 200 ppm

Number of Days on Study	4 1 0	4 2 8	4 3 5	4 5 0	5 0 5	5 0 7	5 2 4	5 3 4	5 4 4	5 4 4	5 6 3	5 6 3	5 7 9	5 9 2	6 0 5	6 1 4	6 1 9	6 1 9	6 3 1	6 3 4	6 4 7	6 4 9	6 6 0	6 6 3	6 6 3
Carcass ID Number	0 6 2	0 6 4	0 9 7	0 7 3	0 7 6	0 8 8	0 7 5	0 8 6	0 7 4	0 9 6	0 7 1	0 7 2	0 8 3	0 9 3	0 6 8	0 7 9	0 8 4	1 0 6	0 8 0	0 8 1	0 8 9	0 6 6	0 7 7	0 9 1	1 0 2
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X						X		X			X	X		X			X	X	X		X
Interstitial cell, adenoma	X	X	X		X	X		X					X	X			X		X	X				X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+	+	+	+	+	+	+		+	+	+	+		+		+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin						X																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma					X																				
Subcutaneous tissue, fibrous histiocytoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																	+								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland																								X	
Fibrous histiocytoma, metastatic, skin						X																			
Mediastinum, hemangiosarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma					X														X						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin						X																			
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						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 Feed Study of Pentachlorophenol: 200 ppm

Number of Days on Study	6 8 4	6 9 8	6 9 8	7 0 2	7 0 8	7 2 2	7 2 3	7 2 3	7 2 6	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 6 9	1 0 9	1 1 0	1 0 5	0 8 5	0 6 5	0 7 8	0 9 0	0 8 2	0 6 1	0 6 3	0 6 7	0 7 0	0 7 7	0 8 7	0 9 2	0 9 4	0 9 5	0 9 8	0 9 9	1 0 0	1 0 1	1 0 3	1 0 4	1 0 7	1 0 8	Total Tissues/ Tumors
Genital System (continued)																											
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	X	X	X	X	X	X	X	X	X	X	X	X	35
Interstitial cell, adenoma																											12
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+	+	+			+	+		+	+	+		+	+	+	+	+	+	+	+		+			34
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																									X		1
Fibroadenoma			X				X					X								X					X		5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma						X															X						2
Squamous cell papilloma								X																			1
Subcutaneous tissue, fibroma																										X	2
Subcutaneous tissue, fibrous histiocytoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X									X		2
Carcinoma, metastatic, thyroid gland																											1
Fibrous histiocytoma, metastatic, skin																											1
Mediastinum, hemangiosarcoma									X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma						X																					3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye					+								+									+					4
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																											1
Renal tubule, adenoma																				X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	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 Feed Study of Pentachlorophenol: 400 ppm

Number of Days on Study	3 6 0	4 4 3	4 8 2	5 2 1	5 2 7	5 5 7	5 6 1	5 6 3	5 7 2	5 8 3	5 9 3	5 9 3	6 0 5	6 1 7	6 1 9	6 2 0	6 2 4	6 4 0	6 4 0	6 4 5	6 4 8	6 6 6	6 7 6	6 8 8	6 9 8
Carcass ID Number	1 6 0	1 1 2	1 5 8	1 5 3	1 4 6	1 5 0	1 3 8	1 5 7	1 3 0	1 3 3	1 3 6	1 5 1	1 2 4	1 5 9	1 2 0	1 4 8	1 3 5	1 2 7	1 2 9	1 4 4	1 2 6	1 1 9	1 2 1	1 1 5	1 1 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																									
Hepatocellular adenoma																				X					
Mesentery								+	+			+					+	+	+					+	+
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																			+						
Squamous cell papilloma																			X						
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign										X									X	X			X		
Bilateral, pheochromocytoma benign																		X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X						X					X						X		X		X	X	
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X		X	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 Feed Study of Pentachlorophenol: 400 ppm

Number of Days on Study	7 0 2	7 1 1	7 2 2	7 2 9	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	1 3 4	1 1 1	1 4 3	1 5 5	1 1 3	1 1 4	1 1 7	1 1 8	1 2 2	1 2 3	1 2 5	1 2 8	1 3 1	1 3 2	1 3 7	1 3 9	1 4 0	1 4 1	1 4 2	1 4 5	1 4 7	1 4 9	1 5 2	1 5 4	1 5 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Fibrous histiocytoma		X																								1
Hepatocellular adenoma																										1
Mesentery	+					+		+		+			+				+						+			15
Oral mucosa											+															1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma								X																		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma													X													1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, liver		X																								1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant								X										X				X				3
Pheochromocytoma benign	X			X				X		X	X			X	X	X					X	X	X	X	X	17
Bilateral, pheochromocytoma benign							X												X							3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Adenoma															X											1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X	X										X	X							X			13
Pars distalis, adenoma, multiple												X														1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X			X			X										X							7
C-cell, carcinoma													X											X		2
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 400 ppm

Number of Days on Study	360	443	482	521	527	557	561	563	572	583	593	593	605	617	619	620	624	640	640	645	648	666	676	688	698
Carcass ID Number	16000	11202	15808	15533	14646	15050	13808	15857	13030	13336	13636	15151	12454	15959	12090	14848	13535	12727	12929	14444	12426	11969	12121	11515	11116
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Carcinoma	X																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X	X		X	X	X	X	X	X	X	X	X	X		X		X	X	X	X
Interstitial cell, adenoma								X																	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver																									
Lymph node					+	+	+		+		+	+	+	+	+	+	+			+	+	+	+	+	+
Mediastinal, fibrous histiocytoma, metastatic, liver																									
Renal, pheochromocytoma malignant, metastatic, adrenal medulla																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver																									
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Fibrous histiocytoma, metastatic, liver																									
Keratoacanthoma																									
Subcutaneous tissue, fibroma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, chordoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant								X																	
Peripheral nerve									+																
Spinal cord									+																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 400 ppm

Number of Days on Study	7 0 2	7 1 1	7 2 2	7 2 9	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	1 3 4	1 1 1	1 4 3	1 5 5	1 1 3	1 1 4	1 1 7	1 1 8	1 2 2	1 2 3	1 2 5	1 2 8	1 3 1	1 3 2	1 3 7	1 3 9	1 4 0	1 4 1	1 4 2	1 4 5	1 4 7	1 4 9	1 5 2	1 5 4	1 5 6	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X											X			3
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma													X													1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	42
Interstitial cell, adenoma			X												X											3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, liver		X																								1
Lymph node	+	+	+	+	+	+	+	+			+	+	+	+	+		+	+		+		+				35
Mediastinal, fibrous histiocytoma, metastatic, liver		X																								1
Renal, pheochromocytoma malignant, metastatic, adrenal medulla																						X				1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, liver		X																								1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, liver		X																								1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, liver		X																								1
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, liver		X																								1
Thymoma malignant															X											1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																X			X				X			4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																								X		1
Fibrous histiocytoma, metastatic, liver		X																								1
Keratoacanthoma																						X				1
Subcutaneous tissue, fibroma																						X				2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, chordoma	X																									1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Peripheral nerve																										1
Spinal cord								+																		2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 400 ppm

Number of Days on Study	360	443	482	521	527	557	561	663	672	683	693	703	705	717	719	720	724	740	740	745	748	766	768	788	798
Carcass ID Number	16 0	11 2	15 8	15 3	14 6	15 0	13 8	15 7	13 0	13 3	13 6	15 1	12 4	15 9	12 0	14 8	13 5	12 7	12 9	14 4	12 6	11 9	12 1	11 5	11 6
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																								X	
Chordoma, metastatic, bone																									
Fibrous histiocytoma, metastatic, liver																									
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																									+
Carcinoma																									X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			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 Feed Study of Pentachlorophenol: 400 ppm

Number of Days on Study	7 0 2	7 1 1	7 2 2	7 2 9	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	1 3 4	1 1 1	1 4 3	1 5 5	1 1 3	1 1 4	1 1 7	1 1 8	1 2 2	1 2 3	1 2 5	1 2 8	1 3 1	1 3 2	1 3 7	1 3 9	1 4 0	1 4 1	1 4 2	1 4 5	1 4 7	1 4 9	1 5 2	1 5 4	1 5 6	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Chordoma, metastatic, bone	X																									1
Fibrous histiocytoma, metastatic, liver		X																								1
Pheochromocytoma malignant, metastatic, adrenal medulla																		X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																		+								1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, liver		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X			X					X		X			X			X		X	X	X		26
Mesothelioma malignant																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 600 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 600 ppm

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	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	1 9 4	1 9 7	2 0 2	2 0 3	1 6 2	1 6 4	1 6 9	1 7 3	1 7 4	1 7 5	1 7 7	1 7 8	1 8 2	1 8 4	1 8 7	1 8 9	1 9 0	1 9 3	1 9 5	2 0 0	2 0 4	2 0 5	2 0 7	2 0 8	2 0 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										1
Mesentery							+									+		+						+	+	11
Fat, osteosarcoma, metastatic, spleen																										1
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										1
Tongue																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant														X												1
Pheochromocytoma benign	X	X					X													X	X	X	X		X	12
Bilateral, pheochromocytoma benign			X		X						X	X			X	X	X	X						X		11
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma																X										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	46
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X			X			X		X				X							X		X	X	13
Pars distalis, carcinoma																		X								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma														X						X			X	X	X	6
C-cell, carcinoma				X																		X				2
Follicular cell, carcinoma		X																								1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 600 ppm

Number of Days on Study	2 1 3	5 1 8	5 4 4	5 6 1	6 0 5	6 1 0	6 1 4	6 1 9	6 2 0	6 2 1	6 6 0	6 8 4	7 0 2	7 0 7	7 0 8	7 0 8	7 0 9	7 1 2	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 8 8	1 8 5	1 6 7	1 7 9	1 9 6	1 6 8	1 8 6	2 0 6	1 7 6	1 9 9	1 7 0	2 1 0	1 6 6	1 9 8	1 6 1	1 6 5	1 9 2	1 7 2	2 0 1	1 6 3	1 7 1	1 8 0	1 8 1	1 8 3	1 9 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X	X	X		X			X	X	X		X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma		X					X																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Deep cervical, carcinoma, metastatic, thyroid gland																									
Mediastinal, osteosarcoma, metastatic, spleen																		X							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, spleen																		X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																		X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma		X																							
Squamous cell papilloma																									
Subcutaneous tissue, fibroma							X													X					
Subcutaneous tissue, fibrosarcoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																		+							
Osteosarcoma, metastatic, spleen																		X							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant						X																			
Carcinoma, metastatic, pituitary gland																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Mediastinum, squamous cell carcinoma, metastatic, lung																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland															+										
Adenoma															X										
Carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 600 ppm

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	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	1 9 4	1 9 7	2 0 2	2 0 3	1 6 2	1 6 4	1 6 9	1 7 3	1 7 4	1 7 5	1 7 7	1 7 8	1 8 2	1 8 4	1 8 7	1 8 9	1 9 0	1 9 3	1 9 5	2 0 0	2 0 4	2 0 5	2 0 7	2 0 8	2 0 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Prostate	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	42
Interstitial cell, adenoma									X						X											4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+		+	+	+	+	+	+	+	+	+	+			+	+	+	+		+	+	+	+	+	41
Deep cervical, carcinoma, metastatic, thyroid gland				X																						1
Mediastinal, osteosarcoma, metastatic, spleen																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma, metastatic, spleen																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma	X				X																					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma							X							X												3
Squamous cell papilloma					X		X																X			3
Subcutaneous tissue, fibroma																										2
Subcutaneous tissue, fibrosarcoma															X											2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Osteosarcoma, metastatic, spleen																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Carcinoma, metastatic, pituitary gland																		X								1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma	X																									1
Mediastinum, squamous cell carcinoma, metastatic, lung	X																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+										+							+							3
Zymbal's gland																				+						2
Adenoma																										1
Carcinoma																				X						1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 600 ppm

Number of Days on Study	213	218	244	261	605	610	614	619	620	621	660	684	702	707	708	708	709	712	731	736	736	736	736	736	736
Carcass ID Number	18838	18855	16867	17879	19696	16868	18866	20066	17676	19699	17700	21006	16668	19898	16961	16655	19292	17022	20121	16663	17171	18801	18811	18833	19091
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		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 Feed Study of Pentachlorophenol: 600 ppm

Number of Days on Study	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	19404	19907	20202	20003	16702	16404	16909	17303	17404	17505	17707	17808	18202	18404	18707	18909	19000	19303	19505	20000	20404	20505	20707	20808	20909	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma														X												2
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma																								X		1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X			X	X	X	X									X				X	X				23

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	2 6 5	3 6 0	4 6 0	5 0 2	5 3 6	5 5 0	5 6 5	5 9 2	6 1 3	6 1 4	6 6 1	6 7 5	6 7 7	6 8 0	6 8 4	6 9 8	6 9 8	7 0 2	7 0 2	7 0 8	7 1 1	7 1 5	7 2 5	7 3 6	7 3 6
Carcass ID Number	2 4 0	2 3 6	2 5 5	2 6 4	2 6 7	2 1 7	2 1 1	2 3 9	2 3 1	2 2 4	2 6 3	2 3 7	2 5 9	2 6 1	2 5 2	2 2 6	2 4 5	2 5 4	2 5 7	2 3 3	2 1 6	2 1 8	2 6 2	2 1 2	2 1 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																X									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Carcinoma, metastatic, intestine small, jejunum										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+		+				+		+				+				+							+
Oral mucosa																									
Squamous cell papilloma																									
Gingival, squamous cell carcinoma, metastatic, nose																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant														X											
Pheochromocytoma benign															X			X	X				X		
Bilateral, pheochromocytoma benign																					X	X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X		X		X		X		X	X		X			X	X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X												X	
Follicular cell, adenoma																					X				
Follicular cell, carcinoma																									
General Body System																									
Peritoneum								+		+															

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	21 4	21 5	21 9	22 0	22 1	22 2	22 3	22 5	22 7	22 8	23 0	23 2	23 4	23 8	24 2	24 3	25 0	25 1	25 3	25 6	26 0	26 5	26 6	26 9	27 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous									X																	1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																				X						1
Carcinoma, metastatic, intestine small, jejunum																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+			+		+	+			+			+				+					+				15
Oral mucosa														+			+									2
Squamous cell papilloma														X												1
Gingival, squamous cell carcinoma, metastatic, nose																	X									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue											+															1
Squamous cell papilloma											X															1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant													X											X		3
Pheochromocytoma benign					X				X		X	X	X			X				X			X			12
Bilateral, pheochromocytoma benign										X					X											4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X						X	X					X					X					X	16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma											X	X														4
Follicular cell, adenoma																		X								2
Follicular cell, carcinoma										X																1
General Body System																										
Peritoneum																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	2 6 5	3 6 0	4 6 0	5 0 2	5 3 6	5 5 0	5 6 5	5 9 2	6 1 3	6 1 4	6 6 1	6 7 5	6 7 7	6 8 0	6 8 4	6 9 8	6 9 8	7 0 2	7 0 2	7 0 8	7 1 1	7 1 5	7 2 5	7 3 6	7 3 6
Carcass ID Number	2 4 0	2 3 6	2 5 5	2 6 4	2 6 7	2 1 7	2 1 1	2 3 9	2 3 1	2 2 4	2 6 3	2 3 7	2 5 9	2 6 1	2 5 2	2 2 6	2 4 5	2 5 4	2 5 7	2 3 3	2 1 6	2 1 8	2 6 2	2 1 2	2 1 3
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma						X	X																		
Carcinoma					X																				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X		X		X		X		X	X	X	X	X		X	X	X	X	X	X
Interstitial cell, adenoma				X			X						X						X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+				+	+	+	+	+		+			+	+	+		+		+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																						X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma								X																	
Keratoacanthoma																					X	X			X
Keratoacanthoma, multiple																				X					
Trichoepithelioma											X									X					
Subcutaneous tissue, fibroma										X															
Subcutaneous tissue, fibrosarcoma														X											
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant	X																								
Oligodendroglioma malignant					X																				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma			X					X								X									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye													+						+				M		
Harderian gland																	+								
Carcinoma																	X								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	21 14	21 15	21 19	22 00	22 01	22 02	22 03	22 05	22 07	22 08	23 00	23 02	23 04	23 08	24 02	24 03	25 00	25 11	25 13	25 16	26 00	26 05	26 06	26 09	27 00	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X				X											4
Carcinoma															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	X	X	X	X		X	X	X	X	X	38
Interstitial cell, adenoma									X			X								X						7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+	+	+	+			+		+			+	+	+	+			+	+	+	+		28
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma							X																			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																			X							2
Keratoacanthoma																		X	X			X				6
Keratoacanthoma, multiple																										1
Trichoepithelioma																										2
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, schwannoma malignant													X													1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Oligodendroglioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																	X	X								5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																	+									3
Harderian gland																										1
Carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	2	3	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	
	6	6	6	0	3	5	6	9	1	1	6	7	7	8	8	9	9	0	0	0	1	1	2	3	3	
	5	0	0	2	6	0	5	2	3	4	1	5	7	0	4	8	8	2	2	8	1	5	5	6	6	
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	4	3	5	6	6	1	1	3	3	2	6	3	5	6	5	2	4	5	5	3	1	1	6	1	1	
	0	6	5	4	7	7	1	9	1	4	3	7	9	1	2	6	5	4	7	3	6	8	2	2	3	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Renal tubule, adenoma																										
Renal tubule, oncocytoma benign															X											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear					X			X					X	X					X		X		X		X	
Mesothelioma malignant				X				X		X	X							X							X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	21 14	21 15	21 19	22 20	22 21	22 22	22 23	22 25	22 27	22 28	23 30	23 32	23 34	23 38	24 42	24 43	25 50	25 51	25 53	25 56	26 00	26 05	26 06	26 69	27 00	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																								X	X	2
Renal tubule, oncocytoma benign																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X	X							X		X			X								X	15
Mesothelioma malignant												X					X							X		9

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	14/50 (28%)	21/50 (42%)	20/50 (40%)	23/50 (46%)
Adjusted rate[b]	35.0%	53.7%	50.0%	52.3%
Terminal rate[c]	5/12 (42%)	11/16 (69%)	13/21 (62%)	19/31 (61%)
First incidence (days)	579	507	583	702
Poly-3 test[d]	P=0.087	P=0.064	P=0.120	P=0.078
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.7%	2.8%	7.9%	2.3%
Terminal rate	1/12 (8%)	1/16 (6%)	3/21 (14%)	1/31 (3%)
First incidence (days)	736 (T)	736 (T)	736 (T)	736 (T)
Poly-3 test	P=0.522	P=0.754	P=0.311	P=0.726N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	16/50 (32%)	22/50 (44%)	21/50 (42%)	24/50 (48%)
Adjusted rate	39.9%	55.1%	52.5%	54.5%
Terminal rate	6/12 (50%)	11/16 (69%)	14/21 (67%)	20/31 (65%)
First incidence (days)	579	450	583	702
Poly-3 test	P=0.125	P=0.115	P=0.173	P=0.122
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	4/50 (8%)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted rate	10.6%	5.5%	0.0%	6.9%
Terminal rate	1/12 (8%)	2/16 (13%)	0/21 (0%)	3/31 (10%)
First incidence (days)	695	736 (T)	—[e]	736 (T)
Poly-3 test	P=0.246N	P=0.356N	P=0.057N	P=0.422N
Kidney (Renal Tubule): Adenoma and Carcinoma (Single and Step Sections)				
Overall rate	4/50 (8%)	2/50 (4%)	0/50 (0%)	5/50 (10%)
Adjusted rate	10.6%	5.5%	0.0%	11.5%
Terminal rate	1/12 (8%)	2/16 (13%)	0/21 (0%)	5/31 (16%)
First incidence (days)	695	736 (T)	—	736 (T)
Poly-3 test	P=0.543	P=0.356N	P=0.057N	P=0.589
Mammary Gland: Fibroadenoma				
Overall rate	5/50 (10%)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rate	13.0%	13.8%	10.4%	4.6%
Terminal rate	1/12 (8%)	3/16 (19%)	3/21 (14%)	2/31 (7%)
First incidence (days)	619	698	698	736 (T)
Poly-3 test	P=0.099N	P=0.598	P=0.501N	P=0.166N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	5/50 (10%)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rate	13.0%	13.8%	10.4%	4.6%
Terminal rate	1/12 (8%)	3/16 (19%)	3/21 (14%)	2/31 (7%)
First incidence (days)	619	698	698	736 (T)
Poly-3 test	P=0.099N	P=0.598	P=0.501N	P=0.166N
Nose: Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	2.7%	8.1%	2.6%	0.0%
Terminal rate	0/12 (0%)	0/16 (0%)	0/21 (0%)	0/31 (0%)
First incidence (days)	643	505	593	—
Poly-3 test	P=0.171N	P=0.299	P=0.756N	P=0.471N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	18/50 (36%)	16/50 (32%)	14/49 (29%)	13/50 (26%)
Adjusted rate	41.5%	40.1%	34.4%	29.5%
Terminal rate	4/12 (33%)	6/16 (38%)	5/21 (24%)	11/31 (36%)
First incidence (days)	396	524	443	620
Poly-3 test	P=0.108N	P=0.540N	P=0.327N	P=0.168N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	18/50 (36%)	16/50 (32%)	14/49 (29%)	14/50 (28%)
Adjusted rate	41.5%	40.1%	34.4%	31.8%
Terminal rate	4/12 (33%)	6/16 (38%)	5/21 (24%)	12/31 (39%)
First incidence (days)	396	524	443	620
Poly-3 test	P=0.156N	P=0.540N	P=0.327N	P=0.232N
Preputial Gland: Adenoma				
Overall rate	4/50 (8%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	10.5%	2.7%	7.7%	2.3%
Terminal rate	1/12 (8%)	0/16 (0%)	2/21 (10%)	0/31 (0%)
First incidence (days)	647	450	521	544
Poly-3 test	P=0.136N	P=0.186N	P=0.490N	P=0.136N
Preputial Gland: Carcinoma				
Overall rate	1/50 (2%)	7/50 (14%)	1/50 (2%)	0/50 (0%)
Adjusted rate	2.6%	18.8%	2.6%	0.0%
Terminal rate	0/12 (0%)	3/16 (19%)	0/21 (0%)	0/31 (0%)
First incidence (days)	396	544	360	—
Poly-3 test	P=0.074N	P=0.025	P=0.757N	P=0.474N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	8/50 (16%)	4/50 (8%)	1/50 (2%)
Adjusted rate	12.8%	21.0%	10.1%	2.3%
Terminal rate	1/12 (8%)	3/16 (19%)	2/21 (10%)	0/31 (0%)
First incidence (days)	396	450	360	544
Poly-3 test	P=0.026N	P=0.254	P=0.488N	P=0.074N
Skin: Squamous Cell Papilloma				
Overall rate	2/50 (4%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	5.3%	2.8%	0.0%	6.9%
Terminal rate	2/12 (17%)	0/16 (0%)	0/21 (0%)	3/31 (10%)
First incidence (days)	736 (T)	723	—	736 (T)
Poly-3 test	P=0.462	P=0.512N	P=0.232N	P=0.569
Skin: Keratoacanthoma				
Overall rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	5.5%	2.6%	6.8%
Terminal rate	0/12 (0%)	1/16 (6%)	1/21 (5%)	2/31 (7%)
First incidence (days)	—	722	736 (T)	518
Poly-3 test	P=0.128	P=0.229	P=0.504	P=0.151
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	5/50 (10%)
Adjusted rate	5.3%	8.3%	2.6%	11.3%
Terminal rate	2/12 (17%)	1/16 (6%)	1/21 (5%)	4/31 (13%)
First incidence (days)	736 (T)	722	736 (T)	518
Poly-3 test	P=0.253	P=0.485	P=0.493N	P=0.289

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted rate	8.0%	8.3%	5.2%	11.3%
Terminal rate	2/12 (17%)	1/16 (6%)	2/21 (10%)	4/31 (13%)
First incidence (days)	684	722	736 (T)	518
Poly-3 test	P=0.378	P=0.647	P=0.493N	P=0.448
Skin (Subcutaneous Tissue): Fibrous Histiocytoma or Fibrosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rate	8.0%	2.7%	0.0%	4.6%
Terminal rate	2/12 (17%)	0/16 (0%)	0/21 (0%)	2/31 (7%)
First incidence (days)	695	507	—	736 (T)
Poly-3 test	P=0.275N	P=0.311N	P=0.114N	P=0.433N
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, or Fibrosarcoma				
Overall rate	5/50 (10%)	3/50 (6%)	2/50 (4%)	4/50 (8%)
Adjusted rate	13.1%	8.0%	5.2%	9.1%
Terminal rate	2/12 (17%)	1/16 (6%)	1/21 (5%)	3/31 (10%)
First incidence (days)	603	505	666	614
Poly-3 test	P=0.304N	P=0.366N	P=0.211N	P=0.413N
Testes: Adenoma				
Overall rate	42/50 (84%)	47/50 (94%)	45/50 (90%)	46/50 (92%)
Adjusted rate	93.8%	97.5%	95.8%	95.6%
Terminal rate	12/12 (100%)	16/16 (100%)	21/21 (100%)	31/31 (100%)
First incidence (days)	561	410	521	518
Poly-3 test	P=0.458	P=0.293	P=0.514	P=0.535
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/50 (10%)	8/50 (16%)	7/50 (14%)	6/50 (12%)
Adjusted rate	12.9%	21.5%	17.7%	13.6%
Terminal rate	1/12 (8%)	5/16 (31%)	3/21 (14%)	5/31 (16%)
First incidence (days)	535	450	593	544
Poly-3 test	P=0.494N	P=0.243	P=0.390	P=0.591
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	10/50 (20%)	9/50 (18%)	8/50 (16%)
Adjusted rate	12.9%	26.7%	22.8%	18.1%
Terminal rate	1/12 (8%)	6/16 (38%)	5/21 (24%)	7/31 (23%)
First incidence (days)	535	450	593	544
Poly-3 test	P=0.400	P=0.106	P=0.196	P=0.363
All Organs: Mononuclear Cell Leukemia				
Overall rate	25/50 (50%)	26/50 (52%)	26/50 (52%)	23/50 (46%)
Adjusted rate	58.8%	61.5%	57.8%	48.9%
Terminal rate	5/12 (42%)	8/16 (50%)	8/21 (38%)	11/31 (36%)
First incidence (days)	561	507	482	518
Poly-3 test	P=0.158N	P=0.485	P=0.552N	P=0.231N
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	50/50 (100%)	48/50 (96%)	48/50 (96%)
Adjusted rate	99.3%	100.0%	99.2%	98.7%
Terminal rate	12/12 (100%)	16/16 (100%)	21/21 (100%)	31/31 (100%)
First incidence (days)	396	410	443	518
Poly-3 test	P=0.453N	P=0.992	P=0.991N	P=0.868N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm
All Organs: Malignant Neoplasms				
Overall rate	32/50 (64%)	37/50 (74%)	36/50 (72%)	32/50 (64%)
Adjusted rate	71.3%	81.3%	75.3%	67.3%
Terminal rate Terminal rate	7/12 (58%)	11/16 (69%)	12/21 (57%)	18/31 (58%)
First incidence (days)	396	450	360	518
Poly-3 test	P=0.274N	P=0.174	P=0.416	P=0.424N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	98.7%
Terminal rate	12/12 (100%)	16/16 (100%)	21/21 (100%)	31/31 (100%)
First incidence (days)	396	410	360	518
Poly-3 test	P=0.262N	—[f]	—	P=0.728N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, nose, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence 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 exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of Pentachlorophenol

	0 ppm	1,000 ppm
Adrenal Medulla: Benign Pheochromocytoma		
Overall rate[a]	14/50 (28%)	16/50 (32%)
Adjusted rate[b]	35.0%	37.8%
Terminal rate[c]	5/12 (42%)	10/27 (37%)
First incidence (days)	579	684
Poly-3 test[d]		P=0.484
Adrenal Medulla: Malignant Pheochromocytoma		
Overall rate	1/50 (2%)	3/50 (6%)
Adjusted rate	2.7%	7.2%
Terminal rate	1/12 (8%)	2/27 (7%)
First incidence (days)	736 (T)	680
Poly-3 test		P=0.337
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma		
Overall rate	16/50 (32%)	18/50 (36%)
Adjusted rate	39.9%	42.3%
Terminal rate	6/12 (50%)	11/27 (41%)
First incidence (days)	579	680
Poly-3 test		P=0.499
Kidney (Renal Tubule): Adenoma (Single and Step Sections)		
Overall rate	4/50 (8%)	4/50 (8%)
Adjusted rate	10.6%	9.5%
Terminal rate	1/12 (8%)	2/27 (7%)
First incidence (days)	695	661
Poly-3 test		P=0.583N
Kidney (Renal Tubule): Adenoma and Carcinoma (Single and Step Sections)		
Overall rate	4/50 (8%)	4/50 (8%)
Adjusted rate	10.60%	9.5%
Terminal rate	1/12 (8%)	2/27 (7%)
First incidence (days)	695	661
Poly-3 test		P=0.583N
Mammary Gland: Fibroadenoma		
Overall rate	5/50 (10%)	2/50 (4%)
Adjusted rate	13.0%	4.8%
Terminal rate	1/12 (8%)	1/27 (4%)
First incidence (days)	619	715
Poly-3 test		P=0.177N
Nose: Squamous Cell Carcinoma		
Overall rate	1/50 (2%)	5/50 (10%)
Adjusted rate	2.7%	11.6%
Terminal rate	0/12 (0%)	2/27 (7%)
First incidence (days)	643	460
Poly-3 test		P=0.128
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	18/50 (36%)	16/50 (32%)
Adjusted rate	41.5%	36.6%
Terminal rate	4/12 (33%)	7/27 (26%)
First incidence (days)	396	565
Poly-3 test		P=0.400N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of Pentachlorophenol

	0 ppm	1,000 ppm
Preputial Gland: Adenoma		
Overall rate	4/50 (8%)	4/49 (8%)
Adjusted rate	10.5%	9.6%
Terminal rate	1/12 (8%)	2/27 (7%)
First incidence (days)	647	550
Poly-3 test		P=0.585N
Preputial Gland: Adenoma or Carcinoma		
Overall rate	5/50 (10%)	5/49 108%)
Adjusted rate	12.8%	11.8%
Terminal rate	1/12 (8%)	2/27 (7%)
First incidence (days)	396	536
Poly-3 test		P=0.570N
Skin: Keratoacanthoma		
Overall rate	0/50 (0%)	7/50 (14%)
Adjusted rate	0.0%	16.7%
Terminal rate	0/12 (0%)	4/27 (15%)
First incidence (days)	—[e]	708
Poly-3 test		P=0.011
Skin: Squamous Cell Papilloma or Keratoacanthoma		
Overall rate	2/50 (4%)	7/50 (14%)
Adjusted rate	5.3%	16.7%
Terminal rate	2/12 (17%)	4/27 (15%)
First incidence (days)	736 (T)	708
Poly-3 test		P=0.103
Skin: Trichoepithelioma or Basal Cell Adenoma		
Overall rate	1/50 (2%)	4/50 (8%)
Adjusted rate	2.7%	9.4%
Terminal rate	0/12 (0%)	1/27 (4%)
First incidence (days)	684	592
Poly-3 test		P=0.210
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma		
Overall rate	3/50 (6%)	9/50 (18%)
Adjusted rate	8.0%	21.1%
Terminal rate	2/12 (17%)	4/27 (15%)
First incidence (days)	684	592
Poly-3 test		P=0.087
Skin (Subcutaneous Tissue): Fibrous Histiocytoma or Fibrosarcoma		
Overall rate	3/50 (6%)	1/50 (2%)
Adjusted rate	8.0%	2.4%
Terminal rate	2/12 (17%)	0/27 (0%)
First incidence (days)	695	680
Poly-3 test		P=0.259N
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, or Fibrosarcoma		
Overall rate	5/50 (10%)	2/50 (4%)
Adjusted rate	13.1%	4.7%
Terminal rate	2/12 (17%)	0/27 (0%)
First incidence (days)	603	614
Poly-3 test		P=0.171N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of Pentachlorophenol

	0 ppm	1,000 ppm
Testes: Adenoma		
Overall rate	42/50 (84%)	45/50 (90%)
Adjusted rate	93.8%	96.3%
Terminal rate	12/12 (100%)	27/27 (100%)
First incidence (days)	561	502
Poly-3 test		P=0.448
Thyroid Gland (C-cell): Adenoma		
Overall rate	5/50 (10%)	4/50 (8%)
Adjusted rate	12.9%	9.6%
Terminal rate	1/12 (8%)	3/27 (11%)
First incidence (days)	535	675
Poly-3 test		P=0.447N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma		
Overall rate	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	7.2%
Terminal rate	0/12 (0%)	2/27 (7%)
First incidence (days)	—	711
Poly-3 test		P=0.132
All Organs: Malignant Mesothelioma		
Overall rate	1/50 (2%)	9/50 (18%)
Adjusted rate	2.6%	20.6%
Terminal rate	0/12 (0%)	4/27 (15%)
First incidence (days)	617	502
Poly-3 test		P=0.014
All Organs: Mononuclear Cell Leukemia		
Overall rate	25/50 (50%)	15/50 (30%)
Adjusted rate	58.8%	34.5%
Terminal rate	5/12 (42%)	8/27 (30%)
First incidence (days)	561	536
Poly-3 test		P=0.016N
All Organs: Benign Neoplasms		
Overall rate	48/50 (96%)	47/50 (94%)
Adjusted rate	99.3%	99.1%
Terminal rate	12/12 (100%)	27/27 (100%)
First incidence (days)	396	502
Poly-3 test		P=0.993N
All Organs: Malignant Neoplasms		
Overall rate	32/50 (64%)	29/50 (58%)
Adjusted rate	71.3%	61.8%
Terminal rate	7/12 (58%)	14/27 (52%)
First incidence (days)	396	265
Poly-3 test		P=0.219N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of Pentachlorophenol

	0 ppm	1,000 ppm
All Organs: Benign or Malignant Neoplasms		
Overall rate	50/50 (100%)	49/50 (98%)
Adjusted rate	100.0%	99.8%
Terminal rate	12/12 (100%)	27/27 (100%)
First incidence (days)	396	265
Poly-3 test		P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, nose, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and the exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in the exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE A4a
Historical Incidence of Mesothelioma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
4,4-Thiobis(6-*t*-butyl-*m*-cresol)	2/50
Ethylene Thiourea	0/50
Manganese (II) Sulfate Monohydrate	2/52
Oxazepam	2/50
Polybrominated Biphenyls (Firemaster FF-1®)	2/50
Triamterene	0/50
Tricresyl Phosphate	1/51
Overall Historical Incidence	
Total	40/1,354 (3.0%)
Standard deviation	2.3%
Range	0%-8%

[a] Data as of 15 October 1996; includes benign, malignant, and unspecified mesotheliomas

TABLE A4b
Historical Incidence of Squamous Cell Carcinoma of the Nose in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
4,4-Thiobis(6-*t*-butyl-*m*-cresol)	0/50
Ethylene Thiourea	0/50
Manganese (II) Sulfate Monohydrate	0/52
Oxazepam	0/50
Polybrominated Biphenyls (Firemaster FF-1®)	0/50
Triamterene	0/50
Tricresyl Phosphate	0/51
Overall Historical Incidence	
Total	5/1,341 (0.4%)
Standard deviation	1.0%
Range	0%-4%

[a] Data as of 15 October 1996

TABLE A4c
Historical Incidence of Skin Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls	
	Keratoacanthoma	Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma
Historical Incidence at Battelle Columbus Laboratories		
4,4-Thiobis(6-*t*-butyl-*m*-cresol)	1/50	3/50
Ethylene Thiourea	1/50	1/50
Manganese (II) Sulfate Monohydrate	1/52	1/52
Oxazepam	3/50	5/50
Polybrominated Biphenyls (Firemaster FF-1®)	2/50	3/50
Triamterene	2/50	3/50
Tricresyl Phosphate	2/51	3/51
Overall Historical Incidence		
Total	54/1,354 (4.0%)	94/1,354 (6.7%)
Standard deviation	3.1%	4.5%
Range	0%-14%	0%-24%

[a] Data as of 15 October 1996

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Pentachlorophenol[a]

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	60	50	50	50	60
7-Month interim evaluation	10				10
Early deaths					
Moribund	28	28	24	11	17
Natural deaths	10	6	5	8	6
Survivors					
Died last week of study	1			2	
Terminal sacrifice	11	16	21	29	27
Animals examined microscopically	60	50	50	50	60
7-Month Interim Evaluation					
Alimentary System					
Liver	(10)				(10)
Basophilic focus	1 (10%)				1 (10%)
Hepatodiaphragmatic nodule	1 (10%)				
Inflammation, chronic	7 (70%)				5 (50%)
Artery, inflammation, chronic					2 (20%)
Bile duct, hyperplasia					2 (20%)
Centrilobular, hypertrophy					3 (30%)
Hepatocyte, hypertrophy					1 (10%)
Hepatocyte, vacuolization cytoplasmic					8 (80%)
Hepatocyte, centrilobular, hypertrophy					6 (60%)
Pancreas	(10)				(10)
Acinus, atrophy	2 (20%)				
Acinus, inflammation, chronic active	2 (20%)				
Cardiovascular System					
Heart	(10)				(10)
Cardiomyopathy, chronic	9 (90%)				10 (100%)
Endocrine System					
Pituitary gland	(10)				(10)
Pars distalis, hyperplasia					1 (10%)
Genital System					
Epididymis	(10)				(10)
Atrophy					1 (10%)
Inflammation, chronic active					1 (10%)
Preputial gland	(10)				(10)
Inflammation, chronic active	10 (100%)				10 (100%)
Prostate	(10)				(10)
Inflammation, chronic active	5 (50%)				7 (70%)
Testes	(10)				(10)
Mineralization					1 (10%)
Necrosis					1 (10%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
7-Month Interim Evaluation (continued)					
Respiratory System					
Lung	(10)				(10)
Inflammation, chronic active	7 (70%)				6 (60%)
Nose	(10)				(10)
Fungus	1 (10%)				1 (10%)
Inflammation, chronic active	3 (30%)				1 (10%)
Urinary System					
Kidney	(10)				(10)
Mineralization	8 (80%)				9 (90%)
Nephropathy, chronic	10 (100%)				9 (90%)
Renal tubule, pigmentation					10 (100%)
Transitional epithelium, hyperplasia					1 (10%)
Systems Examined with No Lesions Observed					
General Body System					
Hematopoietic System					
Integumentary System					
Musculoskeletal System					
Nervous System					
Special Senses System					
2-Year Study					
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(49)	(49)
Parasite metazoan	1 (2%)	3 (6%)	1 (2%)	3 (6%)	3 (6%)
Ulcer					1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic active					1 (2%)
Parasite metazoan	1 (2%)	5 (10%)	3 (6%)	3 (6%)	5 (10%)
Intestine large, cecum	(50)	(50)	(50)	(50)	
Hyperplasia, lymphoid			1 (2%)		
Inflammation, chronic active				1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic active					1 (2%)
Ulcer					1 (2%)
Epithelium, erosion	1 (2%)				
Intestine small, jejunum	(49)				(50)
Inflammation, chronic active					1 (2%)
Intestine small, ileum	(49)	(50)	(50)	(49)	(49)
Parasite metazoan			1 (2%)		
Peyer's patch, inflammation, chronic active				1 (2%)	
Inflammation, chronic active					1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Alimentary System (continued)					
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)		1 (2%)	1 (2%)	2 (4%)
Basophilic focus	17 (34%)	14 (28%)	20 (40%)	16 (32%)	31 (62%)
Clear cell focus	6 (12%)	2 (4%)	7 (14%)	5 (10%)	9 (18%)
Eosinophilic focus	2 (4%)	2 (4%)	1 (2%)	9 (18%)	7 (14%)
Fibrosis					1 (2%)
Hematopoietic cell proliferation					1 (2%)
Hepatodiaphragmatic nodule		7 (14%)	6 (12%)	8 (16%)	5 (10%)
Inflammation, chronic	22 (44%)	16 (32%)	22 (44%)	22 (44%)	34 (68%)
Mixed cell focus	1 (2%)		1 (2%)	1 (2%)	5 (10%)
Pigmentation, bile					1 (2%)
Bile duct, hyperplasia	49 (98%)	47 (94%)	46 (92%)	48 (96%)	46 (92%)
Hepatocyte, degeneration, cystic	16 (32%)	22 (44%)	28 (56%)	39 (78%)	28 (56%)
Hepatocyte, necrosis	3 (6%)		2 (4%)	1 (2%)	2 (4%)
Hepatocyte, vacuolization cytoplasmic	10 (20%)	3 (6%)	5 (10%)	7 (14%)	13 (26%)
Hepatocyte, centrilobular, degeneration	2 (4%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hepatocyte, centrilobular, hypertrophy					1 (2%)
Hepatocyte, centrilobular, necrosis	2 (4%)	4 (8%)	1 (2%)	2 (4%)	2 (4%)
Kupffer cell, hypertrophy	1 (2%)				
Oval cell, hyperplasia		1 (2%)			
Portal vein, thrombosis			1 (2%)		
Mesentery	(15)	(12)	(15)	(11)	(15)
Accessory spleen			1 (7%)		
Inflammation, chronic active				1 (9%)	1 (7%)
Fat, necrosis	12 (80%)	8 (67%)	8 (53%)	8 (73%)	11 (73%)
Oral mucosa tongue	(1)	(1)	(1)		
Gingival, inflammation, suppurative			1 (100%)		
Pharyngeal, necrosis		1 (100%)			
Pancreas	(50)	(50)	(50)	(48)	(50)
Inflammation, chronic active	1 (2%)				
Acinus, atrophy	12 (24%)	27 (54%)	16 (32%)	27 (56%)	19 (38%)
Artery, inflammation, chronic active	1 (2%)				
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic active	10 (20%)	4 (8%)	3 (6%)	2 (4%)	2 (4%)
Epithelium, hyperplasia	8 (16%)	8 (16%)	4 (8%)	3 (6%)	4 (8%)
Epithelium, hyperplasia, basal cell			2 (4%)		
Epithelium, ulcer	8 (16%)	3 (6%)	4 (8%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)		1 (2%)		1 (2%)
Mineralization	1 (2%)			1 (2%)	2 (4%)
Epithelium, erosion	2 (4%)	1 (2%)		2 (4%)	1 (2%)
Epithelium, ulcer	1 (2%)		1 (2%)	1 (2%)	1 (2%)
Tongue	(1)		(1)	(1)	
Inflammation, chronic active			1 (100%)		
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	(50)
Aorta, mineralization	1 (2%)			1 (2%)	2 (4%)
Pulmonary artery, thrombosis	1 (2%)				
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy, chronic	42 (84%)	41 (82%)	41 (82%)	44 (88%)	45 (90%)
Inflammation, suppurative			1 (2%)		
Mineralization				1 (2%)	1 (2%)
Atrium, thrombosis	7 (14%)	7 (14%)	4 (8%)	2 (4%)	1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule			1 (2%)	2 (4%)	2 (4%)
Atrophy	1 (2%)				
Degeneration, cystic	1 (2%)	1 (2%)	1 (2%)		1 (2%)
Degeneration, fatty	28 (56%)	19 (38%)	16 (32%)	20 (40%)	25 (50%)
Hyperplasia	13 (26%)	11 (22%)	13 (26%)	15 (30%)	17 (34%)
Hypertrophy		1 (2%)	2 (4%)	4 (8%)	3 (6%)
Necrosis	1 (2%)				
Adrenal medulla	(50)	(50)	(50)	(50)	(50)
Degeneration, fatty		1 (2%)			
Hyperplasia	18 (36%)	27 (54%)	22 (44%)	25 (50%)	28 (56%)
Islets, pancreatic	(50)	(50)	(50)	(48)	(50)
Hyperplasia	2 (4%)			1 (2%)	
Parathyroid gland	(47)	(45)	(47)	(46)	(47)
Hyperplasia	9 (19%)	3 (7%)			7 (15%)
Pituitary gland	(50)	(50)	(49)	(50)	(50)
Craniopharyngeal duct, cyst	1 (2%)				1 (2%)
Pars distalis, cyst	7 (14%)	8 (16%)	3 (6%)	6 (12%)	6 (12%)
Pars distalis, hemorrhage			1 (2%)		
Pars distalis, hyperplasia	22 (44%)	13 (26%)	15 (31%)	21 (42%)	26 (52%)
Pars intermedia, cyst		1 (2%)	3 (6%)	1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Ectopic tissue				1 (2%)	
Ultimobranchial cyst		1 (2%)			
C-cell, hyperplasia	16 (32%)	8 (16%)	21 (42%)	19 (38%)	17 (34%)
Follicle, cyst		1 (2%)	1 (2%)		
Follicular cell, hyperplasia, cystic	1 (2%)				1 (2%)
General Body System					
None					
Genital System					
Coagulating gland	(2)	(1)			
Inflammation, chronic active	2 (100%)	1 (100%)			
Epididymis	(50)	(50)	(50)	(50)	(50)
Granuloma sperm		2 (4%)			1 (2%)
Preputial gland	(50)	(50)	(50)	(50)	(49)
Hyperplasia	7 (14%)	7 (14%)	7 (14%)	4 (8%)	8 (16%)
Inflammation, chronic active	42 (84%)	40 (80%)	47 (94%)	47 (94%)	44 (90%)
Duct, cyst	2 (4%)		2 (4%)		
Prostate	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic active	38 (76%)	34 (68%)	32 (64%)	26 (53%)	37 (74%)
Epithelium, hyperplasia		1 (2%)			
Seminal vesicle	(50)				(50)
Inflammation, chronic active					1 (2%)
Testes	(50)	(50)	(50)	(50)	(50)
Arteriole, inflammation, chronic	1 (2%)				1 (2%)
Arteriole, necrosis, fibrinoid					1 (2%)
Germinal epithelium, atrophy	2 (4%)	2 (4%)	4 (8%)	4 (8%)	4 (8%)
Interstitial cell, hyperplasia	10 (20%)	10 (20%)	6 (12%)	5 (10%)	8 (16%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Atrophy		1 (2%)	1 (2%)		
Atrophy, focal		1 (2%)			
Hyperplasia	30 (60%)	33 (66%)	36 (72%)	32 (64%)	38 (76%)
Myleofibrosis	1 (2%)	2 (4%)		1 (2%)	1 (2%)
Lymph node	(34)	(34)	(35)	(41)	(28)
Inguinal, inflammation, supprative					1 (4%)
Lumbar, hyperplasia, lymphoid		1 (3%)			
Mediastinal, ectasia					1 (4%)
Mediastinal, hyperplasia, lymphoid		1 (3%)	3 (9%)		1 (4%)
Mediastinal, infiltration cellular, histocyte					1 (4%)
Mediastinal, inflammation, granulomatous					1 (4%)
Mediastinal, necrosis			1 (3%)		
Mediastinal, pigmentation, hemosiderin	25 (74%)	19 (56%)	23 (66%)	36 (88%)	24 (86%)
Pancreatic, ectasia				1 (2%)	
Renal, hyperplasia, lymphoid					1 (4%)
Lymph node, mandibular	(50)	(50)	(50)	(50)	(50)
Ectasia			2 (4%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)		
Hyperplasia, plasma cell	1 (2%)		1 (2%)		
Lymph node, mesenteric	(50)	(50)	(50)	(49)	(50)
Ectasia			1 (2%)	2 (4%)	6 (12%)
Erythrophagocytosis		1 (2%)			1 (2%)
Hyperplasia, lymphoid					3 (6%)
Infiltration cellular, histiocyte	1 (2%)				
Inflammmation, granulomatous					1 (2%)
Pigmentation, hemosiderin			1 (2%)		
Spleen	(50)	(50)	(50)	(50)	(50)
Fibrosis	5 (10%)	3 (6%)	3 (6%)	1 (2%)	6 (12%)
Hematopoietic cell proliferation	4 (8%)		1 (2%)		3 (6%)
Necrosis	2 (4%)		2 (4%)	2 (4%)	
Thymus	(49)	(46)	(49)	(47)	
Ectopic parathyroid gland		1 (2%)			
Integumentary System					
Mammary gland	(49)	(47)	(50)	(49)	(49)
Cyst			1 (2%)	1 (2%)	2 (4%)
Hyperplasia, cystic	36 (73%)	34 (72%)	24 (48%)	28 (57%)	26 (53%)
Inflammation, supprative					1 (2%)
Skin	(50)	(50)	(50)	(50)	(50)
Cyst epithelial inclusion		1 (2%)		2 (4%)	2 (4%)
Inflammation, chronic active			1 (2%)	1 (2%)	1 (2%)
Inflammation, granulomatous		1 (2%)			
Necrosis				1 (2%)	
Epidermis, hyperkeratosis		1 (2%)	3 (6%)	3 (6%)	4 (8%)
Epidermis, hyperplasia	1 (2%)				
Sebaceous gland, hyperplasia	1 (2%)				
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)				3 (6%)
Osteopetrosis		1 (2%)			
Cranium, inflammation, chronic active					1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Gliosis				1 (2%)	
Hemorrhage	4 (8%)		6 (12%)	2 (4%)	1 (2%)
Inflammation, suppurative			1 (2%)		
Necrosis		1 (2%)			
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Foreign body	1 (2%)				
Inflammation, chronic active	3 (6%)		5 (10%)	4 (8%)	6 (12%)
Alveolar epithelium, hyperplasia	1 (2%)	5 (10%)	3 (6%)	2 (4%)	3 (6%)
Alveolus, infiltration cellular, histiocyte	39 (78%)	37 (74%)	39 (78%)	40 (80%)	44 (88%)
Interstitium, mineralization				1 (2%)	1 (2%)
Nose	(50)	(50)	(50)	(50)	(50)
Fungus	21 (42%)	15 (30%)	10 (20%)	11 (22%)	7 (14%)
Hemorrhage			1 (2%)		
Inflammation, chronic active	25 (50%)	19 (38%)	22 (44%)	18 (36%)	21 (42%)
Nasolacrimal duct, inflammation, suppurative	6 (12%)	6 (12%)	6 (12%)	5 (10%)	4 (8%)
Olfactory epithelium, metaplasia, squamous					1 (2%)
Respiratory epithelium, hyperplasia	24 (48%)	16 (32%)	17 (34%)	13 (26%)	11 (22%)
Respiratory epithelium, metaplasia, squamous	12 (24%)	9 (18%)	8 (16%)	7 (14%)	5 (10%)
Special Senses System					
Eye	(1)	(4)	(1)	(3)	(3)
Cornea, inflammation, chronic active			1 (100%)		
Lens, cataract	1 (100%)	3 (75%)		3 (100%)	3 (100%)
Retina, atrophy	1 (100%)	4 (100%)		3 (100%)	3 (100%)
Retina, hemorrhage		1 (25%)			
Sclera, metaplasia, osseous		1 (25%)			
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet		1 (2%)			
Cyst	1 (2%)	4 (8%)	1 (2%)	1 (2%)	3 (6%)
Infarct			1 (2%)		
Inflammation, suppurative			1 (2%)		
Nephropathy, chronic	50 (100%)	49 (98%)	50 (100%)	49 (98%)	49 (98%)
Renal tubule, hyperplasia	1 (2%)				2 (4%)
Renal tubule, pigmentation	49 (98%)	48 (96%)	49 (98%)	50 (100%)	47 (94%)
Urinary bladder	(48)	(50)	(50)	(49)	(49)
Hemorrhage				1 (2%)	
Inflammation, chronic active	1 (2%)				

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF PENTACHLOROPHENOL

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

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	60	50	50	50	60
7-Month interim evaluation	10				10
Early deaths					
Moribund	15	12	12	17	17
Natural deaths	7	5	4	5	5
Survivors					
Terminal sacrifice	28	33	34	28	28
Animals examined microscopically	60	50	50	50	60
Systems Examined at 7 Months with No Neoplasms Observed					
Alimentary System					
Cardiovascular System					
Endocrine System					
General Body System					
Genital System					
Hematopoietic System					
Integumentary System					
Musculoskeletal System					
Nervous System					
Respiratory System					
Special Senses System					
Urinary System					
2-Year Study					
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Intestine large, rectum	(50)	(50)	(50)	(50)	
Intestine small, duodenum	(50)	(50)	(50)	(50)	(50)
Intestine small, jejunum	(50)	(50)	(50)	(50)	(50)
Carcinoma			1 (2%)		
Leiomyoma					1 (2%)
Intestine small, ileum	(50)	(50)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)	(50)
Sarcoma stromal, metastatic, uterus					1 (2%)
Mesentery	(8)	(1)	(5)	(5)	(6)
Carcinoma, metastatic, intestine small, jejunum			1 (20%)		
Schwannoma malignant, metastatic, uterus	1 (13%)				
Fat, sarcoma stromal, metastastic, uterus					1 (17%)
Oral mucosa	(1)			(1)	(2)
Pharyngeal, squamous cell carcinoma					1 (50%)
Pharyngeal, squamous cell papilloma	1 (100%)				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Alimentary System (continued)					
Pancreas	(50)	(49)	(50)	(50)	(50)
Carcinoma, metastatic, intestine small, jejunum			1 (2%)		
Sarcoma stromal, metastic, uterus					1 (2%)
Acinus, adenoma					1 (2%)
Salivary glands	(50)	(49)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, intestine small, jejunum			1 (2%)		
Tongue	(1)				(1)
Squamous cell papilloma	1 (100%)				1 (100%)
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	
Heart	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, intestine small, jejunum			1 (2%)		
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Adenoma				1 (2%)	
Adrenal medulla	(50)	(50)	(50)	(50)	(50)
Pheochromocytoma malignant		1 (2%)			
Pheochromocytoma benign		3 (6%)	1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(50)	(50)
Adenoma	1 (2%)				
Parathyroid gland	(46)	(44)	(41)	(47)	(45)
Adenoma	1 (2%)				
Pituitary gland	(50)	(50)	(50)	(50)	(50)
Pars distalis, adenoma	22 (44%)	20 (40%)	14 (28%)	15 (30%)	18 (36%)
Pars distalis, adenoma, multiple				1 (2%)	
Pars intermedia, adenoma	1 (2%)	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma				1 (2%)	2 (4%)
C-cell, adenoma	3 (6%)	3 (6%)	1 (2%)	3 (6%)	5 (10%)
C-cell, carcinoma	2 (4%)	1 (2%)	2 (4%)		1 (2%)
Follicular cell, adenoma	1 (2%)	1 (2%)			
Follicular cell, carcinoma	1 (2%)				
General Body System					
Tissue NOS				(1)	
Abdominal, paraganglioma				1 (100%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-exposure)
2-Year Study (continued)					
Genital System					
Clitoral gland	(50)	(50)	(48)	(50)	(49)
Adenoma	4 (8%)	1 (2%)	1 (2%)	2 (4%)	5 (10%)
Carcinoma	1 (2%)	1 (2%)	2 (4%)		1 (2%)
Bilateral, adenoma				1 (2%)	
Bilateral, carcinoma	1 (2%)				
Ovary	(50)	(50)	(50)	(50)	(50)
Granulosa cell tumor benign			1 (2%)	1 (2%)	
Leiomyosarcoma, metastatic, uterus				1 (2%)	
Thecoma malignant			1 (2%)		
Uterus	(50)	(50)	(50)	(50)	(50)
Leiomyosarcoma				1 (2%)	
Polyp stromal	6 (12%)	6 (12%)	3 (6%)	4 (8%)	6 (12%)
Sarcoma stromal			1 (2%)	1 (2%)	1 (2%)
Schwannoma malignant, metastatic, uterus	1 (2%)				
Vagina	(2)		(1)		
Schwannoma malignant, metastatic, uterus	1 (50%)				
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(49)
Histiocytic sarcoma				1 (2%)	
Lymph node	(35)	(27)	(26)	(28)	(30)
Deep cervical, carcinoma, metastatic, thyroid gland		1 (4%)	1 (4%)		1 (3%)
Mediastinal, carcinoma, metastatic, intestine small, jejunum			1 (4%)		
Pancreatic, carcinoma, metastatic, intestine small, jejunum			1 (4%)		
Lymph node, mandibular	(50)	(49)	(50)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(50)	(50)	(50)
Sarcoma stromal, metastatic, uterus					1 (2%)
Spleen	(50)	(50)	(50)	(50)	(50)
Thymus	(48)	(44)	(48)	(47)	(49)
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	1 (2%)	
Carcinoma	1 (2%)	2 (4%)	2 (4%)		
Carcinoma, multiple		1 (2%)			
Fibroadenoma	16 (32%)	17 (34%)	18 (36%)	11 (22%)	10 (20%)
Fibroadenoma, multiple	9 (18%)	3 (6%)	1 (2%)	1 (2%)	5 (10%)
Skin	(50)	(50)	(50)	(50)	(50)
Keratoacanthoma				1 (2%)	
Squamous cell papilloma			1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)	1 (2%)			
Subcutaneous tissue, fibrosarcoma	1 (2%)		1 (2%)	1 (2%)	1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	
Vertebra, fibrosarcoma			1 (2%)		
Skeletal muscle			(2)	(1)	(1)
Carcinoma, metastatic, intestine small, jejunum			1 (50%)		
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)		
Cranial nerve, squamous cell carcinoma metastatic, oral mucosa					1 (2%)
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)				
Alveolar/bronchiolar carcinoma	1 (2%)				
Carcinoma, metastatic, intestine small, jejunum			1 (2%)		
Carcinoma, metastatic, clitoral gland					1 (2%)
Nose	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, oral mucosa					1 (2%)
Special Senses System					
None					
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Ureter				(1)	
Carcinoma				1 (100%)	
Urinary bladder	(50)	(50)	(49)	(49)	(49)
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)	
Leukemia mononuclear	15 (30%)	15 (30%)	15 (30%)	18 (36%)	11 (22%)
Lymphoma malignant				1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Neoplasm Summary					
Total animals with primary neoplasms[c]					
2-Year study	45	43	42	43	42
Total primary neoplasms					
2-Year study	93	77	69	69	71
Total animals with benign neoplasms					
2-Year study	37	37	27	30	35
Total benign neoplasms					
2-Year study	70	56	42	45	55
Total animals with malignant neoplasms					
2-Year study	20	18	23	24	16
Total malignant neoplasms					
2-Year study	23	21	27	24	16
Total animals with metastatic neoplasms					
2-Year study	1	1	2	1	4
Total metastatic neoplasms					
2-Year study	3	1	9	1	8

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[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 Feed Study of Pentachlorophenol: 0 ppm

Number of Days on Study	3 9 1	4 6 1	4 7 5	5 0 7	5 2 3	5 4 3	5 4 4	5 6 9	5 7 3	5 8 5	6 2 0	6 4 5	6 4 8	6 6 3	6 6 3	6 9 6	6 9 8	6 9 8	7 0 4	7 0 5	7 1 5	7 3 1	7 3 8	7 3 8	7 3 8
Carcass ID Number	3 0 3	3 0 0	3 0 9	3 1 0	2 8 6	3 2 8	2 8 1	3 0 8	3 0 2	3 1 1	3 2 1	2 9 1	3 0 5	2 7 2	3 3 0	2 7 3	3 0 1	3 1 6	2 2 1	2 7 9	2 8 8	3 2 6	2 7 7	2 8 7	2 9 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+		+															+							
Schwannoma malignant, metastatic, uterus																									
Oral mucosa																							+		
Pharyngeal, squamous cell papilloma																							X		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				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																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma																					X				
Bilateral, carcinoma																									

+: 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 Feed Study of Pentachlorophenol: 0 ppm

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	2 9 7	3 0 6	3 1 3	3 1 4	3 1 8	3 2 4	3 2 9	2 7 9	2 8 2	2 8 4	2 8 5	2 9 2	2 9 8	3 0 4	3 1 7	3 1 9	3 2 5	2 8 9	2 9 3	2 9 4	2 9 6	3 0 7	3 1 2	3 2 3	3 2 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Mesentery									+	+	+			+			+									8
Schwannoma malignant, metastatic, uterus									X																	1
Oral mucosa																										1
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue											+															1
Squamous cell papilloma											X															1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																	X									1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X						X			X	X	X	X		X	X			X			X				22
Pars intermedia, adenoma							X																			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X																3
C-cell, carcinoma									X																X	2
Follicular cell, adenoma																X										1
Follicular cell, carcinoma											X															1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X						X						X				4
Carcinoma																										1
Bilateral, carcinoma																								X		1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 0 ppm

Number of Days on Study	3 9 1	4 6 1	4 7 5	5 0 7	5 2 3	5 4 3	5 4 4	5 6 9	5 7 3	5 8 5	6 2 0	6 4 5	6 4 8	6 6 3	6 6 3	6 9 6	6 9 8	6 9 8	7 0 4	7 0 5	7 1 5	7 3 1	7 3 8	7 3 8	7 3 8
Carcass ID Number	3 0 3	3 0 0	3 0 9	3 1 0	2 8 6	3 2 8	2 8 1	3 0 8	3 0 2	3 1 1	3 2 1	2 9 1	3 0 5	2 7 2	3 3 0	2 7 3	3 0 1	2 1 6	2 7 1	2 9 5	2 8 8	3 2 6	2 7 7	2 8 7	2 9 0
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Schwannoma malignant, metastatic, uterus																									
Vagina																+									
Schwannoma malignant, metastatic, uterus																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+		+		+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma				X			X					X			X		X				X			X	X
Fibroadenoma, multiple								X						X								X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma					X																				
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																	+								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Feed Study of Pentachlorophenol: 0 ppm

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	2 9 7	3 0 6	3 1 3	3 1 4	3 1 8	3 2 4	3 2 9	2 7 9	2 8 2	2 8 4	2 8 5	2 9 2	2 9 8	3 0 4	3 1 7	3 1 9	3 2 5	2 8 9	2 9 3	2 9 4	2 9 6	3 0 7	3 1 2	3 2 3	3 2 7	Total Tissues/ Tumors
Genital System (continued)																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X			X	X		X							X						X						6
Schwannoma malignant, metastatic, uterus									X																	1
Vagina									+																	2
Schwannoma malignant, metastatic, uterus									X																	1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+				+		+	+		+	+	+	+	+	+		+	+			+	+		+	35
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma															X											1
Fibroadenoma	X									X		X		X		X	X			X	X					16
Fibroadenoma, multiple		X				X	X				X				X			X								9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																								X		2
Subcutaneous tissue, fibrosarcoma		X																								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																				X						2
Alveolar/bronchiolar carcinoma																						X				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+		+																					3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X							X						X									15

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 200 ppm

Number of Days on Study	2 8 4	3 3 7	3 9 2	4 3 0	5 2 2	5 3 5	5 3 5	6 2 0	6 2 0	6 5 0	6 9 8	7 0 0	7 0 1	7 1 5	7 1 5	7 2 6	7 3 1	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	3 3 7	3 5 9	3 7 7	3 8 0	3 3 9	3 5 0	3 6 7	3 4 1	3 4 9	3 5 8	3 4 2	3 3 3	3 6 0	3 6 6	3 7 0	3 3 1	3 3 4	3 3 5	3 3 6	3 3 8	3 4 0	4 4 4	4 4 7	4 5 5	3 6 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X			X						X		X	X	X					X	X
Pars intermedia, adenoma																				X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma												X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal														X		X									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+		+	+		+	+	+	+		+	+	+		+	+	+	+	+	+		+
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	M	+	M	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 200 ppm

Number of Days on Study	738	738	738	739	739	739	739	739	739	739	739	739	739	739	739	739	740	740	740	740	740	740	740	740	740	
Carcass ID Number	372	374	376	332	343	345	348	352	354	356	363	364	365	373	378	346	451	353	557	361	462	369	471	475	479	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Mesentery																			+							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant														X												1
Pheochromocytoma benign							X												X		X					3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X	X		X	X		X			X	X			X		X						X	X	20
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma											X								X				X			3
C-cell, carcinoma					X																					1
Follicular cell, adenoma															X											1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X				X			X						X									6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+		+	+				+							+			+					+	+	27
Deep cervical, carcinoma, metastatic, thyroid gland					X																					1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 200 ppm

Number of Days on Study	2 8 4	3 3 7	3 9 2	4 3 0	5 2 2	5 3 5	5 3 5	6 2 0	6 2 0	6 5 0	6 9 8	7 0 0	7 0 1	7 1 5	7 1 5	7 2 6	7 3 1	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	3 3 7	3 5 9	3 7 7	3 8 0	3 3 9	3 5 0	3 6 7	3 4 1	3 4 9	3 5 8	3 4 2	3 3 3	3 6 0	3 6 6	3 7 0	3 3 1	3 3 4	3 3 5	3 3 6	3 3 8	3 4 0	3 4 4	3 4 7	3 5 5	3 6 8
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Carcinoma, multiple																									
Fibroadenoma								X	X							X						X	X		
Fibroadenoma, multiple															X			X							X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye											+														
Zymbal's gland																								+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Feed Study of Pentachlorophenol: 200 ppm

Number of Days on Study	738	738	738	739	739	739	739	739	739	739	739	739	739	739	739	740	740	740	740	740	740	740	740	740	740	
Carcass ID Number	37 2	37 4	37 6	37 2	37 3	37 5	37 8	37 2	37 4	37 6	37 3	37 4	37 5	37 3	37 8	37 6	37 1	37 3	37 7	37 1	37 2	37 9	37 1	37 5	37 9	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									X	2
Carcinoma, multiple				X																						1
Fibroadenoma	X		X				X			X	X	X		X		X		X	X		X				X	17
Fibroadenoma, multiple																										3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye												+					+									3
Zymbal's gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X						X	X			X						X	15

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 400 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 400 ppm

Number of Days on Study	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	4 2 4	4 2 6	3 8 8	3 8 9	3 9 5	3 9 6	3 9 7	4 0 6	4 1 0	4 1 6	4 2 0	4 2 7	4 2 9	3 9 1	4 0 3	4 0 4	4 0 5	4 0 8	4 1 2	4 1 4	4 1 7	4 1 9	4 2 1	4 2 3	4 3 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery							+	+																		5
Carcinoma, metastatic, intestine small, jejunum																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, intestine small, jejunum																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, intestine small, jejunum																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, intestine small, jejunum																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X			X	X								X								X		X		14
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										1
C-cell, carcinoma																				X						2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma									X																	1
Carcinoma												X														2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																							X			1
Thecoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X				X																	3
Sarcoma stromal						X																				1
Vagina																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 400 ppm

Number of Days on Study	3 9 9	4 1 7	4 5 1	5 3 5	5 4 4	5 6 3	5 9 2	6 0 0	6 1 4	6 2 5	6 4 7	6 7 0	6 8 4	6 9 0	7 2 1	7 3 3	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	4 0 1	4 0 7	3 8 1	4 2 8	4 2 5	4 1 1	3 8 7	3 8 2	3 9 2	3 9 8	4 0 9	3 8 5	4 1 5	3 8 3	4 0 2	3 9 0	3 8 4	3 8 6	3 9 3	3 9 4	3 9 9	4 0 0	4 1 3	4 1 8	4 2 2
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+		+	+	+	+	+	+	+	+	+	+		+		+	+			+	
Deep cervical, carcinoma, metastatic, thyroid gland																				X				
Mediastinal, carcinoma, metastatic, intestine small, jejunum										X														
Pancreatic, carcinoma, metastatic, intestine small, jejunum										X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma																								
Fibroadenoma		X		X						X	X		X					X	X	X	X	X		
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Subcutaneous tissue, fibrosarcoma																X								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, fibrosarcoma														X										
Skeletal muscle									+	+														
Carcinoma, metastatic, intestine small, jejunum										X														
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant					X																			
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, jejunum										X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye		+												+										
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
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 Feed Study of Pentachlorophenol: 400 ppm

Number of Days on Study	738	738	739	739	739	739	739	739	739	739	739	739	739	740	740	740	740	740	740	740	740	740	740	740	740	
Carcass ID Number	42 4	42 6	38 8	38 9	39 5	39 6	39 7	40 6	41 0	41 6	42 0	42 7	42 9	43 1	39 1	40 3	40 4	40 5	40 8	41 2	41 4	41 7	41 9	42 1	42 3	43 0	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+								+						+	+	+	+		+					+	26
Deep cervical, carcinoma, metastatic, thyroid gland																											1
Mediastinal, carcinoma, metastatic, intestine small, jejunum																											1
Pancreatic, carcinoma, metastatic, intestine small, jejunum																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																						1
Carcinoma																		X							X		2
Fibroadenoma		X								X			X	X			X					X	X			X	18
Fibroadenoma, multiple					X																						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																X											1
Subcutaneous tissue, fibrosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, fibrosarcoma																											1
Skeletal muscle																											2
Carcinoma, metastatic, intestine small, jejunum																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, intestine small, jejunum																										1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																											2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X															X	X						X		15

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 600 ppm

Number of Days on Study	4 1 7	4 4 4	4 5 9	5 7 1	5 7 2	5 8 6	5 8 6	5 8 8	5 9 2	6 0 5	6 0 5	6 1 3	6 3 2	6 3 4	6 3 4	6 4 2	6 4 6	6 8 4	6 9 0	6 9 2	7 0 4	7 2 2	7 3 8	7 3 8	7 3 8
Carcass ID Number	4 5 2	4 3 4	4 4 2	4 5 1	4 6 0	4 3 3	4 5 4	4 4 4	4 7 8	4 4 8	4 5 7	4 7 0	4 4 9	4 4 0	4 6 5	4 6 2	4 4 3	4 5 9	4 6 7	4 3 5	4 4 1	4 3 1	4 3 2	4 4 5	4 4 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery											+		+					+					+		
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X	X									X	X	X	X	X	X	
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma						X																X		X	
General Body System																									
Tissue NOS																							+		
Abdominal, paraganglioma																							X		
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X																								
Bilateral, adenoma										X															
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Leiomyosarcoma, metastatic, uterus																			X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																			X						
Polyp stromal									X																
Sarcoma stromal																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 600 ppm

Number of Days on Study	738	738	738	738	738	739	739	739	739	739	739	739	739	739	740	740	740	740	740	740	740	740	740	740	740	
Carcass ID Number	450	461	463	468	477	736	747	753	756	766	772	773	774	779	737	738	739	755	758	764	769	771	775	776	780	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Mesentery															+											5
Oral mucosa																			+							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X			X		X										X						X			X	15
Pars distalis, adenoma, multiple													X														1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma													X														1
C-cell, adenoma																											3
General Body System																										
Tissue NOS																										1
Abdominal, paraganglioma																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X														2
Bilateral, adenoma																											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign								X																			1
Leiomyosarcoma, metastatic, uterus																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																											1
Polyp stromal							X	X																X			4
Sarcoma stromal													X														1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 600 ppm

Number of Days on Study	4 1 7	4 4 4	4 5 9	5 7 1	5 7 2	5 8 6	5 8 6	5 8 8	5 9 2	6 0 5	6 0 5	6 1 3	6 3 2	6 3 4	6 3 4	6 4 2	6 4 6	6 8 4	6 9 0	6 9 2	7 0 4	7 2 2	7 3 8	7 3 8	7 3 8
Carcass ID Number	4 5 2	4 3 4	4 4 2	4 5 1	4 6 0	4 3 3	4 5 4	4 4 4	4 7 8	4 4 8	4 5 7	4 7 0	4 4 9	4 4 0	4 6 5	4 6 2	4 4 3	4 5 9	4 6 7	4 3 5	4 4 1	4 3 1	4 4 2	4 3 4	4 4 5	4 4 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Lymph node	+			+	+		+		+	+	+		+	+	+	+	+	+	+	+				+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Fibroadenoma														X	X	X					X	X			X	
Fibroadenoma, multiple																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																										
Subcutaneous tissue, fibrosarcoma																	X									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+														
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye							+																			
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter								+																		
Carcinoma								X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Leukemia mononuclear			X	X	X	X	X				X		X	X		X		X					X		
Lymphoma malignant												X														

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 600 ppm

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	4 5 0	4 6 1	4 6 3	4 6 8	4 7 7	4 3 6	4 4 7	4 5 3	4 5 6	4 6 6	4 7 2	4 7 3	4 7 4	4 7 9	4 3 7	4 3 8	4 3 9	4 5 5	4 5 8	4 6 4	4 6 9	4 7 1	4 7 5	4 7 6	4 8 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X																		1
Lymph node		+		+							+	+	+	+	+	+	+					+		+	+	28
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Fibroadenoma						X				X									X	X	X					11
Fibroadenoma, multiple																						X				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma										X																1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																+										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										1
Carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X																		1
Leukemia mononuclear				X						X				X				X			X	X		X		18
Lymphoma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	0 1 1	3 6 5	4 7 2	5 1 6	5 7 1	5 9 2	6 0 0	6 0 0	6 4 7	6 5 2	6 6 8	6 8 4	6 9 0	7 0 1	7 0 3	7 0 4	7 0 4	7 0 8	7 1 4	7 1 9	7 1 9	7 2 4	7 3 8	7 3 8	7 3 8
Carcass ID Number	5 1 1	4 8 5	5 2 8	4 8 8	5 1 2	5 3 7	4 9 1	5 2 6	5 0 4	5 0 8	5 0 7	4 9 7	4 9 9	5 0 0	5 0 3	5 0 1	5 3 5	5 0 2	4 9 5	5 2 2	5 2 3	5 1 9	4 8 1	4 9 3	4 9 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus												X													
Mesentery			+					+				+			+						+				
Fat, sarcoma stromal, metastatic, uterus												X													
Oral mucosa														+											
Pharyngeal, squamous cell carcinoma														X											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus												X													
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																						+			
Squamous cell papilloma																						X			
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	I	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X		X				X			X		X			X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma											X														
C-cell, adenoma													X						X						
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X											X				X		X						
Carcinoma								X																	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal							X											X					X	X	
Sarcoma stromal												X													

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	738	738	738	738	738	738	738	739	739	739	739	739	739	739	739	739	740	740	740	740	740	740	740	740	740	
Carcass ID Number	50 5	51 3	51 7	52 0	53 0	53 6	53 9	48 2	48 7	49 6	49 8	51 0	51 6	51 8	53 2	53 8	48 3	48 4	50 6	50 9	51 5	52 1	53 1	53 3	54 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																								X		1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Mesentery						+																				6
Fat, sarcoma stromal, metastatic, uterus																										1
Oral mucosa												+														2
Pharyngeal, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Acinus, adenoma																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign															X											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X		X		X	X		X			X	X		X				X					18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma						X																				2
C-cell, adenoma			X	X																			X			5
C-cell, carcinoma																X										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																X										5
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X									X													6
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	0 1 1	3 6 5	4 7 2	5 1 6	5 7 1	5 9 2	6 0 0	6 0 0	6 4 7	6 5 2	6 6 8	6 8 4	6 9 0	7 0 1	7 0 3	7 0 4	7 0 4	7 0 8	7 1 4	7 1 9	7 1 9	7 2 4	7 3 8	7 3 8	7 3 8
Carcass ID Number	5 1 1	4 8 5	5 2 8	4 8 8	5 1 2	5 3 7	4 9 1	5 2 6	5 0 4	5 0 8	5 0 7	4 9 7	4 9 9	5 0 0	5 0 3	5 0 1	5 3 5	5 0 2	4 9 5	5 2 2	5 2 3	5 1 9	4 8 1	4 9 3	4 9 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+			+	
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma							X					X							X	X			X		
Fibroadenoma, multiple																								X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle															+										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranial nerve, squamous cell carcinoma, metastatic, oral mucosa														X											
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, clitoral gland								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, oral mucosa														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+											
Harderian gland														+											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
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 Feed Study of Pentachlorophenol: 1,000 ppm (Stop-Exposure)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	5 0 5	5 1 3	5 1 7	5 2 0	5 3 0	5 3 6	5 3 9	4 8 2	4 8 7	4 9 6	4 9 8	5 1 0	5 1 6	5 1 8	5 3 2	5 3 8	4 8 3	4 8 4	5 0 6	5 0 9	5 1 5	5 2 1	5 3 1	5 3 3	5 4 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+							+	+			+		+		+	+	+	+				+	+	+	30
Deep cervical, carcinoma, metastatic, thyroid gland																X										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma					X				X				X				X					X				10
Fibroadenoma, multiple								X						X	X											5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranial nerve, squamous cell carcinoma, metastatic, oral mucosa																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, clitoral gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, oral mucosa																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye												+														2
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X																			X			11

TABLE B3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	0/50 (0%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate[b]	0.0%	7.0%	2.3%	2.5%
Terminal rate[c]	0/28 (0%)	3/33 (9%)	0/34 (0%)	1/28 (4%)
First incidence (days)	—[e]	738 (T)	690	738 (T)
Poly-3 test[d]	P=0.508	P=0.126	P=0.510	P=0.498
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	0/50 (0%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rate	0.0%	9.3%	2.3%	2.5%
Terminal rate	0/28 (0%)	4/33 (12%)	0/34 (0%)	1/28 (4%)
First incidence (days)	—	738 (T)	690	738 (T)
Poly-3 test	P=0.571N	P=0.065	P=0.510	P=0.498
Clitoral Gland: Adenoma				
Overall rate	4/50 (8%)	1/50 (2%)	1/48 (2%)	3/50 (6%)
Adjusted rate	9.7%	2.3%	2.4%	7.1%
Terminal rate	3/28 (11%)	0/33 (0%)	1/34 (3%)	1/28 (4%)
First incidence (days)	645	701	738 (T)	417
Poly-3 test	P=0.385N	P=0.167N	P=0.178N	P=0.493N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	2/50 (4%)	3/48 (6%)	3/50 (6%)
Adjusted rate	14.4%	4.6%	7.2%	7.1%
Terminal rate	4/28 (14%)	0/33 (0%)	2/34 (6%)	1/28 (4%)
First incidence (days)	645	700	670	417
Poly-3 test	P=0.196N	P=0.120N	P=0.239N	P=0.234N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.2%	0.0%	0.0%	0.0%
Terminal rate	2/28 (7%)	0/33 (0%)	0/34 (0%)	0/28 (0%)
First incidence (days)	645	—	—	—
Poly-3 test	P=0.018N	P=0.113N	P=0.112N	P=0.121N
Mammary Gland: Fibroadenoma				
Overall rate	25/50 (50%)	20/50 (40%)	19/50 (38%)	12/50 (24%)
Adjusted rate	56.7%	45.7%	41.9%	28.6%
Terminal rate	16/28 (57%)	16/33 (49%)	14/34 (41%)	7/28 (25%)
First incidence (days)	507	620	417	634
Poly-3 test	P=0.005N	P=0.202N	P=0.111N	P=0.005N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	25/50 (50%)	20/50 (40%)	19/50 (38%)	13/50 (26%)
Adjusted rate	56.7%	45.7%	41.9%	31.0%
Terminal rate	16/28 (57%)	16/33 (49%)	14/34 (41%)	8/28 (29%)
First incidence (days)	507	620	417	634
Poly-3 test	P=0.009N	P=0.202N	P=0.111N	P=0.011N
Mammary Gland: Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	2.4%	6.9%	4.7%	0.0%
Terminal rate	1/28 (4%)	2/33 (6%)	2/34 (6%)	0/28 (0%)
First incidence (days)	738 (T)	430	738 (T)	—
Poly-3 test	P=0.295N	P=0.326	P=0.516	P=0.502N

TABLE B3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm
Mammary Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.4%	6.9%	7.0%	2.5%
Terminal rate	1/28 (4%)	2/33 (6%)	3/34 (9%)	1/28 (4%)
First incidence (days)	738 (T)	430	738 (T)	738 (T)
Poly-3 test	P=0.561	P=0.326	P=0.321	P=0.759
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	25/50 (50%)	22/50 (44%)	21/50 (42%)	13/50 (26%)
Adjusted rate	56.7%	49.4%	46.3%	31.0%
Terminal rate	16/28 (57%)	17/33 (52%)	16/34 (47%)	8/28 (29%)
First incidence (days)	507	430	417	634
Poly-3 test	P=0.010N	P=0.314N	P=0.215N	P=0.011N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	22/50 (44%)	20/50 (40%)	14/50 (28%)	16/50 (32%)
Adjusted rate	49.1%	44.9%	31.5%	38.1%
Terminal rate	11/28 (39%)	15/33 (46%)	10/34 (29%)	11/28 (39%)
First incidence (days)	507	522	544	592
Poly-3 test	P=0.083N	P=0.425N	P=0.066N	P=0.201N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adjusted rate	7.2%	2.3%	2.3%	2.4%
Terminal rate	2/28 (7%)	1/33 (3%)	0/34 (0%)	0/28 (0%)
First incidence (days)	523	738 (T)	733	646
Poly-3 test	P=0.181N	P=0.296N	P=0.294N	P=0.311N
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted rate	7.2%	7.0%	2.3%	9.7%
Terminal rate	1/28 (4%)	3/33 (9%)	1/34 (3%)	2/28 (7%)
First incidence (days)	585	738 (T)	738 (T)	586
Poly-3 test	P=0.503	P=0.652N	P=0.295N	P=0.494
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	4/50 (8%)	3/50 (6%)	4/50 (8%)
Adjusted rate	12.0%	9.3%	7.0%	9.7%
Terminal rate	3/28 (11%)	4/33 (12%)	3/34 (9%)	2/28 (7%)
First incidence (days)	585	738 (T)	738 (T)	586
Poly-3 test	P=0.367N	P=0.485N	P=0.340N	P=0.507N
Uterus: Stromal Polyp				
Overall rate	6/50 (12%)	6/50 (12%)	3/50 (6%)	4/50 (8%)
Adjusted rate	14.6%	14.0%	7.0%	9.7%
Terminal rate	6/28 (21%)	4/33 (12%)	3/34 (9%)	3/28 (11%)
First incidence (days)	738 (T)	715	738 (T)	592
Poly-3 test	P=0.189N	P=0.591N	P=0.219N	P=0.366N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	6/50 (12%)	6/50 (12%)	4/50 (8%)	5/50 (10%)
Adjusted rate	14.6%	14.0%	9.3%	12.1%
Terminal rate	6/28 (21%)	4/33 (12%)	4/34 (12%)	4/28 (14%)
First incidence (days)	738 (T)	715	738 (T)	592
Poly-3 test	P=0.336N	P=0.591N	P=0.340N	P=0.498N

TABLE B3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rate	15/50 (30%)	15/50 (30%)	15/50 (30%)	18/50 (36%)
Adjusted rate	33.9%	32.6%	32.0%	39.7%
Terminal rate	5/28 (18%)	6/33 (18%)	7/34 (21%)	8/28 (29%)
First incidence (days)	475	392	451	459
Poly-3 test	P=0.323	P=0.537N	P=0.511N	P=0.361
All Organs: Benign Neoplasms				
Overall rate	37/50 (74%)	37/50 (74%)	27/50 (54%)	30/50 (60%)
Adjusted rate	80.3%	81.7%	58.0%	67.5%
Terminal rate	23/28 (82%)	28/33 (85%)	19/34 (56%)	20/28 (71%)
First incidence (days)	507	522	417	417
Poly-3 test	P=0.015N	P=0.536	P=0.014N	P=0.111N
All Organs: Malignant Neoplasms				
Overall rate	20/50 (40%)	18/50 (36%)	23/50 (46%)	24/50 (48%)
Adjusted rate	45.2%	39.1%	48.6%	51.4%
Terminal rate	10/28 (36%)	9/33 (27%)	12/34 (35%)	10/28 (36%)
First incidence (days)	475	392	451	459
Poly-3 test	P=0.210	P=0.355N	P=0.455	P=0.352
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	43/50 (86%)	42/50 (84%)	43/50 (86%)
Adjusted rate	94.2%	89.9%	85.4%	87.4%
Terminal rate	26/28 (93%)	29/33 (88%)	27/34 (79%)	22/28 (79%)
First incidence (days)	475	392	417	417
Poly-3 test	P=0.124N	P=0.340N	P=0.132N	P=0.203N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, lung, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence 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 exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE B3b
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Stop-Exposure Feed Study of Pentachlorophenol

	0 ppm	1,000 ppm
Clitoral Gland: Adenoma		
Overall rate[a]	4/50 (8%)	5/49 (10%)
Adjusted rate[b]	9.7%	11.7%
Terminal rate[c]	3/28 (11%)	1/27 (4%)
First incidence (days)	645	365
Poly-3 test[d]		P=0.519
Clitoral Gland: Adenoma or Carcinoma		
Overall rate	6/50 (12%)	6/49 (12%)
Adjusted rate	14.4%	13.9%
Terminal rate	4/28 (14%)	1/27 (4%)
First incidence (days)	645	365
Poly-3 test		P=0.590N
Mammary Gland: Fibroadenoma		
Overall rate	25/50 (50%)	15/50 (30%)
Adjusted rate	56.7%	34.6%
Terminal rate	16/28 (57%)	11/28 (39%)
First incidence (days)	507	600
Poly-3 test		P=0.027N
Mammary Gland: Fibroadenoma or Carcinoma		
Overall rate	25/50 (50%)	15/50 (30%)
Adjusted rate	56.7%	34.6%
Terminal rate	16/28 (57%)	11/28 (39%)
First incidence (days)	507	600
Poly-3 test		P=0.027N
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	22/50 (44%)	18/50 (36%)
Adjusted rate	49.1%	41.5%
Terminal rate	11/28 (39%)	13/28 (46%)
First incidence (days)	507	652
Poly-3 test		P=0.307N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma		
Overall rate	3/50 (6%)	1/50 (2%)
Adjusted rate	7.2%	2.3%
Terminal rate	2/28 (7%)	0/28 (0%)
First incidence (days)	523	516
Poly-3 test		P=0.290N
Thyroid Gland (C-cell): Adenoma		
Overall rate	3/50 (6%)	7/50 (14%)
Adjusted rate	7.2%	16.3%
Terminal rate	1/28 (4%)	4/28 (14%)
First incidence (days)	585	668
Poly-3 test		P=0.167
Thyroid Gland (C-cell): Adenoma or Carcinoma		
Overall rate	5/50 (10%)	8/50 (16%)
Adjusted rate	12.0%	18.6%
Terminal rate	3/28 (11%)	5/28 (18%)
First incidence (days)	585	668
Poly-3 test		P=0.292

TABLE B3b
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Stop-Exposure Feed Study of Pentachlorophenol

	0 ppm	1,000 ppm
Uterus: Stromal Polyp		
Overall rate	6/50 (12%)	6/50 (12%)
Adjusted rate	14.6%	13.9%
Terminal rate	6/28 (21%)	4/28 (14%)
First incidence (days)	738 (T)	600
Poly-3 test		P=0.585N
Uterus: Stromal Polyp or Stromal Sarcoma		
Overall rate	6/50 (12%)	7/50 (14%)
Adjusted rate	14.6%	16.2%
Terminal rate	6/28 (21%)	4/28 (14%)
First incidence (days)	738 (T)	600
Poly-3 test		P=0.538
All Organs: Mononuclear Cell Leukemia		
Overall rate	15/50 (30%)	11/50 (22%)
Adjusted rate	33.9%	24.4%
Terminal rate	5/28 (18%)	2/28 (7%)
First incidence (days)	475	472
Poly-3 test		P=0.221N
All Organs: Benign Neoplasms		
Overall rate	37/50 (74%)	35/50 (70%)
Adjusted rate	80.3%	76.9%
Terminal rate	23/28 (82%)	22/28 (79%)
First incidence (days)	507	365
Poly-3 test		P=0.443N
All Organs: Malignant Neoplasms		
Overall rate	20/50 (40%)	16/50 (32%)
Adjusted rate	45.2%	34.3%
Terminal rate	10/28 (36%)	3/28 (11%)
First incidence (days)	475	472
Poly-3 test		P=0.195N
All Organs: Benign or Malignant Neoplasms		
Overall rate	45/50 (90%)	42/50 (84%)
Adjusted rate	94.2%	86.6%
Terminal rate	26/28 (93%)	22/28 (79%)
First incidence (days)	475	365
Poly-3 test		P=0.170N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and the exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in the exposed group is indicated by **N**.

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Pentachlorophenol[a]

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	60	50	50	50	60
7-Month interim evaluation	10				10
Early deaths					
Moribund	15	12	12	17	17
Natural deaths	7	5	4	5	5
Survivors					
Terminal sacrifice	28	33	34	28	28
Animals examined microscopically	60	50	50	50	60
7-Month Interim Evaluation					
Alimentary System					
Liver	(10)				(10)
Basophilic focus	4 (40%)				
Hepatodiaphragmatic nodule					3 (30%)
Inflammation, chronic	10 (100%)				10 (100%)
Centrilobular, hypertropy					2 (20%)
Hepatocyte, necrosis					3 (30%)
Hepatocyte, centrilobular, hypertrophy					6 (60%)
Pancreas	(10)				(10)
Acinus, atrophy	1 (10%)				
Cardiovascular System					
Heart	(10)				(10)
Cardiomyopathy, chronic	2 (20%)				1 (10%)
Endocrine System					
Pituitary gland	(10)				(10)
Pars distalis, cyst	1 (10%)				
Genital System					
Clitoral gland	(10)				(10)
Inflammation, chronic active	6 (60%)				2 (20%)
Ovary	(10)				(10)
Cyst	1 (10%)				2 (20%)
Respiratory System					
Lung	(10)				(10)
Inflammation, chronic active	7 (70%)				5 (50%)
Nose	(10)				(10)
Inflammation, chronic active	4 (40%)				1 (10%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
7-Month Interim Evaluation (continued)					
Urinary System					
Kidney	(10)				(10)
Mineralization	10 (100%)				10 (100%)
Nephropathy, chronic	3 (30%)				3 (30%)
Renal tubule, pigmentation					10 (100%)
Systems Examined with No Lesions Observed					
General Body System					
Hematopoietic System					
Integumentary System					
Musculoskeletal System					
Nervous System					
Special Senses System					
2-Year Study					
Alimentary System					
Intestine large, colon	(50)	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)				
Parasite metazoan		2 (4%)	1 (2%)	5 (10%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)	(50)
Parasite metazoan	2 (4%)	5 (10%)	8 (16%)	5 (10%)	4 (8%)
Intestine small, jejunum	(50)				(50)
Inflammation, chronic active					1 (2%)
Ulcer					1 (2%)
Intestine small, ileum	(50)	(50)	(50)	(50)	(50)
Parasite metazoan	1 (2%)				
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)	
Basophilic focus	41 (82%)	42 (84%)	44 (88%)	35 (70%)	34 (68%)
Clear cell focus	11 (22%)	10 (20%)	8 (16%)	3 (6%)	16 (32%)
Eosinophilic focus	2 (4%)	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Fibrosis			1 (2%)		
Hematopoietic cell proliferation				1 (2%)	
Hepatodiaphragmatic nodule	9 (18%)	4 (8%)	7 (14%)	3 (6%)	10 (20%)
Inflammation, chronic	31 (62%)	36 (72%)	33 (66%)	27 (54%)	36 (72%)
Mixed cell focus	7 (14%)	7 (14%)	5 (10%)	2 (4%)	5 (10%)
Pigmentation, bile		2 (4%)	1 (2%)		
Pigmentation, hemosiderin	1 (2%)				2 (4%)
Thrombosis	2 (4%)	1 (2%)			
Bile duct, cyst		1 (2%)			
Bile duct, hyperplasia	24 (48%)	18 (36%)	22 (44%)	19 (38%)	18 (36%)
Hepatocyte, degeneration, cystic				1 (2%)	
Hepatocyte, necrosis		1 (2%)	2 (4%)		1 (2%)
Hepatocyte, vacuolization cytoplasmic	7 (14%)	2 (4%)	1 (2%)	3 (6%)	9 (18%)
Hepatocyte, centrilobular, degeneration			1 (2%)	1 (2%)	2 (4%)
Hepatocyte, centrilobular, necrosis	2 (4%)		2 (4%)		
Kupffer cell, hypertrophy				1 (2%)	1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Alimentary System (continued)					
Mesentery	(8)	(1)	(5)	(5)	(6)
Accessory spleen	1 (13%)	1 (100%)			
Artery, inflammation, chronic active	1 (13%)				
Fat, necrosis	3 (38%)		3 (60%)	1 (20%)	3 (50%)
Oral mucosa	(1)				(2)
Pharnygeal, hyperplasia					1 (50%)
Pancreas	(50)	(49)	(50)	(50)	(50)
Cyst			1 (2%)		1 (2%)
Inflammation, chronic active				1 (2%)	
Acinus, atrophy	10 (20%)	14 (29%)	14 (28%)	9 (18%)	13 (26%)
Acinus, hyperplasia			1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)		3 (6%)	1 (2%)	
Epithelium, hyperplasia	3 (6%)	1 (2%)	3 (6%)	3 (6%)	4 (8%)
Epithelium, ulcer	2 (4%)		3 (6%)	1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Epithelium, erosion	1 (2%)	2 (4%)	1 (2%)	2 (4%)	
Epithelium, Ulcer					1 (2%)
Cardiovascular System					
Blood vessel	(50)	(50)	(50)	(50)	(50)
Aorta, inflammation, chronic active	1 (2%)				
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy, chronic	27 (54%)	31 (62%)	36 (72%)	35 (70%)	25 (50%)
Necrosis			1 (2%)		
Atrium, thrombosis		1 (2%)			1 (2%)
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)	2 (4%)			
Atrophy	1 (2%)	1 (2%)			
Degeneration, cystic		4 (8%)	3 (6%)		2 (4%)
Degeneration, fatty	9 (18%)	11 (22%)	17 (34%)	15 (30%)	14 (28%)
Fibrosis				1 (2%)	
Hyperplasia	7 (14%)	12 (24%)	23 (46%)	12 (24%)	17 (34%)
Hypertrophy	1 (2%)	6 (12%)	8 (16%)	7 (14%)	3 (6%)
Necrosis					1 (2%)
Pigmentation	1 (2%)				
Adrenal medulla	(50)	(50)	(50)	(50)	(50)
Hyperplasia	3 (6%)	7 (14%)	6 (12%)	7 (14%)	4 (8%)
Necrosis					1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(50)	(50)
Hyperplasia				1 (2%)	1 (2%)
Parathyroid gland	(46)	(44)	(41)	(47)	(45)
Hyperplasia	1 (2%)				1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Endocrine System (continued)					
Pituitary gland	(50)	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)			
Necrosis	1 (2%)				
Thrombosis				1 (2%)	
Pars distalis, cyst	35 (70%)	28 (56%)	34 (68%)	32 (64%)	24 (48%)
Pars distalis, hemorrhage	1 (2%)				
Pars distalis, hyperplasia	24 (48%)	21 (42%)	26 (52%)	27 (54%)	24 (48%)
Pars intermedia, cyst	1 (2%)	2 (4%)		1 (2%)	2 (4%)
Pars intermedia, hyperplasia			1 (2%)		1 (2%)
Pars nervosa, ectopic tissue					1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)	(50)
C-cell, hyperplasia	16 (32%)	23 (46%)	27 (54%)	20 (40%)	17 (34%)
Follicular cell, hyperplasia, cystic	1 (2%)				
General Body System					
None					
Genital System					
Clitoral gland	(50)	(50)	(48)	(50)	(49)
Hyperplasia	10 (20%)	11 (22%)	13 (27%)	11 (22%)	10 (20%)
Inflammation, chronic active	4 (8%)	11 (22%)	4 (8%)	5 (10%)	3 (6%)
Bilateral, hyperplasia		1 (2%)	1 (2%)		
Duct, cyst	1 (2%)			1 (2%)	
Ovary	(50)	(50)	(50)	(50)	(50)
Cyst	3 (6%)	6 (12%)	4 (8%)	8 (16%)	6 (12%)
Bilateral, cyst	1 (2%)				1 (2%)
Uterus	(50)	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)		
Hydrometra		2 (4%)		2 (4%)	
Endometrium, hyperplasia, cystic		1 (2%)	1 (2%)	1 (2%)	1 (2%)
Vagina	(2)		(1)		
Hypertrophy	1 (50%)				
Inflammation, suppurative			1 (100%)		
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(49)
Hyperplasia	11 (22%)	13 (26%)	17 (34%)	21 (42%)	16 (33%)
Hyperplasia, histiocytic		1 (2%)		1 (2%)	
Myelofibrosis	1 (2%)	1 (2%)			
Lymph node	(35)	(27)	(26)	(28)	(30)
Mediastinal, hemorrhage			1 (4%)		
Mediastinal, pigmentation, hemosiderin	30 (86%)	22 (81%)	21 (81%)	24 (86%)	26 (87%)
Renal, ectasia					1 (3%)
Renal, hyperplasia, lymphoid					1 (3%)
Lymph node, mandibular	(50)	(49)	(50)	(50)	(50)
Ectasia	1 (2%)				
Lymph node, mesenteric	(50)	(50)	(50)	(50)	
Ectasia			3 (6%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Hematopoietic System (continued)					
Spleen	(50)	(50)	(50)	(50)	(50)
Accessory spleen				1 (2%)	
Fibrosis	1 (2%)				
Hematopoietic cell proliferation	9 (18%)	12 (24%)	6 (12%)	10 (20%)	7 (14%)
Necrosis	1 (2%)			1 (2%)	
Pigmentation, hemosiderin		1 (2%)			
Thymus	(48)	(44)	(48)	(47)	
Cyst		1 (2%)	3 (6%)		
Ectopic parathyroid gland				2 (4%)	
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Cyst	2 (4%)	2 (4%)			
Hyperplasia, cystic	43 (86%)	44 (88%)	45 (90%)	42 (84%)	45 (90%)
Inflammation, chronic				1 (2%)	
Skin	(50)	(50)	(50)	(50)	(50)
Cyst epithelial inclusion					1 (2%)
Inflammation, chronic active			1 (2%)		
Epidermis, hyperplasia	1 (2%)		2 (4%)		
Epidermis, ulcer			1 (2%)		
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(49)
Osteopetrosis	6 (12%)	1 (2%)	4 (8%)	2 (4%)	2 (4%)
Mandible, cyst		1 (2%)			
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Gliosis		1 (2%)			
Hemorrhage		1 (2%)		2 (4%)	1 (2%)
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Cyst					1 (2%)
Inflammation, chronic active	12 (24%)	12 (24%)	17 (34%)	15 (30%)	15 (30%)
Metaplasia, osseous		1 (2%)			
Alveolar epithelium, hyperplasia	5 (10%)	2 (4%)	5 (10%)	3 (6%)	5 (10%)
Alveolus, infiltration cellular, histiocyte	41 (82%)	42 (84%)	45 (90%)	46 (92%)	46 (92%)
Nose	(50)	(50)	(50)	(50)	(50)
Fungus	6 (12%)	2 (4%)	1 (2%)		2 (4%)
Inflammation, chronic active	13 (26%)	13 (26%)	7 (14%)	6 (12%)	7 (14%)
Nasolacrimal duct, inflammation, suppurative	9 (18%)	6 (12%)	10 (20%)	6 (12%)	10 (20%)
Respiratory epithelium, hyperplasia	10 (20%)	3 (6%)	2 (4%)	4 (8%)	2 (4%)
Respiratory epithelium, metaplasia, squamous	3 (6%)	3 (6%)		1 (2%)	
Vein, turbinate, septum, thrombosis			1 (2%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Pentachlorophenol

	0 ppm	200 ppm	400 ppm	600 ppm	1,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Special Senses System					
Eye	(3)	(3)	(2)	(2)	(2)
Atrophy	2 (67%)				1 (50%)
Anterior chamber, cornea, inflammation, chronic active					1 (50%)
Lens, cataract		2 (67%)	2 (100%)	2 (100%)	
Lens, fibrosis		1 (33%)			
Lens, synechia		2 (67%)			
Retina, atrophy		3 (100%)	2 (100%)	2 (100%)	
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet				1 (2%)	
Cyst	1 (2%)				
Hydronephrosis				1 (2%)	
Inflammation, suppurative					1 (2%)
Mineralization		1 (2%)			
Nephropathy, chronic	44 (88%)	46 (92%)	44 (88%)	48 (96%)	49 (98%)
Papilla, necrosis		1 (2%)			1 (2%)
Pelvis, inflammation, suppurative		1 (2%)			
Renal tubule, hyperplasia					1 (2%)
Renal tubule, pigmentation	48 (96%)	48 (96%)	50 (100%)	50 (100%)	49 (98%)
Urinary bladder	(50)	(50)	(49)	(49)	(49)
Calculus, microscopic observation only		1 (2%)			
Calculus, gross observation					1 (2%)
Inflammation, chronic active		1 (2%)			
Transitional epithelium hyperplasia					1 (2%)

APPENDIX C
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). Pentachlorophenol was sent to the laboratory as a coded aliquot by 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 five doses of pentachlorophenol. The high dose was limited by toxicity. 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, is not reproducible, or is not of sufficient 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). Pentachlorophenol 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 pentachlorophenol; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 to 28 hours with pentachlorophenol in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 to 28 hours, the medium containing pentachlorophenol 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 pentachlorophenol, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no pentachlorophenol. Incubation proceeded for an additional 26 to 28 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.

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 ($P < 0.005$) 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 pentachlorophenol for 12 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 pentachlorophenol and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 12 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.

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. One hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was 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.

RAT AND MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOL

Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by pentachlorophenol exposure. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male F344/N rats or $B6C3F_1$ mice (5 per dose group) were injected intraperitoneally three times at 24-hour intervals with pentachlorophenol dissolved in corn oil; total dosing volume was 0.4 mL. Solvent control animals were injected with 0.4 mL of corn oil only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored per surviving animal for the frequency of micronucleated cells.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dose group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the

number of dose groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

RESULTS

Pentachlorophenol (91.6% pure) was tested in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 at doses up to 30 μg/plate with and without induced rat or hamster liver S9; no significant increases in the number of revertant colonies were observed in any of the strain/activation combinations (Haworth *et al.*, 1983; Table C1). When tested for cytogenetic effects in cultured CHO cells (Galloway *et al.*, 1987), pentachlorophenol was weakly positive for induction of SCEs (Table C2) and Abs (Table C3). In the SCE test, a weakly positive response was observed within a concentration range of 3 to 30 μg/mL in the absence of S9; with S9, no induction of SCEs was noted. In the Abs test, pentachlorophenol was negative without S9 but induced small but significant increases in the frequency of aberrant cells in the presence of S9 at concentrations of 80 and 100 μg/mL. In contrast to the positive *in vitro* results in the test for induction of chromosomal aberrations, no increase in the frequency of micronucleated erythrocytes was noted in bone marrow of male rats (Table C4) or mice (Table C5) administered pentachlorophenol by intraperitoneal injection three times at 24-hour intervals. The highest doses administered to rats (75 mg/kg) and mice (150 mg/kg) were lethal.

TABLE C1
Mutagenicity of Pentachlorophenol in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] S9 Trial 1	S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	128 ± 8.3	137 ± 7.9	105 ± 11.7	121 ± 2.3	132 ± 3.9	129 ± 13.5
	0.3	132 ± 1.7	135 ± 12.3	109 ± 6.5	125 ± 3.3	137 ± 7.5	122 ± 1.5
	1	128 ± 3.5	147 ± 11.6	110 ± 8.9	124 ± 3.3	141 ± 4.6	124 ± 8.3
	3	123 ± 2.9	137 ± 4.5	96 ± 6.3	107 ± 7.0	141 ± 8.5	102 ± 1.2
	10	116 ± 8.7[c]	102 ± 8.5	125 ± 20.0	120 ± 1.8	142 ± 14.4	115 ± 4.8
	30	Toxic	Toxic	102 ± 16.6	107 ±10.1	142 ± 9.1	106 ± 9.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,394 ± 61.4	1,310 ± 24.6	3,233 ± 197.3	1,856 ± 63.4	2,147 ± 60.5	831 ± 38.6
TA1535	0	23 ± 0.3	16 ± 2.8	11 ± 2.9	7 ± 0.7	10 ± 2.3	8 ± 0.9
	0.3	24 ± 3.5	12 ± 1.2	11 ± 3.4	10 ± 1.5	14 ± 0.3	7 ± 1.7
	1	25 ± 2.9	13 ± 3.0	11 ± 1.9	10 ± 2.0	13 ± 2.2	7 ± 0.9
	3	27 ± 4.5	16 ± 0.9	15 ± 3.3	12 ± 2.4	16 ± 0.3	9 ± 2.0
	10	18 ± 1.7[c]	9 ± 1.2[c]	10 ± 1.8	8 ± 1.9	10 ± 3.5	10 ± 1.8
	30	Toxic	Toxic	12 ± 1.5	9 ± 0.7	14 ± 2.9	9 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		850 ± 19.7	983 ± 23.7	188 ± 4.2	82 ± 0.7	114 ± 6.8	54 ± 3.6
TA1537	0	8 ± 1.5	10 ± 1.2	14 ± 3.8	10 ± 0.3	15 ± 1.7	5 ± 1.2
	0.3	11 ± 1.2	15 ± 0.9	12 ± 0.6	13 ± 1.0	16 ± 0.3	7 ± 0.9
	1	9 ± 2.7	12 ± 1.5	13 ± 0.9	9 ± 0.7	16 ± 3.5	7 ± 1.7
	3	9 ± 1.3	12 ± 1.8	14 ± 1.2	9 ± 1.3	13 ± 2.2	6 ± 1.2
	10	8 ± 2.3[c]	9 ± 1.9[c]	20 ± 1.5	7 ± 1.7	19 ± 4.3	6 ± 1.7
	30	Toxic	Toxic	12 ± 2.6	4 ± 1.2	12 ± 2.8	9 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		425 ± 66.9	202 ± 26.3	324 ± 49.4	163 ± 17.5	158 ± 2.3	40 ± 3.1
TA98	0	27 ± 2.1	24 ± 0.9	33 ± 3.6	31 ± 1.0	32 ± 3.2	26 ± 4.4
	0.3	20 ± 4.2	18 ± 1.5	39 ± 1.5	24 ± 1.2	30 ± 1.2	23 ± 2.0
	1	24 ± 4.2	23 ± 4.1	42 ± 7.0	19 ± 2.3	32 ± 4.0	21 ± 0.9
	3	22 ± 0.6	20 ± 0.3	41 ± 4.6	28 ± 3.2	32 ± 2.2	26 ± 3.5
	10	20 ± 1.9[c]	16 ± 1.2	34 ± 0.0	26 ± 5.0	41 ± 4.4	19 ± 2.6
	30	Toxic	Toxic	32 ± 2.1	23 ± 0.9	33 ± 4.6	26 ± 3.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,808 ± 33.4	1,096 ± 35.9	2,609 ± 36.7	1,515 ± 72.9	1,754 ± 85.7	1,064 ± 31.3

[a] Study was performed at EG&G Mason Research Institute. The detailed protocol and these data are presented by Haworth *et al.*, 1983. 0 μg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slightly toxic
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Pentachlorophenol[a]

Compound	Concentration (μg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
S9								
Summary: Weakly positive								
Dimethylsulfoxide[c]		50	1,050	413	0.39	8.3	26.0	
Triethylenemelamine[d]	0.015	50	1,051	1,506	1.43	30.1	26.0	362.7
Pentachlorophenol	1	50	1,048	410	0.39	8.2	26.0	98.8
	3	50	1,047	498	0.48	10.0	26.0	120.5*
	10	50	1,041	449	0.43	9.0	26.0	108.4*
	30	45	939	425	0.45	9.4	28.0	113.3*
					P=0.008[e]			
+S9								
Summary: Negative								
Dimethylsulfoxide		50	1,049	474	0.45	9.5	26.0	
Cyclophosphamide[d]	1	50	1,049	1,114	1.06	22.3	26.0	234.7
Pentachlorophenol	3	50	1,047	555	0.53	11.1	26.0	116.8
	10	50	1,050	523	0.50	10.5	26.0	110.5
	30	50	1,050	529	0.50	10.6	26.0	111.6
	100	50	1,050	548	0.52	11.0	28.0	115.8
					P=0.049			

* Positive response (20% increase over solvent control)
[a] Study was performed at Columbia University. The detailed protocol and these data are presented in Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Positive control
[e] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE C3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Pentachlorophenol[a]

Compound	Concentration (μg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
S9					
Harvest time: 14.0 hours					
Summary: Negative					
Dimethylsulfoxide[b]		100	2	0.02	2.0
Triethylenemelamine[c]	0.015	100	25	0.25	22.0
Pentachlorophenol	10	100	5	0.03	3.0
	30	100	5	0.05	4.0
	100	100	5	0.05	5.0
					P=0.112[d]
+S9					
Trial 1					
Harvest time: 14.0 hours					
Summary: Weakly positive					
Dimethylsulfoxide		100	3	0.03	3.0
Cyclophosphamide[c]	15	100	33	0.33	26.0
Pentachlorophenol	3	100	5	0.05	5.0
	10	100	9	0.09	7.0
	30	100	5	0.05	5.0
	100	100	65	0.65	33.0*
					P<0.001
Trial 2					
Harvest time: 14.0 hours					
Summary: Equivocal					
Dimethylsulfoxide		100	4	0.04	3.0
Cyclophosphamide	15	100	33	0.33	27.0
Pentachlorophenol	10	100	9	0.09	9.0
	60	100	14	0.14	10.0
	70	100	10	0.10	10.0
	80	100	15	0.15	12.0*
					P=0.018

* Positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at Columbia University. The detailed protocol and these data are presented in Galloway *et al*. (1987).
[b] Solvent control
[c] Positive control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE C4
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Rats Treated with Pentachlorophenol by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Rats with Erythrocytes Scored	Micronucleated PCEs/1,000 PCEs[b]
Corn oil[c]		5	0.8 ± 0.3
Cyclophosphamide[d]	25	5	13.7 ± 3.8
Pentachlorophenol	25	4	0.8 ± 0.3
	50	5	1.5 ± 0.4
	75	0	Lethal
		P=0.062[e]	

[a] Study was performed at Integrated Laboratory Systems. The detailed protocol is presented in Shelby *et al*. (1993).
[b] Mean ± standard error
[c] Solvent control
[d] Positive control
[e] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)

TABLE C5
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with Pentachlorophenol by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/1,000 PCEs[b]
Corn oil[c]		5	2.2 ± 0.3
Cyclophosphamide[d]	50	4	17.9 ± 3.3
Pentachlorophenol	50	3	1.0 ± 0.0
	100	3	2.0 ± 0.8
	150	0	Lethal
		P=0.698[e]	

[a] Study was performed at Integrated Laboratory Systems. The detailed protocol is presented in Shelby *et al*. (1993).
[b] Mean ± standard error
[c] Solvent control
[d] Positive control
[e] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)

APPENDIX D
CLINICAL CHEMISTRY RESULTS

TABLE D1
Clinical Chemistry Data for Rats at the 7-Month Interim Evaluation in the 2-Year Feed Study of Pentachlorophenol[a]

	0 ppm	1,000 ppm
n	10	10
Male		
Alanine aminotransferase (IU/L)	87 ± 6	127 ± 32
Alkaline phosphatase (IU/L)	441 ± 7	514 ± 7**
Sorbitol dehydrogenase (IU/L)	28 ± 2	54 ± 16*
Bile salts (μmol/L)	19.7 ± 1.9	19.1 ± 2.5
Female		
Alanine aminotransferase (IU/L)	47 ± 2	51 ± 2
Alkaline phosphatase (IU/L)	342 ± 10	362 ± 12
Sorbitol dehydrogenase (IU/L)	20 ± 1	28 ± 2**
Bile salts (μmol/L)	50.7 ± 6.0	37.5 ± 3.0*

* Significantly different ($P \leq 0.05$) from the control group by Wilcoxon's rank sum test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

APPENDIX E
LIVER WEIGHTS AND LIVER-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE E1
Liver Weights and Liver-Weight-to-Body-Weight Ratios for Rats in the 28-Day Feed Study of Pentachlorophenol[a]

	0 ppm	200 ppm	400 ppm	800 ppm	1,600 ppm	3,200 ppm
Male						
n	10	10	10	10	10	9
Necropsy body wt	263 ± 3	277 ± 3	266 ± 3	254 ± 3*	213 ± 1**	129 ± 3**
Liver						
Absolute	14.167 ± 0.400	15.875 ± 0.450*	15.989 ± 0.406**	16.695 ± 0.449**	16.213 ± 0.272**	10.392 ± 0.273**
Relative	53.83 ± 1.16	57.15 ± 1.25	60.11 ± 1.18**	65.83 ± 1.83**	76.26 ± 1.41**	80.64 ± 1.33**
Female						
n	10	10	10	10	10	8
Necropsy body wt	174 ± 2	172 ± 2	166 ± 2*	161 ± 2**	141 ± 3**	98 ± 2**
Liver						
Absolute	7.473 ± 0.145	8.420 ± 0.192*	8.020 ± 0.189*	8.550 ± 0.211**	9.145 ± 0.309**	8.001 ± 0.317**
Relative	43.10 ± 0.77	48.96 ± 0.84**	48.44 ± 1.25**	53.19 ± 1.00**	64.83 ± 1.60**	81.69 ± 2.45**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Liver weights (absolute weights) and body weights are given in grams; liver-weight-to-body-weight ratios (relative weights) are given as mg liver weight/g body weight (mean ± standard error).

TABLE E2
Liver Weights and Liver-Weight-to-Body-Weight Ratios for Rats at the 7-Month Interim Evaluation in the 2-Year Feed Study of Pentachlorophenol[a]

	0 ppm	1,000 ppm
n	10	10
Male		
Necropsy body wt	441 ± 6	364 ± 5**
Liver		
Absolute	14.147 ± 0.282	14.447 ± 0.414
Relative	32.10 ± 0.42	39.68 ± 0.69**
Female		
Necropsy body wt	229 ± 4	191 ± 3**
Liver		
Absolute	6.873 ± 0.138	6.767 ± 0.125
Relative	30.00 ± 0.51	35.53 ± 0.46**

** Significantly different ($P \leq 0.01$) from the control group by Student's *t*-test
[a] Liver weights (absolute weights) and body weights are given in grams; liver-weight-to-body-weight ratios (relative weights) are given as mg liver weight/g body weight (mean ± standard error).

APPENDIX F
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF PENTACHLOROPHENOL

Pentachlorophenol was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (10412KY), which was used during the 28-day and 2-year studies. Identity and purity analyses were conducted by the study laboratory; additional information was supplied by the manufacturer. Reports on analyses performed in support of the pentachlorophenol studies are on file at the National Institute of Environmental Health Sciences.

The chemical, an off-white powder, was identified as pentachlorophenol by infrared spectroscopy. The spectrum was consistent with that expected for the structure, with a literature spectrum (*Sadtler Standard Spectra*) of pentachlorophenol, and with spectra of previously analyzed lots (MB 528 and 05217D) not used in the current studies (MRI, 1978b,c). The infrared spectrum is presented in Figure F1. The melting point range of 181° to 191° C supplied by the manufacturer was consistent with a literature reference of 190° to 191° C (*Merck Index*, 1989).

The purity of lot 10412KY was determined by gas chromatography. Gas chromatography was performed using a flame ionization detector with a helium carrier gas at a flow rate of 31 mL/minute. The system used a J&W DB-1 fused silica capillary column (15 m *X* 0.53 mm) with an oven temperature program of 100° to 275° C at 5° C per minute. The analysis indicated one major peak area and one impurity with an area of 1.0% relative to the major peak area. Results of analyses performed by the manufacturer indicated a purity of 99.9% by titration (with silver nitrate after oxygen combustion) and 99.3% by gas chromatography. The overall purity of lot 10412KY was determined to be approximately 99%.

The impurity was tentatively identified as tetrachlorophenol by gas chromatography/mass spectrometry with a Supelco SPB-5 column (10 m *X* 0.20 mm with 0.30μm film thickness) and an oven temperature program of 200° C for 1 minute, then 200° to 280° C at 10° C/minute. This system was also used to quantify chlorinated dibenzo-*p*-dioxins, dibenzofurans, diphenylethers, and hydroxyphenylethers. A 10 mL sample of pentachlorophenol was dissolved in benzene and passed through a deactivated aluminum column and eluted with benzene. The eluent was reduced to approximately 5 mL with a Kuderna-Danish concentrator in a water bath at approximately 98° C and then further evaporated to 1 mL in a micro Kuderna-Danish concentrator. A 300 μL aliquot of the eluent was then passed through a microcolumn of aluminum oxide eluted with 10 mL of 2% methylene chloride in hexane; the fraction was used to determine chlorinated diphenyl- and hydroxydiphenylethers. The column was then eluted with 10 mL of 50% methylene chloride in hexane to obtain the chlorinated dibenzodioxin and dibenzofuran fractions. Each fraction was reduced to 1 mL and then analyzed by gas chromatography/mass spectrometry. Because no impurities were detected, samples were reanalyzed concurrently with positive control samples spiked with chlorinated dibenzo-*p*-dioxins and dibenzofurans. Again, no chlorinated impurities were detected. Based on the limits of detection, maximum concentrations of less than 0.33 ppm dibenzo-*p*-dioxins and less than 1.0 ppm dibenzofurans were present in the bulk chemical; no maximum concentration of diphenyl- or hydroxydiphenylethers was estimated because no standards were available for these compounds.

Additional analyses of lot 10412KY with gas chromatography/mass spectrometry at lower limits of detection were performed by Vulcan Chemical Company (Wichita, KS). No tetra-, penta-, or hexachlorodibenzodioxins or -furans were detected at limits of 1 ppb, 50 ppb, or 0.02 ppm, respectively. For the hepta isomers, no chlorinated dibenzofurans were detected at a limit of 0.02 ppm, but at 0.03 ppm dibenzodioxins were found. A minimum concentration of 0.32 ppm octachlorodibenzodioxins and

0.10 ppm octachlorodibenzofurans were present in the bulk chemical. Other impurities identified included 17.0 ppm pentachlorobenzene and 113.3 ppm hexachlorobenzene.

Storage conditions of the bulk chemical were based on information from Midwest Research Institute (Kansas City, MO) that pentachlorophenol is stable for 2 weeks at temperatures up to 60° C (MRI, 1978a). Throughout the studies, the bulk chemical was stored at room temperature, protected from light, in amber glass bottles with Teflon-lined lids.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared twice during the 28-day study and approximately every 4 weeks during the 2-year study by mixing ground and sieved pentachlorophenol with feed in a premix, which was then blended with additional feed in a Patterson-Kelly twin-shell blender for 15 minutes, using an intensifier bar for the first 5 minutes (28-day study) or the entire 15 minutes (2-year study) (Table F1). Formulations were stored at –20° C for up to 25 days (28-day study) or approximately 5° C for up to 35 days (2-year study).

Homogeneity studies of the 200 and 3,200 ppm formulations for the 28-day study and the 200 and 1,000 ppm formulations for the 2-year study were performed by the study laboratory. Additional undosed feed was added to the 3,200 ppm bottles. Pentachlorophenol was extracted from the dose formulations with methanol:concentrated hydrochloric acid (100 mL of a 99:1 solution). Extracted feed samples were analyzed by gas chromatography with ^{63}Ni electron capture detection and the following system: a Supelco PTE-5 (QTM) fused silica capillary column (15 m *X* 0.53 mm with 0.5 μm film thickness) with an oven temperature program of 70° C for 1 minute, then increased at 15° C per minute to a final temperature of 250° C (temperature program was adjusted slightly for the 2-year study). The carrier gas was argon:methane (9:1) at a flow rate of approximately 40 mL/minute. Stability studies of the 50 (2-year study) and 200 (28-day study) ppm formulations were also performed by the study laboratory using the same gas chromatography system. Homogeneity was confirmed, and the stability of the 200 ppm formulation was confirmed for at least 25 days at –20° C or 14 days at 5° C when stored protected from light. The 50 ppm formulation was confirmed to be stable for 35 days when stored at temperatures up to 5° C, protected from ultraviolet light. The dose formulations showed slight decreases in concentration when stored under dosing conditions, open to air and light. These results were consistent with feed stability studies reported by Midwest Research Institute for technical grade pentachlorophenol at 20 ppm (MRI, 1979); pentachlorophenol was reported to bind with feed components during storage, which affects recovery.

Periodic analyses of the dose formulations of pentachlorophenol were conducted at the study laboratory using gas chromatography. Dose formulations were analyzed once during the 28-day study (Table F2) and approximately every 8 weeks during the 2-year study (Table F3). All five of the dose formulations analyzed during the 28-day study were within 10% of the target concentrations, with no value more than 3% from the target concentration; four of the five animal room samples were within 10% of the target concentrations with no value more than 12% from the target concentration. Of the dose formulations analyzed and used during the 2-year study, 94% (64/68) were within 10% of the target concentrations, with no value more than 24% from the target concentration; 64% (16/25) of the animal room samples were within 10% of the target concentrations, with no value more than 14% from the target concentration.

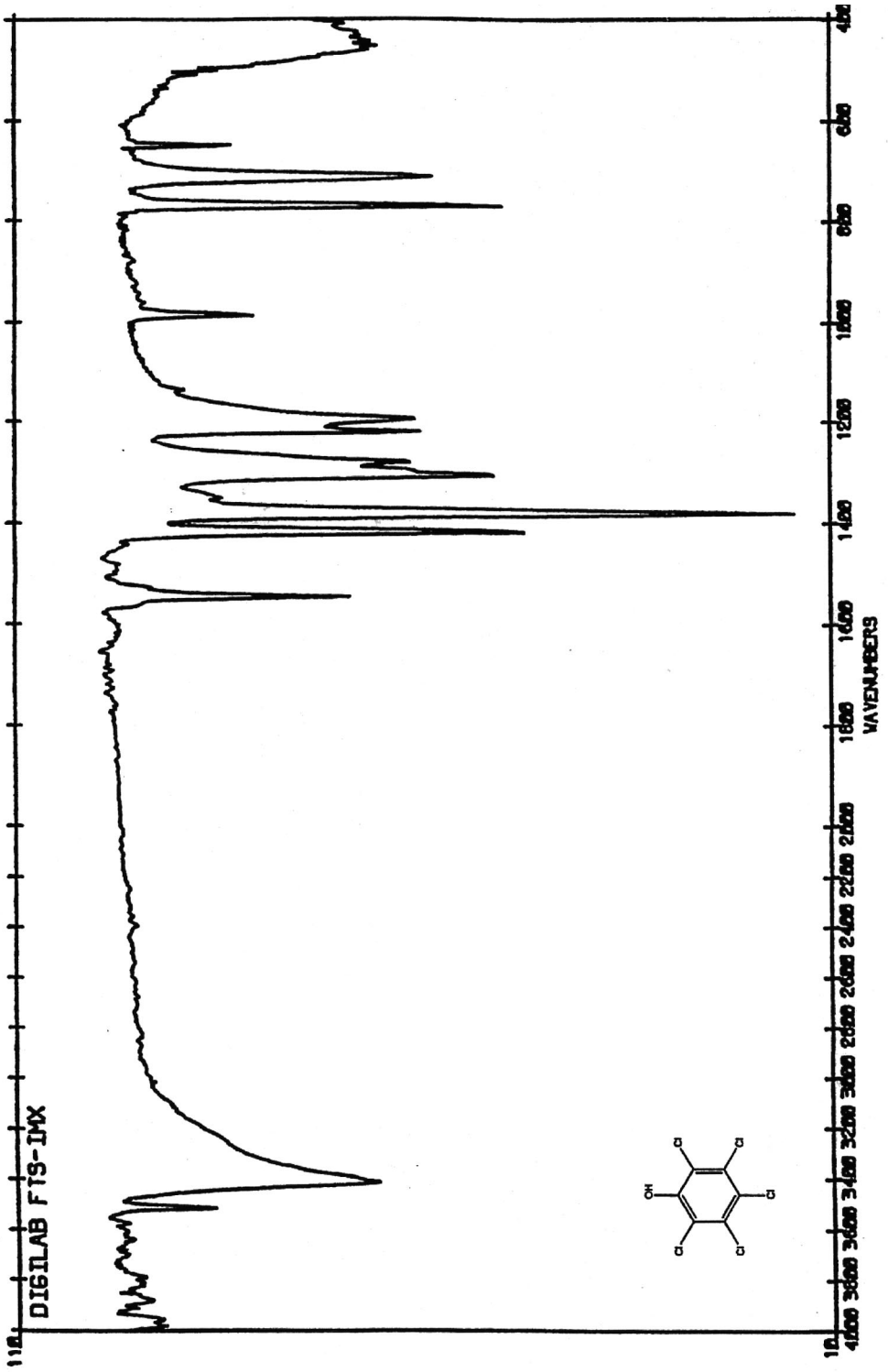

FIGURE F1
Infrared Absorption Spectrum of Pentachlorophenol

TABLE F1
Preparation and Storage of Dose Formulations in the Feed Studies of Pentachlorophenol

28-Day Study	2-Year Study
Preparation	
The bulk pentachlorophenol was ground and sieved. The premix of feed and pentachlorophenol was prepared then layered with the remaining feed and blended in a Patterson-Kelly twin-shell blender with the intensifier bar on for 5 minutes and off for 10 minutes. Dose formulations were prepared twice.	Same as 28-day study. For dose formulations prepared during October through December 1993, the feed was mixed in a blender for 15 minutes before the premix was prepared. Dose formulations were prepared every 4 weeks.
Chemical Lot Number	
10412KY	10412KY
Maximum Storage Time	
25 days	35 days
Storage Conditions	
Stored protected from light at −20° C	Stored protected from light at approximately 5° C
Study Laboratory	
Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats in the 28-Day Feed Study of Pentachlorophenol

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
21 May 1992	29 May 1992	200	196	−2
		400	391	−2
		800	772	−3
		1,600	1,613	+1
		3,200	3,215	0
	12 June 1992[b]	200	175	−12
		400	372	−7
		800	816	+2
		1,600	1,528	−4
		3,200	3,132	−2

[a] Results of duplicate analyses
[b] Animal room samples

TABLE F3
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Feed Study of Pentachlorophenol

Date Prepared	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
13 November 1992	0.2	0.200	0
	0.2	0.200	0
	0.4	0.393	−2
	0.4	0.408	+2
	0.6	0.600	0
	0.6	0.612	+2
	1.0	0.991	−1
	1.0	1.05	+5
13 November 1992[b]	0.2	0.187	−6
	0.2	0.189	−5
	0.4	0.370	−7
	0.4	0.387	−3
	0.6	0.587	−2
	0.6	0.596	−1
	1.0	0.989	−1
	1.0	0.960	−4
8 January 1993	0.2	0.213	+7
	0.2	0.216	+8
	0.4	0.381	−5
	0.4	0.375	−6
	0.6	0.574	−4
	0.6	0.579	−3
	1.0	0.979	−2
	1.0	1.02	+2
5 March 1993	0.2	0.187	−6
	0.4	0.420	+5
	0.6	0.586	−2
	1.0	1.02	+2
30 April 1993	0.2	0.196	−2
	0.4	0.401	0
	0.6	0.596	−1
	1.0	1.04	+4
30 April 1993[b]	0.2	0.182	−9
	0.4	0.363	−9
	0.6	0.562	−6
	1.0	1.04	+4
25 June 1993	0.2	0.190	−5
	0.4	0.382	−4
	0.6	0.595	−1
	1.0	0.901	−10
23 August 1993	0.2	0.196	−2
	0.4	0.398	0
	0.6	0.553	−8
	1.0	0.947	−5

TABLE F3
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Feed Study of Pentachlorophenol

Date Prepared	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
18 October 1993	0.2	0.211	+6
	0.4	0.407	+2
	0.6	0.746[c]	+24
	1.0	1.06	+6
26 October 1993	0.2	0.202	+1
	0.4	0.419	+5
	0.6	0.646	+8
	1.0	0.990	-1
5 November 1993	0.2	0.206	+3
	0.4	0.392	-2
	0.6	0.569	-5
	1.0	0.972	-3
5 November 1993[b]	0.2	0.177	-11
	0.4	0.381	-5
	0.6	0.553	-8
	1.0	0.960	-4
13 December 1993	0.2	0.225[d]	+13
	0.4	0.437[d]	+9
	0.6	0.464[d]	-23
15 December 1993[e]	0.2	0.210	+5
	0.2	0.189	-5
	0.4	0.394	-1
	0.4	0.362	-9
	0.6	0.669[c]	+12
	0.6	0.666[c]	+11
7 February 1994	0.2	0.209	+5
	0.4	0.408	+2
	0.6	0.547	-9
4 April 1994	0.2	0.203	+2
	0.4	0.396	-1
	0.6	0.603	+1
4 April 1994[b]	0.2	0.175	-12
	0.4	0.356	-11
	0.6	0.528	-12
30 May 1994	0.2	0.188	-6
	0.4	0.390	-2
	0.6	0.542	-10

TABLE F3
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Feed Study of Pentachlorophenol

Date Prepared	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
25 July 1994	0.2	0.212	+6
	0.4	0.402	+1
	0.6	0.599	0
19 September 1994	0.2	0.190	-5
	0.4	0.371	-7
	0.6	0.543	-9
19 September 1994[b]	0.2	0.173	-13
	0.4	0.390	-2
	0.6	0.528	-12
14 November 1994	0.2	0.196	-2
	0.4	0.453[c]	+13
	0.6	0.614	+2
14 November1994[b]	0.2	0.176	-12
	0.4	0.352	-12
	0.6	0.518	-14

[a] Results of duplicate analyses 0.2 mg/g=200 ppm; 0.4 mg/g=400 ppm; 0.6 mg/g=600 ppm; 1.0=1,000 ppm
[b] Animal room samples
[c] Not within 10% of target concentration, but considered adequate for dosing
[d] Samples were not homogeneous and were not used for dosing.
[e] Results of remix

APPENDIX G
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDY OF PENTACHLOROPHENOL

TABLE G1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Pentachlorophenol

Week	0 ppm		200 ppm			400 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	14.8	137	15.2	139	22	16.0	139	46
2	16.0	179	16.4	178	18	17.4	178	39
5	16.9	262	16.9	264	13	17.5	257	27
6	15.6	278	17.8	282	13	18.1	274	26
9	17.3	327	17.6	325	11	18.2	313	23
10	16.5	337	17.0	335	10	17.7	325	22
12	16.3	358	17.0	353	10	17.5	342	20
13	17.0	366	18.2	361	10	18.6	349	21
17	16.8	395	17.6	390	9	18.0	377	19
21	16.8	415	18.2	413	9	17.7	395	18
25	17.1	437	16.3	427	8	17.7	412	17
29	16.4	452	18.3	449	8	18.0	428	17
33	17.6	467	17.3	460	8	19.0	441	17
37	17.0	476	18.6	470	8	18.5	449	16
41	16.9	486	16.9	474	7	17.8	451	16
45	16.4	494	17.6	483	7	17.8	459	15
49	17.3	500	17.0	489	7	18.2	463	16
52	15.8	500	17.1	491	7	16.9	464	15
57	17.0	509	16.6	495	7	17.7	472	15
61	16.4	508	18.3	493	7	18.9	470	16
65	16.9	515	17.2	492	7	17.8	474	15
69	16.7	514	16.6	492	7	17.2	472	15
73	16.2	510	16.4	491	7	17.7	470	15
77	15.6	504	15.5	485	6	16.6	467	14
81	15.8	503	15.8	479	7	16.4	461	14
85	15.4	498	15.2	473	6	16.0	456	14
89	15.7	492	14.3	460	6	15.2	448	14
93	15.2	483	14.7	453	6	16.5	442	15
97	15.6	465	15.4	449	7	17.2	436	16
101	15.8	449	15.1	434	7	15.5	417	15
105	13.8	423	16.6	436	8	17.5	417	17
Mean for weeks								
1-13	16.3	280	17.0	280	13	17.6	272	28
14-52	16.8	462	17.5	455	8	18.0	434	17
53-105	15.9	490	16.0	472	7	17.0	454	15

TABLE G1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Pentachlorophenol

Week	600 ppm Feed (g/day)	600 ppm Body Weight (g)	600 ppm Dose/ Day (mg/kg)	1,000 ppm (Stop-Exposure) Feed (g/day)	1,000 ppm (Stop-Exposure) Body Weight (g)	1,000 ppm (Stop-Exposure) Dose/ Day (mg/kg)
1	16.3	140	70	15.3	136	113
2	17.7	177	60	18.1	165	110
5	18.8	258	44	18.9	241	78
6	18.6	274	41	19.6	256	76
9	18.6	312	36	18.7	287	65
10	18.7	318	35	18.8	294	64
12	18.2	339	32	18.7	313	60
13	18.8	347	32	19.3	319	61
17	17.6	366	29	18.2	335	54
21	19.5	387	30	19.4	352	55
25	18.3	407	27	18.8	366	52
29	19.4	419	28	19.7	381	52
33	18.6	436	26	19.7	396	50
37	18.7	436	26	19.5	396	49
41	19.5	443	26	19.4	400	48
45	18.4	453	24	19.2	410	47
49	19.7	454	26	19.3	413	47
52	17.4	458	23	18.4	412	45
57	19.0	460	25	18.1	445	
61	19.2	457	25	17.0	451	
65	18.0	456	24	17.3	458	
69	18.4	462	24	16.8	472	
73	17.4	458	23	16.6	477	
77	17.1	453	23	16.2	478	
81	17.4	452	23	15.9	472	
85	16.1	444	22	16.2	479	
89	15.0	437	21	15.9	472	
93	16.7	430	23	17.1	459	
97	17.1	427	24	15.9	450	
101	15.5	411	23	15.0	447	
105	16.0	396	24	16.0	433	
Mean for weeks						
1-13	18.2	271	44	18.4	251	78
14-52	18.7	426	26	19.2	386	50
53-105	17.1	442	23	16.5	461	

[a] Grams of feed consumed per animal per day
[b] Milligrams of pentachlorophenol consumed per kilogram body weight per day

TABLE G2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Pentachlorophenol

Week	0 ppm		200 ppm			400 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	10.9	114	11.4	114	20	11.6	113	41
2	11.0	132	11.4	133	17	12.0	131	37
5	11.3	164	10.6	166	13	11.0	164	27
6	10.6	172	11.1	172	13	11.0	168	26
9	11.2	187	10.9	188	12	11.3	183	25
10	10.5	192	10.6	191	11	11.0	187	24
12	10.4	198	10.6	196	11	11.2	192	23
13	10.1	200	10.3	200	10	11.1	196	23
17	10.5	211	10.0	207	10	10.3	204	20
21	10.3	219	10.6	215	10	10.6	209	20
25	10.2	224	10.3	219	9	10.7	217	20
29	10.8	231	10.7	227	9	10.9	221	20
33	10.6	237	10.5	233	9	10.8	229	19
37	11.8	246	11.8	239	10	11.3	231	19
41	11.4	256	12.1	249	10	12.1	241	20
45	10.6	267	10.9	256	9	10.6	243	17
49	11.9	275	11.7	263	9	12.0	252	19
52	11.2	283	11.0	270	8	11.3	260	17
57	11.6	300	13.0	288	9	12.9	274	19
61	11.7	307	12.4	294	8	13.2	283	19
65	11.4	315	12.0	303	8	12.3	290	17
69	12.3	324	11.6	309	8	12.2	298	16
73	11.7	326	11.3	307	7	11.9	299	16
77	11.9	330	11.5	311	7	12.5	304	16
81	11.7	330	12.1	315	8	11.8	306	15
85	12.3	334	12.4	322	8	12.1	308	16
89	11.5	336	11.0	320	7	11.9	313	15
93	12.6	337	12.4	320	8	12.8	314	16
97	12.8	339	12.8	326	8	13.3	317	17
101	11.7	334	11.1	320	7	12.6	323	16
105	12.9	335	12.8	322	8	13.9	322	17
Mean for weeks								
1-13	10.8	170	10.9	170	13	11.3	167	28
14-52	10.9	245	11.0	238	9	11.1	231	19
53-105	12.0	327	12.0	312	8	12.6	304	17

TABLE G2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Pentachlorophenol

Week	600 ppm			1,000 ppm (Stop-Exposure)		
	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	11.3	114	60	10.9	109	100
2	12.4	131	57	12.4	123	101
5	11.3	159	43	11.5	149	77
6	11.2	164	41	11.6	155	75
9	11.4	178	39	11.0	166	66
10	11.4	182	38	11.4	169	67
12	10.6	186	34	11.3	174	65
13	11.0	189	35	11.1	176	63
17	10.8	196	33	10.8	183	59
21	11.1	202	33	11.0	188	58
25	10.5	206	31	10.6	193	55
29	11.5	211	33	11.2	198	57
33	10.5	216	29	11.1	203	55
37	12.2	219	33	11.3	204	56
41	12.3	228	32	11.7	210	56
45	10.9	230	28	11.0	214	51
49	12.1	233	31	11.5	218	53
52	11.3	241	28	11.3	220	51
57	12.7	252	30	13.2	255	
61	13.6	261	31	12.0	271	
65	12.5	269	28	11.5	284	
69	12.7	276	28	12.1	297	
73	11.7	276	25	11.8	306	
77	12.1	282	26	11.9	313	
81	11.8	282	25	11.1	316	
85	12.3	285	26	12.1	321	
89	11.7	289	24	11.6	325	
93	13.5	291	28	11.6	322	
97	13.2	297	27	13.1	327	
101	11.9	293	24	11.4	327	
105	13.8	297	28	13.8	340	
Mean for weeks						
1-13	11.3	163	43	11.4	153	77
14-52	11.3	218	31	11.2	203	55
53-105	12.6	281	27	12.1	308	

[a] Grams of feed consumed per animal per day
[b] Milligrams of pentachlorophenol consumed per kilogram body weight per day

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

TABLE H1
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 H2
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 H3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.91 ± 0.55	21.7) 24.0	24
Crude fat (% by weight)	5.27 ± 0.26	4.60) 5.70	24
Crude fiber (% by weight)	3.21 ± 0.34	2.50) 3.70	24
Ash (% by weight)	6.36 ± 0.18	6.08) 6.78	24
Amino Acids (% of total diet)			
Arginine	1.273 ± 0.083	1.100) 1.390	12
Cystine	0.307 ± 0.068	0.181) 0.400	12
Glycine	1.152 ± 0.051	1.060) 1.220	12
Histidine	0.581 ± 0.029	0.531) 0.630	12
Isoleucine	0.913 ± 0.034	0.867) 0.965	12
Leucine	1.969 ± 0.053	1.850) 2.040	12
Lysine	1.269 ± 0.050	1.200) 1.370	12
Methionine	0.436 ± 0.104	0.306) 0.699	12
Phenylalanine	0.999 ± 0.114	0.665) 1.110	12
Threonine	0.899 ± 0.059	0.824) 0.985	12
Tryptophan	0.216 ± 0.146	0.107) 0.671	12
Tyrosine	0.690 ± 0.091	0.564) 0.794	12
Valine	1.079 ± 0.057	0.962) 1.170	12
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.223	1.830) 2.570	11
Linolenic	0.273 ± 0.034	0.210) 1.170	11
Vitamins			
Vitamin A (IU/kg)	6,811 ± 492	5,940) 8,580	24
Vitamin D (IU/kg)	4,450 ± 1,382	3,000) 6,300	4
α-Tocopherol (ppm)	35.24 ± 8.58	22.5) 48.9	12
Thiamine (ppm)	16.33 ± 2.18	14.0) 24.0	24
Riboflavin (ppm)	7.78 ± 0.899	6.10) 9.00	12
Niacin (ppm)	98.73 ± 23.21	65.0) 150.0	12
Pantothenic acid (ppm)	32.94 ± 8.92	23.0) 59.2	12
Pyridoxine (ppm)	9.28 ± 2.49	5.60) 14.0	12
Folic acid (ppm)	2.56 ± 0.70	1.80) 3.70	12
Biotin (ppm)	0.265 ± 0.046	0.190) 0.354	12
Vitamin B_{12} (ppb)	41.6 ± 18.6	10.6) 65.0	12
Choline (ppm)	2,955 ± 382	2,300) 3,430	11
Minerals			
Calcium (%)	1.18 ± 0.07	1.04) 1.32	24
Phosphorus (%)	0.90 ± 0.04	0.840) 1.00	24
Potassium (%)	0.886 ± 0.059	0.772) 0.971	10
Chloride (%)	0.531 ± 0.082	0.380) 0.635	10
Sodium (%)	0.316 ± 0.031	0.258) 0.370	12
Magnesium (%)	0.165 ± 0.010	0.148) 0.180	12
Sulfur (%)	0.266 ± 0.060	0.208) 0.420	11
Iron (ppm)	348.0 ± 83.7	255.0) 523.0	12
Manganese (ppm)	93.27 ± 5.62	81.7) 102.0	12
Zinc (ppm)	59.42 ± 9.73	46.1) 81.6	12
Copper (ppm)	11.63 ± 2.46	8.09) 15.4	12
Iodine (ppm)	3.49 ± 1.14	1.52) 5.83	11
Chromium (ppm)	1.57 ± 0.53	0.60) 2.09	12
Cobalt (ppm)	0.81 ± 0.27	0.49) 1.23	8

TABLE H4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.53 ± 0.15	0.10) 0.80	24
Cadmium (ppm)	0.04 ± 0.01	0.04) 0.6	24
Lead (ppm)	0.26 ± 0.08	0.18) 0.40	24
Mercury (ppm)	<0.02		24
Selenium (ppm)	0.36 ± 0.09	0.10) 0.50	24
Aflatoxins (ppb)	<5.0		24
Nitrate nitrogen (ppm)[c]	7.30 ± 2.76	2.80) 12.0	24
Nitrite nitrogen (ppm)[c]	1.28 ± 1.02	0.02) 3.20	24
BHA (ppm)[d]	1.44 ± 1.85	0.60) 10.0	24
BHT (ppm)[d]	1.73 ± 1.05	0.50) 5.0	24
Aerobic plate count (CFU/g)	314,000 ± 351,431	10,000) 1,200,000	24
Coliform (MPN/g)	316 ± 471	3) 1,600	24
Escherichia coli (MPN/g)	5 ± 3.4	3) 10	24
Salmonella (MPN/g)	Negative		24
Total nitrosoamines (ppb)[e]	11.97 ± 4.59	2.3) 19.7	24
N-Nitrosodimethylamine (ppb)[e]	9.77 ± 4.31	1.3) 18.0	24
N-Nitrosopyrrolidine (ppb)[e]	2.23 ± 1.21	1.0) 5.8	24
Pesticides (ppm)			
α-BHC	<0.01		24
β-BHC	<0.02		24
γ-BHC	<0.01		24
δ-BHC	<0.01		24
Heptachlor	<0.01		24
Aldrin	<0.01		24
Heptachlor epoxide	<0.01		24
DDE	<0.01		24
DDD	<0.01		24
DDT	<0.01		24
HCB	<0.01		24
Mirex	<0.01		24
Methoxychlor	<0.05		24
Dieldrin	<0.01		24
Endrin	<0.01		24
Telodrin	<0.01		24
Chlordane	<0.05		24
Toxaphene	<0.10		24
Estimated PCBs	<0.20		24
Ronnel	<0.01		24
Ethion	<0.02		24
Trithion	<0.05		24
Diazinon	<0.10		24
Methyl parathion	<0.02		24
Ethyl parathion	<0.02		24
Malathion	0.09 ± 0.07	0.02) 24.00	24
Endosulfan I	<0.01		24
Endosulfan II	<0.01		24
Endosulfan sulfate	<0.03		24

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX I
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 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.

Serum samples were collected from randomly selected rats during the 2-year study. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	1, 6, 12, and 18 months, study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	1, 6, 12, and 18 months, study termination
KRV (Kilham rat virus)	1, 6, 12, and 18 months, study termination

RESULTS

Five rats were positive for *M. arthritidis* at study termination. Samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. There were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered false positives.