NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 414

TOXICOLOGY AND CARCINOGENESIS STUDIES OF PENTACHLOROANISOLE

(CAS NO. 1825-21-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

FOREWORD

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

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

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

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

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NTP TECHNICAL REPORT

ON THE

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

April 1993

NTP TR 414

NIH Publication No. 93-3145

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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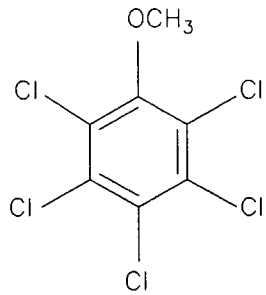
ABSTRACT



PENTACHLOROANISOLE

CAS No. 1825-21-4

Chemical Formula: $C_7H_3Cl_5O$ Molecular Weight: 280.5

Synonyms: 2,3,4,5,6-pentachloroanisole; methyl pentachlorophenate; methyl pentachlorophenyl ether; *o*-methylpentachlorophenol; pentachloromethoxybenzene; pentachlorophenyl methyl ether

Pentachloroanisole is a chlorinated aromatic compound which is widely distributed at low levels in the environment and in food products. Formation of pentachloroanisole in the environment may result from the degradation of structurally related, commercially important, ubiquitous chlorinated aromatic compounds such as pentachlorophenol and pentachloronitrobenzene which are known rodent toxins or carcinogens. Toxicology and carcinogenesis studies were conducted by administering pentachloroanisole (>99% pure) in corn oil by gavage to groups of male and female F344/N rats and B6C3F$_1$ mice for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* strains, mouse lymphoma cells, and Chinese hamster ovary cells.

16-Day Studies in Rats

Groups of five male and five female F344/N rats were administered pentachloroanisole in corn oil by gavage once per day, 5 days per week, for 16 days at doses of 0, 100, 125, 150, 175, or 200 mg/kg body weight. Deaths occurred during days 2 and 3 in rats receiving doses of 125 mg/kg or greater; these deaths were considered directly related to pentachloroanisole administration. No biologically significant changes in mean body weight gains or final body weights were noted in the 100 mg/kg groups of rats. Because of the high early mortality rate, valid comparisons of body weight differences in other dose groups could not be made. Inactivity was noted in all dose groups. Rats administered doses of 125 mg/kg or greater also exhibited dyspnea.

16-Day Studies in Mice

Groups of five male and five female B6C3F$_1$ mice were administered pentachloroanisole in corn oil by gavage once per day, 5 days per week, for 16 days at doses of 0, 100, 175, 250, 325, or 400 mg/kg. Deaths occurred during days 2 and 3 in mice receiving doses of 175 mg/kg or greater; these deaths were considered directly related to chemical administration. No biologically significant changes in mean body weight gains or final body weights were noted in 100 mg/kg males or 100 or 175 mg/kg females. Because of the high early mortality rate, valid comparisons of body

weight differences in other dose groups could not be made. Inactivity was noted in dosed mice.

13-Week Studies in Rats

Groups of 10 male and 10 female rats were administered pentachloroanisole in corn oil by gavage once per day, 5 days per week, for 13 weeks at doses of 0, 40, 80, 120, 140, or 180 mg/kg body weight. Most rats receiving doses of 120 mg/kg or greater died during the first week of the study as a direct result of pentachloroanisole administration.

Mean body weight gains of males administered 40 or 80 mg/kg and of females administered 40, 80, or 120 mg/kg pentachloroanisole were significantly lower than those of the controls. Most dosed rats exhibited temporary inactivity for several hours after dosing. Relative liver and kidney weights of males administered 40 or 80 mg/kg and absolute and/or relative liver and kidney weights of females administered 40 to 120 mg/kg were significantly greater than those of the controls.

Lesions observed in males administered 80 mg/kg or more and in females administered 120 mg/kg or more included pulmonary congestion, hemorrhage, and/or edema, meningeal congestion, and hepatocellular necrosis, glycogen depletion, and degeneration of biliary epithelium in the liver.

13-Week Studies in Mice

Groups of 10 male and 10 female mice were administered pentachloroanisole in corn oil by gavage once per day, 5 days per week, for 13 weeks at doses of 0, 40, 80, 120, 140, or 180 mg/kg body weight. Most mice administered doses of 120 mg/kg or higher died during the first week of the study as a direct result of pentachloroanisole administration.

Mean body weight gains of females administered 40 to 140 mg/kg were significantly greater than that of the controls, but those of dosed males were similar to that of the controls. Most dosed mice exhibited temporary inactivity for several hours after dosing. Absolute and relative liver weights of males administered 80 mg/kg, absolute and relative liver weights of females administered 40 to 180 mg/kg, and absolute and relative kidney weights of females administered 80 to 180 mg/kg pentachloroanisole were also significantly greater than those of the controls.

Lesions observed in males administered 40 mg/kg or more and in females administered 80 mg/kg or more included pulmonary congestion and/or edema, adrenal congestion, lymphoid depletion of lymph nodes and thymus, hepatocellular cytomegaly and karyomegaly, and pigment accumulation in hepatocytes and Kupffer cells.

2-Year Studies in Rats

Based on the chemical-related mortality and liver lesions seen in the 16-day and 13-week studies, doses selected for the 2-year studies were 0, 10, 20, and 40 mg/kg for males and 0, 20, and 40 mg/kg for females. Groups of 70 male and 70 female rats were administered pentachloroanisole in corn oil by gavage 5 days per week for up to 2 years. At 9 and 15 months, up to 10 animals per group were selected for interim evaluations.

Survival, Body Weights, and Clinical Findings

The survival of high-dose males was significantly decreased (vehicle control, 24/50; low-dose, 20/50; mid-dose, 24/50; high-dose, 14/50); most deaths in the high-dose group occurred at or before week 16. The majority of deaths in the mid- and high-dose groups may have been due to pentachloroanisole-related hyperthermia. The survival of dosed females was greater than that of the controls (29/50, 35/50, 44/50). Final mean body weights of mid- and high-dose males were 7% and 10% lower than that of the controls; final mean body weight of high-dose females was 11% lower than that of the controls. Final mean body weights of other dose groups were similar to those of the vehicle controls. At the 9-month interim evaluation, mean rectal temperature of males administered 40 mg/kg was significantly greater than that of the controls. Relative liver and kidney weights of males and females administered 20 or 40 mg/kg were significantly greater than those of controls. At the 15-month interim evaluation, relative liver weights of dosed females and absolute liver weights of 40 mg/kg females were significantly greater than those of the controls, as were relative liver and kidney weights of 40 mg/kg males.

Pathology Findings

In the 2-year studies, administration of pentachloroanisole to males was associated with significant increases in the incidences of benign adrenal medulla pheochromocytomas. The incidence of benign

adrenal medulla pheochromocytomas was marginally increased in high-dose females and slightly exceeded the range of the historical controls. Incidences of adrenal medulla hyperplasia were increased in dosed female rats, but not in dosed males. The incidences of pancreatic adenomas and focal hyperplasia were decreased in dosed males. The incidences of mammary gland fibroadenomas and uterine stromal polyps and sarcomas (combined) were decreased in high-dose females. Treatment-related increased incidences of intracytoplasmic pigmentation occurred in renal tubule epithelium, olfactory epithelium, and hepatocytes of males and females. Congestion and hemorrhage of the lungs, lymph nodes, thymus, adrenal cortex, and meninges, as well as hepatocellular centrilobular necrosis occurred almost exclusively in mid- and high-dose males that died or were killed moribund before the end of the studies.

2-Year Studies in Mice

Based on the chemical-related mortality and liver lesions seen in the 16-day and 13-week studies, doses selected for the 2-year studies were 0, 20, and 40 mg/kg. Groups of 70 male and 70 female mice were administered pentachloroanisole in corn oil by gavage 5 days per week for up to 2 years. At 9 and 15 months, up to 10 animals per group were selected for interim evaluations.

Survival, Body Weights, and Clinical Findings

The survival of dosed males was similar to that of the controls; survival of high-dose females was lower than that of the controls (24/50, 25/50, 16/50). The decreased survival of the high-dose females was attributed primarily to ovarian abscesses which were observed after moribund sacrifice. At the 9-month interim evaluation, the mean body weight of males administered 40 mg/kg was significantly lower than that of the vehicle controls. Absolute and relative liver weights of females and the relative liver weight of males administered 40 mg/kg were significantly greater than those of the controls. Final mean body weights of low- and high-dose males were 11% and 17% lower than that of the controls. Final mean body weights of dosed females were similar to that of the controls. There were no clinical findings attributed to pentachloroanisole administration.

Pathology Findings

Centrilobular hepatocyte cytomegaly and pigment accumulation in hepatocytes and Kupffer cells were seen in dosed mice, but not in controls at the 9- and 15-month interim evaluations. In the 2-year studies, the incidence of benign pheochromocytomas was significantly increased in high-dose males. Dosed males also exhibited increased incidences of adrenal medulla hyperplasia and hypertrophy. The incidences of hemangiosarcomas of the liver were significantly increased in dosed males. Increased incidences of hepatocellular cytologic alteration, biliary tract hyperplasia, and Kupffer cell pigmentation occurred in dosed males and females; the incidences of mixed cell foci were also increased in dosed males. Cytologic alteration encompassed hepatocellular cytomegaly, karyomegaly, hepatocyte degeneration and necrosis, and multinucleated giant cell formation, and was considered an advanced stage of the pathologic process observed at 13 weeks.

Genetic Toxicology

Pentachloroanisole was mutagenic in *Salmonella typhimurium* strains TA98 and TA1537 in the absence but not in the presence of exogenous metabolic activation (S9). No clear mutagenic activity was observed in TA100 with hamster S9, without S9, or in TA1535 with or without S9. An equivocal response was observed in TA100 with rat S9. Pentachloroanisole was positive for induction of trifluorothymidine resistance in mouse lymphoma L5178Y cells with S9; the response observed without S9 was weak and inconsistent. In cytogenetic tests with Chinese hamster ovary cells, pentachloroanisole induced sister chromatid exchanges, but not chromosomal aberrations, with and without S9.

Toxicokinetics

Male and female F344/N rats and B6C3F$_1$ mice were administered 10, 20, or 40 mg/kg pentachloroanisole by gavage or 10 mg/kg pentachloroanisole intravenously (Appendix H). A rapid elimination of pentachloroanisole and a rapid formation of its main metabolite, pentachlorophenol, were seen in both species after an intravenous or an oral dose of pentachloroanisole. The area under the concentration-versus-time curve of pentachloroanisole increased with dosage in each species but the dose proportionality was lost above 20 mg/kg. No sex-related differences were found in the rate of absorption of pentachloroanisole from the GI tract, in the area under the concentration-versus-time curve, or in the overall rate elimination of pentachloroanisole. However, in female rats the area

under the concentration-versus-time curve of pentachlorophenol was significantly larger than in male rats. No such difference was observed in mice.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of pentachloroanisole in male F344/N rats based on increased incidences of benign pheochromocytomas of the adrenal medulla. There was *equivocal evidence of carcinogenic activity* of pentachloroanisole in female F344/N rats based on marginally increased incidences of benign pheochromocytomas of the adrenal medulla. There was *some evidence of carcinogenic activity* of pentachloroanisole in male $B6C3F_1$ mice based on increased incidences of benign pheochromocytomas of the adrenal medulla and hemangiosarcomas of the liver. There was *no evidence of carcinogenic activity* of pentachloroanisole in female $B6C3F_1$ mice given doses of 20 or 40 mg/kg.

Pentachloroanisole administration was associated with increased incidences of adrenal medulla hyperplasia in female rats and increased incidences of pigmentation in the renal tubule epithelium, olfactory epithelium, and hepatocytes of male and female rats. In addition, decreased incidences of pancreatic adenomas and focal hyperplasia in male rats and decreased incidences of mammary gland fibroadenomas and uterine stromal polyps and sarcomas (combined) in female rats were observed. Hyperthermia-related lesions in male rats receiving 20 or 40 mg/kg were considered indirectly related to pentachloroanisole administration.

Pentachloroanisole administration was associated with increased incidences of adrenal medulla hyperplasia and hypertrophy and hepatocellular mixed cell foci in male mice. In male and female mice, nonneoplastic liver lesions associated with pentachloroanisole administration included hepatocellular cytologic alteration, Kupffer cell pigmentation, biliary tract hyperplasia, and subacute inflammation.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 10, 20, or 40 mg/kg in corn oil by gavage	0, 20, or 40 mg/kg in corn oil by gavage	0, 20, or 40 mg/kg in corn oil by gavage	0, 20, or 40 mg/kg in corn oil by gavage
Body weights	Mid- and high-dose groups lower than vehicle controls	High-dose group lower than vehicle controls	Dosed groups lower than vehicle controls	Dosed groups similar to vehicle controls
2-Year survival rates	24/50, 20/50, 24/50, 14/50	29/50, 35/50, 44/50	30/50, 27/50, 28/50	24/50, 25/50, 16/50
Nonneoplastic effects	Pigmentation: renal tubule epithelium (1/50, 23/50, 22/50, 16/50); olfactory epithelium (0/50, 29/50, 40/50, 25/50); hepatocytes (0/50, 0/50, 1/50, 4/50)	Adrenal medulla: hyperplasia (10/50, 18/50, 25/50) Pigmentation: renal tubule epithelium (0/50, 43/50, 45/50); olfactory epithelium (0/49, 46/50, 50/50); hepatocytes (0/50, 18/50, 24/50)	Adrenal medulla: hyperplasia (0/50, 13/50, 29/48); hypertrophy (0/50, 3/50, 36/48) Liver: cytologic alteration (0/50, 50/50, 50/50); Kupffer cell pigmentation (1/50, 50/50, 50/50); biliary tract hyperplasia (0/50, 47/50, 48/50); subacute inflammation (0/50, 49/50, 49/50); mixed cell foci (9/50, 15/50, 27/50)	Liver: cytologic alteration (1/50, 34/50, 39/50); Kupffer cell pigmentation (0/50, 37/50, 48/50); biliary tract hyperplasia (1/50, 16/50, 30/50); subacute inflammation (1/50, 28/50, 32/50)
Neoplastic effects	Adrenal medulla: benign pheochromocytoma (12/50, 17/50, 23/50, 15/48)	None	Adrenal medulla: benign pheochromocytoma (0/50, 4/50, 7/48) Liver: hemangiosarcoma (2/50, 8/50, 10/50)	None
Uncertain findings	None	Adrenal medulla: benign pheochromocytoma (3/50, 7/50, 9/50)	None	None
Decreased incidences	Pancreas: adenoma (12/49, 1/49, 1/49, 0/50); hyperplasia (19/49, 17/49, 8/49, 1/50)	Mammary gland: fibroadenoma (19/50, 10/50, 7/50) Uterus: stromal polyp (13/50, 13/50, 7/50); stromal sarcoma (2/50, 1/50, 0/50); stromal polyp or sarcoma (15/50, 14/50, 7/50)	None	None

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pentachloroanisole (continued)

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence	Some evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:	Positive without S9 in strains TA98 and TA1537 Equivocal with rat S9 in strain TA100 Negative with and without S9 in strains TA100 and TA1535			
L5178Y mouse lymphoma mutations:	Positive with S9			
Sister chromatid exchanges Chinese hamster ovary cells *in vitro*:	Positive with and without S9			
Chromosomal aberrations Chinese hamster ovary cells *in vitro*:	Negative with and without S9			

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 chemically 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 chemically related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemically 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 pentachloroanisole on November 21, 1991, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 21, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of pentachloroanisole received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of pentachloroanisole by discussing the rationale for study, describing the experimental design, reporting on the survival and body weight effects, and commenting on compound related neoplasms and nonneoplastic lesions in rats and mice. He reported on pharmacokinetic studies in rats with pentachloroanisole and a major metabolite, pentachlorophenol, and concluded from the results that differences between male and female rats in toxic response to the chemical were not due to differences in absorption or bioavailability. The proposed conclusions were *some evidence of carcinogenic activity* for male F344/N rats, *equivocal evidence of carcinogenic activity* for female F344/N rats, *some evidence of carcinogenic activity* for male $B6C3F_1$ mice and *no evidence of carcinogenic activity* for female $B6C3F_1$ mice.

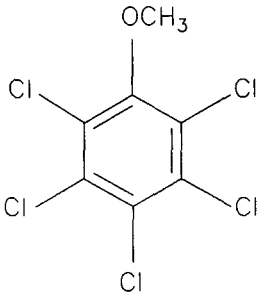
Dr. R.H. Garman, a principal reviewer, agreed with the proposed conclusions. He asked for clarification of the histomorphologic criteria for diagnostic terminology used in designating malignancy of adrenal medullary lesions.

Dr. L. Zeise, the second principal reviewer, agreed with the proposed conclusions. However, she asked for discussion on whether the level of evidence in female rats should be elevated to *some evidence* based on an incidence of adrenal neoplasms in the 40 mg/kg group. The incidence was above the historical control range and was supported by increased incidences of these neoplasms in male rats and male mice. She suggested that a statement be added to the report indicating that the incidence of pheochromocytomas in 40 mg/kg female rats fell outside that of historical controls. Dr. J. K. Haseman, NIEHS, noted that the increased incidence of adrenal neoplasms in dosed female rats was not significant, reflecting in part that survival in the high-dose groups was increased compared to concurrent and historical control survival rates. Dr. Zeise requested that information on the pharmacokinetic studies be added to the report.

Dr. B. McKnight, the third principal reviewer, agreed with the proposed conclusions for male and female rats and male mice but thought the conclusion for female mice should be changed to *equivocal evidence* based on the dose-related marginally increased incidence of malignant lymphoma supported by a statistically significant trend test. Dr. Irwin commented that since these are common neoplasms, the historical rates are rather variable. The high dose rate, being slightly higher than average, is well within the historical range and therefore not considered to be chemical related. Dr. McKnight said that because the 13 accidental deaths among male rats were indirectly associated with treatment, they should be counted as deaths rather than censored observations. Dr. Haseman said that a second set of survival curves adjusted for the relatively small number of accidental deaths would likely be almost indistinguishable from the first set.

Dr. Garman moved that the Technical Report on pentachloroanisole be accepted with the revisions discussed and with the conclusions as written, *some evidence of carcinogenic activity* for male rats and male mice, *equivocal evidence of carcinogenic activity* for female rats, and *no evidence of carcinogenic activity* for female mice. Dr. D.W. Hayden seconded the motion. Dr. McKnight offered an amendment that the level of evidence for female mice be changed to *equivocal evidence* based on the malignant lymphomas. Dr. Zeise seconded the amendment which was defeated by two yes (Drs. McKnight, Zeise) to eight no votes. The original motion by Dr. Garman was then accepted unanimously with ten votes.

INTRODUCTION



PENTACHLOROANISOLE

CAS No. 1825-21-4

Chemical Formula: $C_7H_3Cl_5O$ Molecular Weight: 280.5

Synonyms: 2,3,4,5,6-pentachloroanisole; methyl pentachlorophenate; methyl pentachlorophenyl ether; *o*-methylpentachlorophenol; pentachloromethoxybenzene; pentachlorophenyl methyl ether

Chemical and Physical Properties

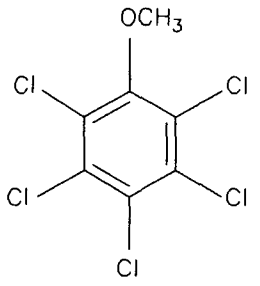
Pentachloroanisole is a colorless, crystalline solid that is stable under normal laboratory conditions; the melting point is 106° to 107° C. It is fairly soluble in ethanol, acetone, and dimethyl sulfoxide, and poorly soluble in water (Keith and Walters, 1985).

Pentachloroanisole differs only by a single methyl substitution from pentachlorophenol, a widely used wood preservative and biocide, and is structurally related to several other commercially important chlorinated aromatic compounds including pentachloronitrobenzene, sodium pentachlorophenate, and hexachlorobenzene (Figure 1).

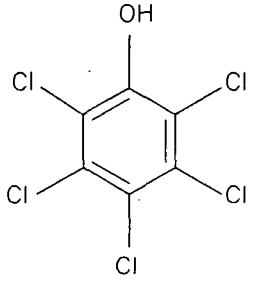
Environmental Sources and Metabolism

Pentachloroanisole has no industrial or agricultural applications and is not manufactured commercially, but its presence as an environmental contaminant is widespread. Pentachloroanisole in the environment is probably derived from ubiquitous related chlorinated aromatic compounds, especially pentachlorophenol (Ahlborg and Thunberg, 1980; Crosby *et al.*, 1981; Engelhardt *et al.*, 1986; WHO, 1987). Degradation of pentachlorophenol to pentachloroanisole has been simulated in the laboratory in various lentic environments (Boyle *et al.*, 1980) and in aerobic and anaerobic soil environments (Murthy *et al.*, 1979).

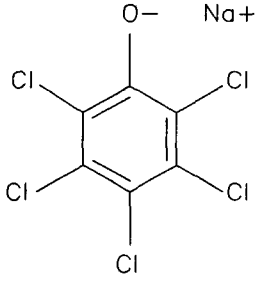
Many bacteria and fungi can methylate the hydroxyl oxygen of pentachlorophenol to form pentachloroanisole *in vitro* (Cserjesi and Johnson, 1972; Curtis *et al.*, 1972; Kaufman, 1978; Suzuki, 1983; Häggblom *et al.*, 1988). The *in vitro* microbial decomposition of sodium pentachlorophenate to pentachloroanisole has also been reported (Rott *et al.*, 1979). Microbial metabolism has been hypothesized to play a major role in pentachloroanisole production in wood-shaving litter from poultry houses (Curtis *et al.*, 1972, 1974; Parr *et al.*, 1974; Dennis *et al.*, 1975). Similar metabolic processes may also occur in packages and containers of tainted processed foods (Whitfield, 1983; Whitfield *et al.*, 1984; Whitfield and Last, 1986; Tindale, 1987). The importance of other biological, chemical, or physical mechanisms in the production of pentachloroanisole from related compounds is undetermined.



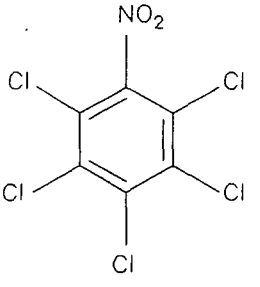
PENTACHLOROANISOLE



PENTACHLOROPHENOL



SODIUM PENTACHLOROPHENATE



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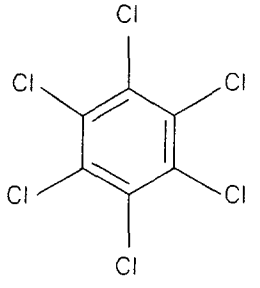

HEXACHLOROBENZENE

FIGURE 1
Chlorinated Aromatic Compounds Structurally Related to Pentachloroanisole

In laboratory settings, soybean and spinach plants can take up pentachlorophenol from soil and biotransform it to pentachloroanisole (Casterline *et al.*, 1985). In field experiments, pentachloroanisole has been identified in onions and rice plants grown in soil treated with pentachloronitrobenzene (Begum *et al.*, 1979) or pentachlorophenol (Weiss *et al.*, 1982), and in goldenrod plants sprayed with sodium pentachlorophenate (Haque *et al.*, 1988). In these cases, it is uncertain if pentachloroanisole was preformed in the soil or was a product of plant metabolism.

Animal and Human Exposure

Although widely distributed in the environment, pentachloroanisole has been detected only at low levels (Schmitt *et al.*, 1985). Pentachloroanisole has been found in fresh and marine waters at concentrations of 1 mg/L, in sediments at concentrations from 0.1 to 0.3 mg/kg, in marine air at concentrations of 2 to 9 pg/m^3, and in soils throughout the world (Kopperman *et al.*, 1978; Pierce and Victor, 1978; Giam *et al.*, 1984; Watanabe *et al.*, 1985; Atlas *et al.*, 1986; Finger and Bulak, 1988; Fox *et al.*, 1988; Lee, 1988; Maguire and Tkacz, 1988, 1989; Knuutinen *et al.*, 1990).

Pentachloroanisole has also been identified in mollusks, fish, and earthworms (Kopperman *et al.*, 1978; Miyazaki *et al.*, 1981; Renberg *et al.*, 1983; Jaffe *et al.*, 1985; Jaffe and Hites, 1986; Paasivirta *et al.*, 1986, 1987; DeVault *et al.*, 1988; Herve *et al.*, 1988; Swackhamer and Hites, 1988; Knuutinen *et al.*, 1990). In many instances, the affected organisms came from aquatic or terrestrial environments known to be contaminated with pentachlorophenol or other chlorinated aromatic compounds.

In general, pentachloroanisole has been detected rarely, if at all, in surveys for chlorinated aromatic compounds levels in wild mammals or birds (Mes *et al.*, 1982; Brunn *et al.*, 1985; Ellenton *et al.*, 1985; Paasivirta *et al.*, 1987; Somers *et al.*, 1987) and in human fat and breast milk (Pellizzari *et al.*, 1982; Williams *et al.*, 1984; Mes *et al.*, 1986; Kashimoto *et al.*, 1989). However, because the experimental conditions for many of these studies may not have been optimal for pentachloroanisole detection, the possibility of false negatives cannot be excluded.

"Market basket" surveys by the Food and Drug Administration have shown that low concentrations of pentachloroanisole are present in typical adult and toddler diets (Gartrell *et al.*, 1986a,b; Gunderson, 1988). Pentachloroanisole residues have been detected in foods of plant origin, such as dried fruits, cocoa, flour, and peanut butter (Heikes, 1980; Whitfield, 1983; Whitfield and Last, 1986; Tindale, 1987), and in foods of animal origin, such as broiler chickens and catfish (Curtis *et al.*, 1972, 1974; Dennis *et al.*, 1975; Harper and Balnave, 1975; Frank *et al.*, 1983; Jaffe and Hites, 1986).

Human exposure would most likely result from ingestion of food or water contaminated with pentachloroanisole. Pentachloroanisole has a higher detection threshold than some of the less-substituted chloroanisoles (Frijters and Bemelmans, 1977), and it usually occurs with them in tainted foods (Engel *et al.*, 1966; Curtis *et al.*, 1972, 1974; Harper and Balnave, 1975; Whitfield and Last, 1986). Chloroanisoles produce extremely objectionable musty odors and unusual flavors which are discernible at very low concentrations (Curtis *et al.*, 1972, 1974; Bemelmans and ten Noever de Brauw, 1974; Whitfield *et al.*, 1984; Tindale, 1987). Therefore, human consumption of food or water contaminated by high levels of pentachloroanisole would be unlikely.

Absorption, Distribution, Metabolism, and Excretion

Pentachloroanisole appears to be absorbed and distributed rapidly in fish. Rapid uptake was noted in male guppies (*Poecilia reticulata*) exposed to pentachloroanisole in laboratory tank water (Opperhuizen and Voors, 1987) and in fathead minnows (*Pimphales promelas*) raised in contaminated wastewater (Kopperman *et al.*, 1978). Similarly, in rainbow trout (*Salmo gairdneri*) exposed to 24 μg/L ^{14}C-labeled pentachloroanisole in tank water, pentachloroanisole uptake occurred in 1 to 2 hours (Glickman *et al.*, 1977; Lech *et al.*, 1978). In these studies, pentachloroanisole was widely distributed through the fish with the highest levels found in fat with decreasingly lower levels found in the liver, muscle, and blood.

In vivo formation of pentachloroanisole via metabolism of pentachlorophenol and other chlorinated aromatic compounds has been occasionally reported. Pentachloroanisole and unchanged pentachlorophenol were identified in the hepatopancreas of blue crabs, *Callinectes sapidus*, injected with pentachlorophenol (Bose and Fujiwara, 1978). When

fathead minnows were exposed for 31 days to 50 μg/L of either purified or industrial grade pentachlorophenol in the tank water, pentachlorophenol and the pentachlorophenyl-β-glucuronide metabolite were the major residues extracted, and only very small amounts of pentachloroanisole were detected in minnows exposed to purified pentachlorophenol (Huckins and Petty, 1983). In addition to the presence of several other chlorinated aromatic compounds, very low levels of pentachloroanisole (1.0 to 2.0 mg/kg) were found in blood and milk of dairy cows fed pentachlorophenol (Firestone *et al.*, 1979). Along with at least 15 other metabolites, pentachloroanisole has been detected in feces and urine of male and female Sprague-Dawley rats administered pentachloronitrobenzene by gavage (Renner, 1980).

Overall, pentachloroanisole appears to be a very minor or nonexistent metabolite of pentachlorophenol and other related chlorinated aromatic compounds in both vertebrates and invertebrates. Based on a very large body of experimental evidence, the general consensus is that in most species, including rats, mice, and humans, the major or sole metabolic products of pentachlorophenol are the glucuronide and sulfate conjugates, tetrachlorohydroquinone, and other less-substituted chlorophenols (Kobayashi, 1978; Lu *et al.*, 1978; Ahlborg and Thunberg, 1980; Crosby *et al.*, 1981; Renner and Mücke, 1986).

Various species can metabolize pentachloroanisole to pentachlorophenol. Hepatic microsomes of rat and miniature pig converted pentachloroanisole to pentachlorophenol *in vitro* by a cytochrome P-450 dependent demethylation reaction (Agins *et al.*, 1982; Agins, 1984). Bile from rainbow trout exposed for 24 hours to 50 μg/L pentachlorophenol in the tank water contained only pentachlorophenol, but bile from trout exposed to pentachloroanisole under similar conditions contained pentachlorophenol β-glucuronide and small amounts of pentachlorophenol, which indicated that *in vivo* demethylation may have taken place (Glickman *et al.*, 1977; Lech *et al.*, 1978). When female mice were administered a single intraperitoneal injection of 20 mg/kg ^{14}C-pentachloroanisole, radioactivity was concentrated in liver and fat, and the total carcass half-life ($t_{½}$) of ^{14}C was 10 hours (Vodicnik *et al.*, 1980). Elimination proceeded rapidly, primarily via the urine ($t_{½}$, 5.6 hours). Most urine or fecal radioactivity was associated with pentachlorophenol or a pentachlorophenol conjugate, suggesting to the authors that pentachloroanisole must be demethylated prior to conjugation and excretion.

In fish, pentachloroanisole generally is eliminated more slowly than other chlorinated aromatic compounds. Rainbow trout exposed to pentachloroanisole had elimination half-lives of ^{14}C radioactivity of 6.3 days in blood and muscle, 6.9 days in liver, and 23.4 days in fat. By comparison, the ^{14}C radioactivity elimination half-lives for pentachlorophenol for the same tissues in trout were shorter at 6.2, 6.9, 9.8, and 23.7 hours, respectively (Glickman *et al.*, 1977). Detectable levels of pentachloroanisole were found in rainbow trout and in the tank water up to 96 days after exposure (Oliver and Niimi, 1985). However, in other experiments, pentachloroanisole was rapidly cleared (elimination half-life, 1 to 4 days) from the tissues of male guppies (Opperhuizen and Voors, 1987).

TOXICITY

Little information is available on the acute toxicity of pentachloroanisole; however, it is considered to be less toxic than pentachlorophenol or other related chlorinated aromatic compounds (Cserjesi and Johnson, 1972; Engelhardt *et al.*, 1986). When juvenile coho salmon (*Oncorhynchus kisutch*) were exposed to 4 mg/L pentachloroanisole or 2 mg/L pentachlorophenol in the tank water, the toxicity of pentachloroanisole was roughly estimated to be 1,000 times less than that of pentachlorophenol (Cserjesi and Johnson, 1972).

When rats were administered a single gavage dose of 2, 10, 30, or 50 mg/kg body weight pentachloroanisole or pentachlorophenol daily for 3 days, rectal temperature and serum glucose levels were elevated, feed consumption was decreased, and uncoupled succinate respiration occurred in the 30 and 50 mg/kg groups (Garthoff *et al.*, 1982). These changes were more prominent in rats receiving pentachlorophenol than in those receiving pentachloroanisole. In an earlier study, pentachloroanisole administration to male rats increased levels of α-aminolevulinic acid synthetase activity, although urinary and fecal porphyrin excretions were unaffected (Simon *et al.*, 1978).

No acute mortality occurred when female mice were administered single intraperitoneal injections of 12 to

250 mg/kg (Vodicnik *et al.*, 1980). In recent reproductive and teratogenicity studies (Welsh *et al.*, 1987), no mortality was observed in male or female rats fed diets containing 60, 200, or 600 ppm pentachloroanisole for 181 days.

Respiration was increased in rat kidney explants exposed to 0.1 mM pentachloroanisole for 18 hours, but was unaffected when slices of rat kidney or liver were exposed to 0.1 or 0.8 mM pentachloroanisole for 1 hour. In contrast, when pentachlorophenol was tested under similar conditions, respiration was reduced in kidney explants and in kidney and liver slices (Braunberg *et al.*, 1981). Oral administration of pentachloroanisole to young miniature pigs increased the activities of several hepatic mixed-function oxidase system enzymes (P-450 and b_5, NADPH-cytochrome c_2 reductase, aniline hydroxylase, *p*-nitroanisole demethylase, and pentachloroanisole demethylase; Agins, 1984).

Reproductive and Developmental Toxicity

Based on the limited data available, pentachloroanisole does not appear to be highly embryotoxic or teratogenic. Neilson *et al.* (1984) exposed zebra fish (*Brachydanio reiro*) eggs and larvae to 2.8 μg pentachlorophenol/L culture dish water resulting in increased embryo/larval mortality and deformation (larval curvature). When larval striped bass (*Morone saxatilis*) were placed in river water containing 12.7 to 37.5 ng/L pentachloroanisole, lethargic swimming behavior was observed in all exposed groups, but mortality occurred only in larvae exposed to the highest concentration range of pentachloroanisole, and the water was not comprehensively tested for chlorophenols and other related chlorinated aromatic compounds (Finger and Bulak, 1988).

In recent studies, diets containing 60, 200, or 600 ppm pentachloroanisole or pentachlorophenol were fed to male and female Sprague-Dawley rats for 181 days prior to breeding and through pregnancy (Welsh *et al.*, 1987). Teratogenicity and decreased fertility were not observed following treatment with either compound, although embryo death and reduced fetal body weights were noted. In general, adverse effects were more pronounced in rats exposed to pentachlorophenol than in rats exposed to pentachloroanisole.

Carcinogenicity

No information was available concerning chronic toxicity or carcinogenicity of pentachloroanisole in laboratory rodents or other species.

Genetic Toxicity

Two studies on the genotoxicity of pentachloroanisole have reported positive results. Pentachloroanisole was mutagenic in *Salmonella typhimurium* strains TA98 and TA1537 without exogenous metabolic activation (S9) only in the presence of precipitated pentachloroanisole, but was not mutagenic with S9 (Mortelmans *et al.*, 1986). In the same study, gene mutations were not induced in *S. typhimurium* strains TA100 and TA1535 treated with up to 10 mg pentachloroanisole per plate. In the mouse lymphoma assay, pentachloroanisole induced trifluorothymidine resistance in mouse L5178Y cells, but only in the presence of S9 (McGregor *et al.*, 1987); the increases in the number of trifluorothymidine-resistant colonies were not dose related.

Pentachlorophenol, a metabolite of pentachloroanisole, is not mutagenic in most strains of *S. typhimurium* (Simmon *et al.*, 1977; Haworth *et al.*, 1983; Moriya *et al.*, 1983). However, isolated positive responses have been reported in strain TA100 without S9 (Commoner, 1976) and in strain TA98 with S9 (Nishimura *et al.*, 1982). In *Saccharomyces cerevisiae*, pentachlorophenol induced gene conversion and mutation (Fahrig *et al.*, 1978), but no mitotic recombination was observed (Simmon and Kauhanen, 1978). Pentachlorophenol was also negative for induction of nondisjunction in germ cells of *Drosophila melanogaster* (Ramel and Magnusson, 1979). In mammalian cells, pentachlorophenol was negative in gene mutation tests with hamster V79 cells (Hattula and Knuutinen, 1985; Jansson and Jansson, 1986), but was weakly positive without S9 activation for induction of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells (Galloway *et al.*, 1987). In contrast, results from sister chromatid exchange and chromosomal aberrations tests with human lymphocytes exposed *in vitro* or *in vivo* to pentachlorophenol were negative (Ziemsen *et al.*, 1987). Tetrachlorohydroquinone, a metabolite of pentachlorophenol, was found to bind covalently to calf thymus DNA and to induce single strand breaks in bacteriophage PM2 DNA, but these effects were not observed with pentachlorophenol (Witte *et al.*, 1985).

Several structural analogues of pentachloroanisole including pentachlorobenzene, 1,3,3,4-tetrachlorobenzene, 1,2,3,5-tetrachlorobenzene, 1,2,4,5-tetrachlorobenzene, pentabromomethylbenzene, 2,3,4,5,6-pentabromomethylbenzene, 2,3,4,5-tetrachlorophenol, 2,3,5,6-tetrachlorophenol, and 2,3,4,6-tetrachlorophenol have been tested for induction of gene mutations in *S. typhimurium*, with and without S9. All results were negative (Räsänen *et al.*, 1977; Haworth *et al.*, 1983; Zeiger *et al.*, 1987; 1988). Paradi and Lovenyak (1981) reported positive results for induction of sex-linked recessive lethal mutations in male *Drosophila melanogaster* with 1,2,4,5-tetrachlorobenzene (maximum dose, 755.6 μg/mL). Induction of gene mutations in hamster V79 lung cells by 2,3,4,6-tetrachlorophenol was observed without S9 activation (Hattula and Knuutinen, 1985). The chlorobenzenes and chlorophenols have also been tested for induction of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The chlorobenzenes are uniformly negative for induction of chromosomal aberrations and only 1,2,3,4-tetrachlorobenzene gave a positive response in the sister chromatid exchange test (Loveday *et al.*, 1990). Positive responses were observed in the chromosomal aberrations test with all three chlorophenol isomers listed above; however, only 2,3,5,6-tetrachlorophenol gave clearly positive results in the sister chromatid exchange test (NTP, unpublished data).

STUDY RATIONALE

Pentachloroanisole was nominated for toxicity and carcinogenicity testing by the Food and Drug Administration and NIEHS because its wide distribution in the environment and in human foods presents a potential for low-level human exposure through drinking water and through food.

Pentachloroanisole is almost identical structurally to pentachlorophenol, which has been demonstrated in previous NTP studies to have clear evidence of carcinogenicity in B6C3F$_1$ mice (NTP, 1989). Pentachloroanisole is also structurally related to other chlorinated aromatic compounds such as pentachloronitrobenzene, sodium pentachlorophenate, and polychlorinated benzenes, biphenyls, dibenzodioxins and dibenzofurans which are known or suspected toxins, carcinogens, or teratogens (IARC, 1979a; Kimbrough, 1981; NTP, 1982, 1991a,b; D'Itri and Kamrin, 1983; Kimbrough and Jensen, 1989; Kutz *et al.*, 1991). No information on the chronic toxicity and carcinogenicity of pentachloroanisole in laboratory rodents or other species is available.

For these reasons, pentachloroanisole was selected by the NTP for chronic toxicity and carcinogenicity testing in F344/N rats and B6C3F$_1$ mice. Oral administration of pentachloroanisole was chosen to most closely approximate the primary route of human exposure. Administration by gavage was employed to avoid decreased consumption of dosed feed or water due to possible poor palatability, and because pentachloroanisole is poorly soluble in water and unstable in feed.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PENTACHLOROANISOLE

Pentachloroanisole was obtained in three lots. Lot HE052008, which was obtained from the Aldrich Chemical Company (Milwaukee, WI), was used in the 16-day studies. The analytical chemistry laboratory, Midwest Research Institute (MRI) (Kansas City, MO), synthesized lot M012882 for use in the 13-week studies and lot M062783 for use in the 2-year studies. The identity and purity analyses were performed by MRI. Details of these analyses are presented in Appendix I.

The study material, a white crystalline solid, was identified as pentachloroanisole by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy (Figures I1 and I2). The purity of all lots was determined by elemental analyses, Karl Fischer water analyses, thin-layer chromatography, and gas chromatography. The purity of all lots was determined to be 99% or greater. Gas chromatography for all lots indicated a single major peak and no impurities greater than 0.2%. No chlorinated dibenzodioxins, dibenzofurans, or diphenyl ethers were detected in lots M012882 or M062783 by gas chromatography/mass spectroscopy. Less than 0.1% pentachlorophenol was detected in all lots by gas chromatography. Concurrent analysis of lots M012882 and M062783 by gas chromatography/mass spectroscopy detected the following impurities: 192 ppm tetrachloroanisole and 361 ppm tetrachlorobromoanisole in lot M062783; and 1,664 ppm tetrachloroanisole, 165 ppm tetrachlorobromoanisole, and 1 ppm and 389 ppb for two unidentified chlorinated impurities in M012882. Hexachlorobenzene (3 ppm in lot M012882 and 7 ppm in lot M062783) was detected using packed column gas chromatography with electron capture detection.

Stability studies performed using gas chromatography with flame ionization detection indicated that pentachloroanisole was stable as a bulk chemical for 2 weeks at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in amber serum bottles in the dark at 5° C (16-day studies) or at room temperature (13-week and 2-year studies). The stability of the bulk chemical was monitored periodically using ultraviolet/visible spectroscopy and gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulation solutions were prepared by mixing the appropriate quantities of pentachloroanisole and corn oil on a weight-to-volume basis for the 16-day studies and on a weight-to-weight basis for the 13-week and 2-year studies. Dose formulations were prepared three times and stored at 5° C during the 16-day studies. For the 13-week and 2-year studies, dose formulations were prepared weekly and stored at room temperature (approximately 22° C); maximum storage time for dose formulations did not exceed 21 days (Table I1). Stability analyses of the dose formulations were performed by the analytical chemistry laboratory. No significant loss in stability was detected when dose formulations were stored for 3 weeks in the dark at room temperature.

Dose formulation solutions of pentachloroanisole were periodically analyzed by the study laboratory and by the analytical chemistry laboratory using flame ionization gas chromatography with octadecane as the internal standard. Dose formulations were within 10% of the theoretical concentrations throughout the studies (Tables I2 and I3). Periodic peroxide analyses of the corn oil vehicle by the study laboratory indicated that peroxide levels were within the acceptable limit of 10 mEq/kg. Results of periodic referee analyses by the analytical chemistry laboratory were in good agreement with the results obtained by the study laboratory (Table I4).

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Kingston, NY). Animals were quarantined for 18 days before the studies began. The rats were

51 days old and the mice were 57 days old when the studies began.

Groups of five male and five female rats were administered 0, 100, 125, 150, 175, or 200 mg/kg body weight pentachloroanisole in corn oil by gavage daily for 16 days. Groups of five male and five female mice were administered 0, 100, 175, 250, 325, or 400 mg/kg in corn oil by gavage daily for 16 days. Doses were not administered on weekends, and two consecutive days of dosing occurred before necropsy. Animals were housed five per cage. Water and feed were available *ad libitum*. Details of study design and animal maintenance are listed in Table 1.

Animals were weighed at the beginning of the studies, and on days 8 and 15. Animals were observed twice daily for chemical-related toxicity, except on weekends. Complete necropsy was performed on all animals.

13-Week Studies

These studies were conducted to evaluate the cumulative toxic effects of repeated exposure to pentachloroanisole. Male and female F344/N rats and B6C3F$_1$ mice were obtained from the Charles River Breeding Laboratories (Kingston, NY). Rats were observed for 17 days and mice were observed for 19 days before being assigned to treatment groups. The rats were 50 days old and the mice were 59 days old when dosing began.

Groups of 10 male and 10 female rats and mice were administered 0, 40, 80, 120, 140, or 180 mg/kg body weight pentachloroanisole in corn oil by gavage, 5 days per week for 13 weeks. Rats and mice were housed five per cage. Feed and water were available *ad libitum*. Blood for hematology and clinical chemistry was collected from the inferior vena cava of rats and from cardiac puncture of mice. Details of study design and animal maintenance are listed in Table 1.

Animals were observed twice daily. Individual animal weights were recorded initially, once weekly, and at the end of the studies. Clinical findings were recorded weekly. Organs weighed at the end of the studies included the brain, heart, right kidney, liver, lung, right testis, and thymus. Complete histopathologic examinations were performed on all animals dying before the end of the studies, on all rats except females in the 40 mg/kg group, on all male mice except those in the 40 mg/kg group, and on female mice in the 0, 140, and 180 mg/kg groups. Tissues routinely examined microscopically are listed in Table 1. The health of the rats and mice was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

2-Year Studies

Study Design

Groups of 70 male rats were administered 0, 10, 20, or 40 mg/kg body weight pentachloroanisole in corn oil by gavage, 5 days per week, for up to 103 weeks. Dosing was completed 10 days prior to study end. Groups of 70 female rats and 70 male and 70 female mice were given 0, 20, or 40 mg/kg pentachloroanisole in corn oil by gavage, 5 days per week, for up to 103 weeks for rats and 104 weeks for mice. In each dose group, 10 rats and 10 mice were designated for interim evaluation at 9 and 15 months. The organs weighed and the tissues routinely examined microscopically are listed in Table 1. At the 9- and 15-month interim evaluations, liver porphyrin levels were measured using ultraviolet (350 nm) light.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). Rats were 29 days old when received by the study laboratory and were quarantined for 11 to 12 days; mice were 29 days old and were quarantined for 12 days. During quarantine, the animals were observed daily. To assess the health status of the animals, five male and five female rats and mice were killed and examined for disease and parasite infection. The rats were 40 days old and the mice were 41 days old when the studies began. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Rats were housed five per cage; mice were housed individually. Cages were rotated vertically on the rack within dose groups and racks were rotated within the animal room every 2 weeks. Feed and water were available *ad libitum*. Information on ingredients, nutrient composition, and contaminant levels of the feed is presented in Appendix J. Further details of animal maintenance are listed in

Table 1. Temperature and humidity significantly exceeded the normal range on day 185 of the 2-year rat studies due to a failure of the environmental control system.

Clinical Examinations and Pathology

All animals were observed twice daily, 5 days per week. Body weights and clinical findings were recorded weekly for the first 13 weeks and then monthly until the end of the studies. Rectal temperatures in all male rats designated for 9-month interim evaluation were recorded from week 21 to week 39. Temperatures were taken on Monday morning prior to dosing and on Wednesday and Friday afternoons approximately 6 hours after dosing. In addition to the scheduled temperature measurements for 9-month interim male rats, rectal temperatures were measured for any mid- or high-dose male rat designated for 15-month interim evaluation and rats in the 2-year study that exhibited clinical signs of hyperthermia during weeks 17 to 39. Blood for hematology and clinical chemistry was collected from the inferior vena cava of rats and by cardiac puncture for mice at 9 and 15 months. Animals were anesthetized with ether before blood collection.

All animals were necropsied. At necropsy, all organs and tissues were examined for gross lesions, all major tissues were fixed and preserved in phosphate-buffered neutral formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Complete histopathology was performed on all rats and low-dose mice killed moribund or that died prior to scheduled evaluation, as well as on all dosed male rats and control and high-dose female rats and male and female mice. Tissues routinely examined microscopically are listed in Table 1.

Pathology evaluations were completed by the study laboratory pathologist and the pathology data were entered into the Toxicology Data Management System. The microscope slides, paraffin blocks, and residual wet-tissues were sent to the NTP Archives for inventory, slide/block match, and wet-tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. A quality assessment pathologist reviewed the adrenal gland, kidney, liver, and nose of rats of each sex, the pancreas of male rats, and the adrenal medulla, forestomach, and liver of mice for accuracy and consistency of lesion diagnosis.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) chair, who reviewed selected slides of tissues and any other tissues when there was disagreement in diagnosis between the laboratory and quality assessment pathologist. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnosis between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair to the PWG for review. The PWG included the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without knowledge of dose groups or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the PWG consensus. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined in general accordance with the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in this report in the form of graphs. Animals were censored from the survival analyses at the time they were found dead from other than natural causes. Animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect 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 incidence of neoplasms or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number

of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histopathologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary gland neoplasms) prior to histopathology sampling or when neoplasms (e.g., mononuclear cell leukemia) had multiple potential sites of occurrence, the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidences

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

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

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

Analysis of Nonneoplastic Lesion Incidences

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

Analysis of Continuous Variables

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

Historical Control Data

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

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, they

were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of pentachloroanisole was assessed by testing the ability of the chemical to induce mutations in *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537), mutations in the mouse lymphoma L5178Y cells, and sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The protocols for these studies and tabular presentations of the findings are given in Appendix E.

The genetic toxicity studies of pentachloroanisole conducted by the NTP are part of a larger effort to develop a database that would permit the evaluation of the contribution of these four *in vitro* short-term genetic toxicity tests to predicting chemical carcinogenicity in experimental animals. These *in vitro* tests were developed to study mechanisms of chemically induced DNA damage, but their use has been extended to the prediction of carcinogenicity based on the somatic mutation theory and electrophilic theory of chemical carcinogenesis (Miller and Miller, 1977; Straus, 1981; Crawford, 1985). Although *Salmonella typhimurium* and mouse lymphoma cell assays are capable of detecting mutations, neither of the specific gene loci tested appear to be related to the cellular changes that occur in the induction of neoplasia in humans or animals. Moreover, none of the chromosomal aberrations or sister chromatid exchanges observed in Chinese hamster ovary cells have been clearly related to heritable changes involved in the induction or progression of neoplasia. Thus, a positive response in any of these tests by a chemical that produces increases in tumor incidences in experimental animals does not necessarily implicate a specific mechanism of carcinogenicity involving direct DNA damage. Nevertheless, there is a strong correlation between structural alerts to DNA reactivity (electrophilicity), mutagenicity in *S. typhimurium*, and carcinogenicity in two rodent species or at multiple tissue sites, which provides support for the electrophilic theory of chemical carcinogenesis in a subset of chemical carcinogens. Details regarding the correlation of structural alerts (or absence thereof), mutagenicity, and carcinogenicity results of 301 chemicals in the NTP database appear in Ashby and Tennant, 1991.

Toxicokinetics

Toxicokinetics of pentachloroanisole was studied in male and female F344 rats and B6C3F$_1$ mice. Fifteen male and 15 female rats were administered 5 mL/kg pentachloroanisole intravenously; 34 male and 34 female mice received 2.5 mg/mL intravenously. Blood samples were collected from rats and mice at 2, 10, 20, and 30 minutes, and at 1, 3, 6, 12, 18, 26, and 32 hours, with blood being taken from the orbital sinus of three animals at each time interval. Twelve male and 12 female rats and 24 male and 24 female mice were administered 10, 20, or 24 mg/kg pentachloroanisole by gavage. Blood samples were collected from rats and mice at 30 minutes, and at 1, 3, 6, 12, 18, 26, and 32 hours. Blood was collected as in the intravenous study. Further details of these studies are outlined in Appendix H.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Pentachloroanisole

16-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Southern Research Institute (Birmingham, AL)	Same as 16-day studies	Same as 16-day studies
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Same as 16-day studies	Same as 16-day studies
Animal Source		
Charles River Breeding Laboratories (Kingston, NY)	Same as 16-day studies	Frederick Cancer Research Facility (Frederick, MD)
Time Held Before Study		
Rats: 18 days Mice: 18 days	Rats: 17 days Mice: 19 days	Rats: 11-12 days Mice: 12 days
Average Age When Placed on Study		
Rats: 51 days Mice: 57 days	Rats: 50 days Mice: 59 days	Rats: 40 days Mice: 41 days
Date of First Dose		
Rats: 4 August 1980 Mice: 4 August 1980	Rats: 19 April 1982 Mice: 6 April 1982	Rats: 26 September 1983 Mice: 30 January 1984
Date of Last Dose		
Rats: 19 August 1980 Mice: 19 August 1980	Rats: 21 July 1982 Mice: 8 July 1982	Rats: 13 September 1985 Mice: 20 January 1986
Duration of Dosing		
5 days/week for 12 dosing days	5 days/week for 13 weeks	5 days/week for 103 weeks (rats) 5 days/week for 104 weeks (mice)
Average Age at Necropsy		
Rats: 9 weeks Mice: 10 weeks	Rats: 20 weeks Mice: 21 weeks	Rats: 9-month evaluation, 45 weeks; 15-month evaluation, 71 weeks; terminal, 110-111 weeks Mice: 9-month evaluation, 45 weeks; 15-month evaluation, 69 weeks; terminal 110-111 weeks
Necropsy Dates		
Rats: 20-21 August 1980 Mice: 20 August 1980	Rats: 20-22 July 1982 Mice: 6-9 July 1982	Rats: 9-month evaluation, 20-22 June 1984; 15-month evaluation, 19-21 December 1984; terminal, 23 September-1 October 1985 Mice: 9-month evaluation, 31 October-2 November 1984; 15-month evaluation, 17-19 April 1985; terminal, 27-31 January 1986
Size of Study Groups		
5 males and 5 females	10 males and 10 females	70 males and 70 females
Animals per Cage		
Rats: 5 Mice: 5	Same as 16-day studies	Rats: 5 Mice: 1

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Pentachloroanisole (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Method of Animal Distribution		
Distributed by sex and weight classes to cages, then assigned to dose groups using appropriate random number tables.	Same as 16-day studies	Same as 16-day studies. The remaining 15 animals of each sex were assigned to the Sentinel Animal Program.
Method of Animal Identification		
Rats: earmark Mice: earmark	Same as 16-day studies	Rats: earmark and toe clip Mice: toe clip
Diet		
NIH-07 Rat and Mouse Ration, pellet (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as 16-day studies	Same as 16-day studies
Water		
Source: tap water, city of Birmingham, Alabama. Available *ad libitum* using an automatic water system (Edstrom Industries, Inc., Waterford, WI). Checked daily, system flushed every 2 weeks	Same as 16-day studies	Same as 16-day studies. Rats: water bottles for animals designated for 9- and 15-month interim evaluations were Nalgene®, Teflon FEP® wide-mouth bottles (Nalge Company, Rochester, NY) with rubber stoppers and fitted with stainless steel sipper tubes. Changed twice weekly.
Cages		
Polycarbonate, solid bottoms (Lab Products, Inc., Garfield, NJ), changed twice weekly	Same as 16-day studies; changed biweekly. Cages rotated within dose groups on racks	Same as 13-week studies.
Racks		
Stainless steel, (Lab Products, Inc., Garfield, NJ)	Same as 16-day studies, changed every 2 weeks and racks rotated in the animal room every 2 weeks	Same as 13-week studies
Bedding		
BetaChips, heat-treated hardwood chips (Northeastern Products Corp., Warrensburg, NY), changed twice weekly	Same as 16-day studies	Same as 16-day studies
Cage Filters		
Reemay spun-bonded polyester fiber filters (Snow Filtration, Cincinnati, OH), changed once every 2 weeks	Same as 16-day studies	Same as 16-day studies
Animal Room Environment		
Temperature range: 22°-24° C Relative humidity range: 54%-60% Fluorescent light: 12 hours/day Room air flow: minimum 15 changes/hour	Temperature range: 22°-24° C Relative humidity range: 28%-63% Fluorescent light: 12 hours/day Room air flow: minimum of 15 changes/hour	Average temperature: 22° C Relative humidity: 51.7% Fluorescent light: 12 hours/day Room air flow: 10-15 changes/hour

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Pentachloroanisole (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Doses		
Rats: 0, 100, 125, 150, 175, and 200 mg/kg body weight in corn oil administered by gavage in a dose volume of 5 mL/kg Mice: 0, 100, 175, 250, 325, and 400 mg/kg in corn oil administered by gavage in a dose volume of 10 mL/kg	Rats: 0, 40, 80, 120, 140, and 180 mg/kg in corn oil administered by gavage in a dose volume of 5 mL/kg Mice: 0, 40, 80, 120, 140, and 180 mg/kg in corn oil administered by gavage in a dose volume of 10 mL/kg	Rats: 0, 10 (males only), 20, and 40 mg/kg in corn oil administered by gavage in a dose volume of 5 mL/kg Mice: 0, 20, and 40 mg/kg in corn oil administered by gavage in a dose volume of 10 mL/kg
Type and Frequency of Observation		
Observed twice/day, except on weekends; body weight initially, on day 8, and day 15; clinical findings were noted daily	Observed twice/day; body weight initially, once/week, and at study termination; clinical observations once/week.	Observed twice/day, 5 days/week; body weights once/week for first 13 weeks, then once/month until the end of the study, or scheduled evaluation; clinical findings noted at body weight determinations. Rectal temperatures of male rats were recorded from week 17 to week 39.
Method of Sacrifice		
Carbon dioxide asphyxiation	Moribund animals by carbon dioxide asphyxiation; terminal sacrifice by thoracotomy under ether anesthesia	Moribund animals and terminal sacrifice by carbon dioxide asphyxiation; 9- and 15-month interim evaluations by thoracotomy following blood collection under ether anesthesia
Necropsy		
Necropsy performed on all animals	Necropsy performed on all animals. Organs weighed at the end of the studies were brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals. Organs weighed at each scheduled evaluation were brain, right kidney, liver, and thymus.
Histopathology		
None	Complete histopathologic examinations were performed on all animals dying before the end of the studies, all male rats, all female rats, and male mice except those in the 40 mg/kg groups, and 0, 140, and 180 mg/kg female mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (including marrow), brain, clitoral gland, epididymis, esophagus, gallbladder (mice only), heart, kidney, large intestine, liver, lung, mammary gland, mandibular lymph node, mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathology was conducted on all rats and low-dose mice killed moribund or that died prior to scheduled evaluation, as well as on all male rat dose groups and control and high-dose rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (including marrow), brain, clitoral gland, epididymis, esophagus, gallbladder, heart, kidney, large intestine, liver, lung, mammary gland, mandibular or mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicles, skin, small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Only selected tissues were examined in low-dose mice that survived until the end of the study; these included adrenal gland, liver, mandibular lymph node, (continued on next page)

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Pentachloroanisole (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Histopathology (continued)		
		mesenteric lymph node, nose, spleen, stomach, and thyroid gland. In the low-dose female rats, the following tissues were examined microscopically: adrenal gland, gross lesions, kidney, liver, nose, pituitary gland, and uterus. The following organs were examined at the 9-month interim evaluation in both male and female control and high-dose rats: adrenal gland, heart, kidney, large intestine, liver, lung, nose, pancreas, pituitary gland, and stomach. In addition tissues from the mesenteric lymph node, preputial gland, prostate gland, testis, and urinary bladder were examined in the control and high-dose males. The brain, bone marrow, uterus and clitoral gland were examined, as well, in the same female dose groups. In the 9-month interim evaluation of male and female control and high-dose mice, a complete histopathology was performed. In the low-dose group in male and female mice, only the liver and gross lesions were evaluated. At the 15-month interim evaluation, a complete histopathology was performed on all control and high-dose male and female rats, as well as on all control and high-dose male and female mice. In the low-dose mice groups, only the liver and gross lesions were evaluated.
Clinical Pathology		
None	Clinical pathology studies were performed at 13 weeks from blood collected from all animals (rats, interior vena cava; mice, cardiac puncture). ***Hematology:*** hematocrit, hemoglobin, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total leukocyte count ***Clinical chemistry:*** alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, serum cholinesterase (rats only), sorbitol dehydrogenase (rats only)	Clinical pathology studies were performed at 9 and 15 months from blood collected from all animals (rats, interior vena cava; mice, cardiac puncture). ***Hematology:*** hematocrit, hemoglobin, methemoglobin (at 9 months only), erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total and differential leukocyte counts, platelet count, reticulocytes ***Clinical chemistry:*** blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase At 9- and 15-month interim evaluation, liver porphyrin was qualitatively evaluated using ultraviolet (350 nm) light.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Pentachloroanisole (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Toxicokinetics		
None	None	Fifteen male and 15 female rats were administered 2.5 mg/mL pentachloroanisole intravenously, and 34 male and 34 female mice were administered 5 mg/mL pentachloroanisole intravenously. Blood was collected at 2, 10, 20, and 30 minutes and at 1, 3, 6, 12, 18, 26, and 32 hours. Twelve male and 12 female rats and 24 male and 24 female mice were administered 10, 20, or 24 mg/kg pentachloroanisole by gavage. Blood samples were collected at 30 minutes, and at 1, 3, 6, 12, 18, 26, and 32 hours.

RESULTS

RATS

16-Day Studies

Rats died in all but the control and 100 mg/kg groups (Table 2). Most deaths occurred on days 2 or 3 and all were considered directly related to pentachloroanisole administration. Because of the high early mortality, valid comparisons of body weight gains and mean final body weights could not be made for rats administered doses greater than 100 mg/kg. No biologically significant changes in body weight gain or final mean body weights were noted in male or female rats administered 100 mg/kg. Clinical findings in rats administered 125 mg/kg or greater included inactivity, wet fur around the mouth from excessive salivation, and labored gasping breathing. Rats administered 100 mg/kg displayed inactivity only. Inactivity was characterized by animals lying separated on the cage floor; when disturbed, these animals became temporarily active but soon resumed their prone positions. Treatment-related gross findings observed at necropsy in all but the 100 mg/kg groups included pulmonary edema and subcutaneous muscular congestion. These lesions are consistent with death from acute circulatory collapse and shock subsequent to hyperthermia.

TABLE 2
Survival and Mean Body Weights of Rats in the 16-Day Gavage Studies of Pentachloroanisole

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	130 ± 2	206 ± 4	76 ± 3	
100	5/5	130 ± 1	204 ± 4	73 ± 3	91
125	3/5[c]	134 ± 2	208 ± 0	74 ± 3	101
150	2/5[d]	122 ± 1	170 ± 17**	52 ± 16*	83
175	0/5[e]	133 ± 1	–	–	–
200	1/5[f]	126 ± 4	162	35	79
Female					
0	5/5	108 ± 2	143 ± 3	35 ± 2	
100	5/5	110 ± 4	142 ± 4	32 ± 2	99
125	4/5[g]	108 ± 2	140 ± 3	33 ± 2	97
150	2/5[h]	102 ± 1	140 ± 8	36 ± 8	97
175	3/5[c]	105 ± 2	129 ± 7	24 ± 5*	90
200	0/5[i]	105 ± 2	–	–	–

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No data were calculated for groups with 100% mortality.
[c] Day of death: 3, 3
[d] Day of death: 3, 3, 13
[e] Day of death: 2, 3, 3, 3, 3
[f] Day of death: four on day 2. No standard error calculated due to high mortality in this group.
[g] Day of death: 3
[h] Day of death: 2, 3, 3
[i] Day of death: 2, 2, 3, 3, 3

13-Week Studies

All male rats administered 120 mg/kg body weight pentachloroanisole or greater and all female rats administered 140 mg/kg or greater died before the end of the studies (Table 3). Seven males in the 80 mg/kg group and eight females in the 120 mg/kg group also died before the end of the studies. Most deaths occurred during the first week; these deaths were considered directly related to pentachloroanisole administration.

Mean body weight gains were 10% and 16% lower than that of the vehicle controls for male rats in the 40 and 80 mg/kg (based on three animals) groups (Table 3). The final mean body weight of the 80 mg/kg male group was 10% lower than that of the vehicle controls. Body weight gains of dosed females were 10%, 15%, and 21% lower than that of the vehicle controls for females administered 40, 80, and 120 mg/kg (based on two animals). The final mean body weights of dosed females receiving 40 to 120 mg/kg were similar to that of the vehicle controls. Body weight comparisons were not performed in dose groups with high early mortality.

High early mortality also limited comparisons of absolute and relative organ weights. Relative kidney

TABLE 3
Survival and Mean Body Weights of Rats in the 13-Week Gavage Studies of Pentachloroanisole

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	150 ± 3	352 ± 6	202 ± 3	
40	10/10	148 ± 4	328 ± 4**	181 ± 3**	93
80	3/10[c]	148 ± 3	316 ± 7**	169 ± 10**	90
120	0/10[d]	151 ± 4	–	–	–
140	0/10[e]	148 ± 4	–	–	–
180	0/10[f]	150 ± 4	–	–	–
Female					
0	10/10	113 ± 3	201 ± 4	89 ± 3	
40	10/10	114 ± 2	195 ± 3	80 ± 3*	97
80	10/10	113 ± 2	189 ± 3*	76 ± 2**	94
120	2/10[g]	114 ± 2	186 ± 10	70 ± 1**	92
140	0/10[f]	113 ± 2	–	–	–
180	0/10[h]	114 ± 3	–	–	–

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No data were calculated for groups with 100% mortality.
[c] Week of death: 1, 1, 1, 1, 3, 5, 8
[d] Week of death: 9 during week 1, 1 during week 8
[e] Week of death: 9 during week 1, 1 during week 5
[f] Week of death: 10 during week 1
[g] Week of death: 7 during week 1, 1 during week 12
[h] Week of death: 9 during week 1, 1 during week 2

and liver weights of males administered 40 or 80 mg/kg were significantly greater than those of the vehicle controls as were the absolute and relative kidney and liver weights of females administered 40, 80 or 120 mg/kg (Table F1). Absolute kidney and liver weights of females administered 80 or 120 mg/kg were also significantly increased. No other biologically significant changes in organ weights or in hematologic or clinical chemistry parameters (Table G1) occurred in dosed rats.

Male rats administered doses of 80 mg/kg or greater and female rats administered doses of 120 mg/kg or greater exhibited a common pattern of clinical findings. For several hours after dosing, animals lay separated in the cage. Respiration was labored and the skin was cyanotic. Rats that survived until the next dosing period appeared normal. Rats that died overnight were often found with wet, reddish-brown stained fur around the mouth and nose. One 120 mg/kg female rat underwent rigor mortis within several minutes after death.

Treatment-associated gross observations in both sexes at necropsy included pulmonary and tracheal edema, cerebral swelling, and meningeal congestion. Dose-related increased incidences of these observations occurred in all male dose groups with the exception of those in the 40 mg/kg group, with virtually all males in the two highest dose groups affected. Increased incidences of these observations in females occurred in the 120 mg/kg and greater groups, with most animals in the 140 and 180 mg/kg groups affected.

Several treatment-related microscopic lesions were attributed to shock with circulatory collapse and subsequent ischemia. These lesions included pulmonary congestion, hemorrhage and edema, and meningeal vascular congestion. These lesions occurred in all dosed male groups and most males administered 120 mg/kg or greater were affected; in females, a similar response occurred at dose levels greater than 80 mg/kg. In general, severity of these lesions increased with dose.

Liver lesions occurred in most males administered 80 mg/kg or greater and females administered 120 mg/kg or greater (Table 4). In general, the severity of these lesions did not vary among dose groups or between sexes. Collectively, the lesions were considered as a hepatotoxic effect directly related to pentachloroanisole administration. Foci of coagulative necrosis consisted of shrunken, eosinophilic hepatocytes still arranged in hepatic cords. Areas of more extensive necrosis had a loss of lobular architecture with individualized, vacuolated, necrotic hepatocytes and mononuclear inflammatory cells scattered in irregularly shaped, clear cavitations. Hepatocytes with glycogen depletion were smaller with condensed cytoplasm in contrast to hepatocytes in the vehicle controls, which had abundant reticulated cytoplasm compatible with the normal glycogen accumulation in well-nourished rodents. Periportal hepatocellular vacuolation in female rats was characterized by numerous small, clear, cytoplasmic vacuoles.

Acute inflammation was characterized by periportal edema and inflammatory infiltrates consisting primarily of neutrophils and a few macrophages. Kupffer cell hypertrophy consisted of enlargement and vacuolation of Kupffer cells primarily in the periportal areas. Bile duct hydropic degeneration was characterized by swollen epithelial cells with abundant, clear cytoplasm and prominent nuclei; mineralized bile ducts had basement membrane deposits of basophilic granular material.

Based on low survival and the occurrence of toxic lesions in the livers of animals in the 16-day and 13-week studies, the dose levels of pentachloroanisole selected for administration by gavage to male and female rats for the 2-year studies were 0, 20, and 40 mg/kg. Because male rats exhibited greater mortality and more severe hepatic lesions than female rats at 80 mg/kg, an additional dose of 10 mg/kg was selected for males to ensure study adequacy.

TABLE 4
Incidences of Liver Lesions in Rats in the 13-Week Gavage Studies of Pentachloroanisole

	Vehicle Control	40 mg/kg	80 mg/kg	120 mg/kg	140 mg/kg	180 mg/kg
Male						
n	10	10	10	10	10	10
Hepatocyte						
Coagulative necrosis	0	0	5* (0.7)[a]	4* (0.5)	4* (0.5)	0
Necrosis	0	0	5* (0.9)	10** (1.2)	9** (0.9)	10** (1.1)
Glycogen depletion	0	0	7** (2.7)	10** (3.9)	10** (3.2)	10** (4.0)
Acute inflammation	0	0	7** (1.6)	10** (1.9)	10** (1.6)	10** (1.6)
Bile duct						
Hydropic degeneration	0	0	6** (1.1)	10** (3.0)	10** (2.9)	10** (2.8)
Mineralization	0	0	3 (0.3)	9** (1.0)	10** (1.3)	9** (1.0)
Kupffer cell						
Hypertrophy	0	0	7** (1.0)	10** (1.9)	10** (1.7)	10** (2.0)
Female						
n	10		10	10	10	10
Hepatocyte						
Coagulative necrosis	0		0	3 (0.6)	2 (0.4)	1 (0.1)
Necrosis	0		0	8** (1.0)	10** (1.1)	9** (1.0)
Glycogen depletion	0		0	8** (3.2)	10** (3.9)	9** (3.6)
Periportal cytoplasmic vacuolation	0		0	8** (0.9)	8** (1.0)	8** (0.9)
Acute inflammation	0		0	8** (1.3)	10** (1.5)	9** (1.3)
Bile duct						
Hydropic degeneration	0		0	8** (2.2)	10** (2.5)	8** (2.4)
Mineralization	0		0	2 (0.3)	5* (0.5)	5* (0.5)
Kupffer cell						
Hypertrophy	0		0	8** (1.4)	10** (1.9)	9** (1.7)

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test
** $P \leq 0.01$
[a] Severity grades: 1=minimal; 2=mild; 3=moderate; 4=marked

2-Year Studies

Survival

Estimates of survival probabilities for male and female rats administered pentachloroanisole by gavage for 2 years are presented in Table 5 and in Kaplan-Meier survival curves (Figure 2). Survival of males in the high-dose group was significantly lower than that of the vehicle controls and was lower than the historical survival rate, 511/820 (62.3%, range 24%-78%), in control male rats from recent NTP corn oil gavage studies. Many deaths in the 40 and 80 mg/kg male groups may have been due to hyperthermia associated with pentachloroanisole administration. Of the 36 deaths in the high-dose

TABLE 5
Survival of Rats in the 2-Year Gavage Studies of Pentachloroanisole

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
Animals initially in study	70	70	70	70
9-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[b]	10	10	10	10
Natural deaths	3	5	7	27
Moribund	23	21	14	5
Accidental deaths[c]	0	4	5	4
Animals surviving to study termination	24	20	24	14
Percent probability of survival at end of study[d]	48	45	53	36
Mean survival days[e]	591	569	556	385
Survival analysis[f]	P=0.004	P=0.442	P=0.709N	P=0.004
Female				
Animals initially in study	70		70	70
9-Month interim evaluation[a]	10		10	10
15-Month interim evaluation[b]	10		10	10
Natural deaths	4		2	2
Moribund	17		13	4
Animals surviving to study termination	29		35	44
Percent probability of survival at end of study[d]	58		71	88
Mean survival days[e]	579		600	617
Survival analysis[f]	P<0.001N		P=0.219N	P<0.001N

[a] Censored from survival analyses. Four males in the 10 mg/kg dose group and two males in the 40 mg/kg dose group died as a result of dosing accidents.
[b] Censored from survival analysis. One male in the 10 mg/kg group, one in the 20 mg/kg group, and five in the 40 mg/kg group died prior to the 15-month interim evaluation. One female rat in the vehicle control group died prior to the 15-month interim evaluation.
[c] Censored from survival analysis
[d] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths and interim evaluations.
[e] Mean of all deaths (uncensored, censored, terminal sacrifice)
[f] 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 dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

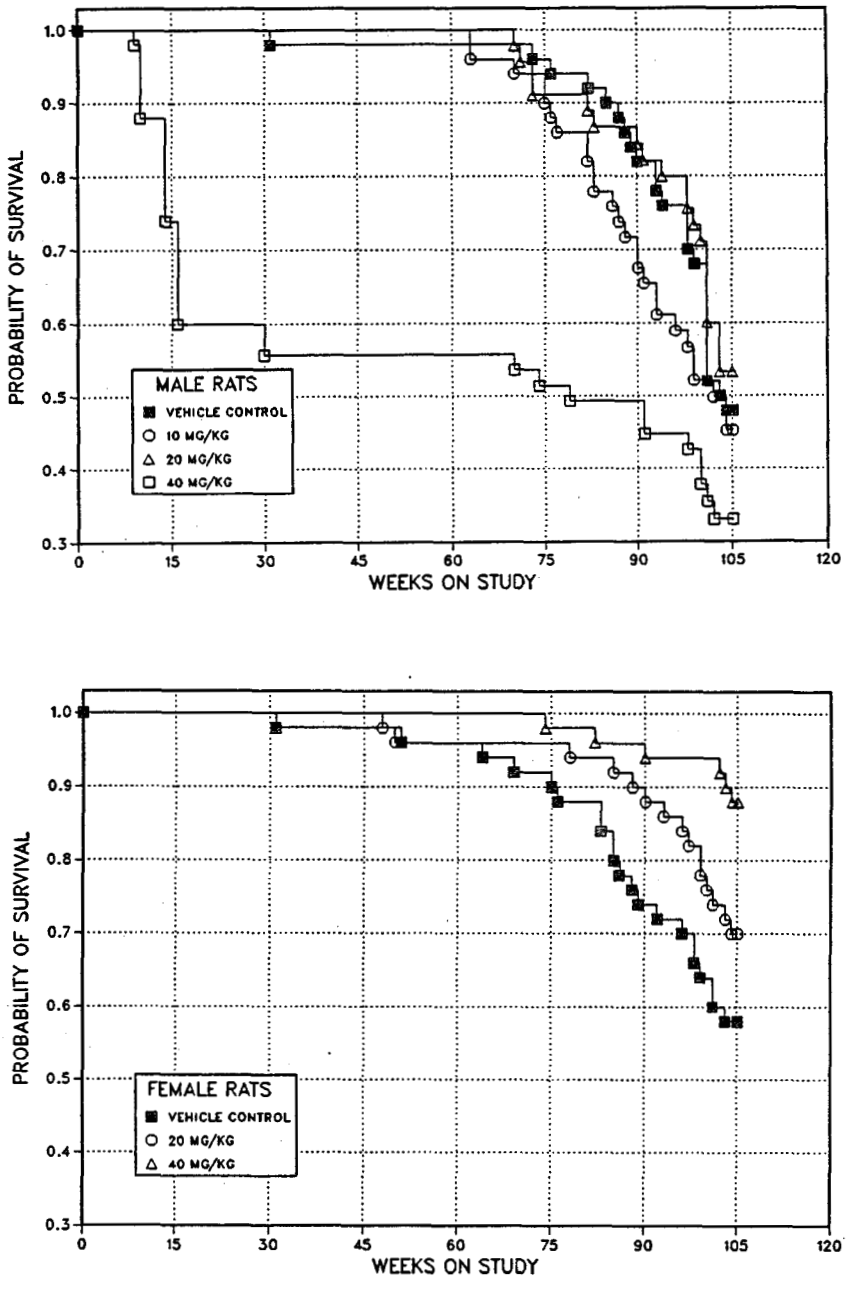

FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered Pentachloroanisole by Gavage for 2 Years

male group, 20 occurred before or during week 16. At 18 months (week 81, Table 6), survival of male rats was greater than 80% for all but the high-dose group.

Mortality in high-dose males often exhibited a striking temporal and cage association. In several instances, multiple cagemates (housed five per cage) with gross and histopathologic lesions consistent with hyperthermia were found dead on the same or consecutive days. For example, four cagemates were found dead on day 96. In another episode, three cagemates died on day 66 and the remaining two cagemates died on day 67. Three cagemates died on day 108 and the remaining two cagemates died on days 109 and 110. In males, the cage association in mortality was highly significant ($P \leq 0.01$; Kruskal-Wallis test) in the high-dose group. A significant ($P \leq 0.05$), but less pronounced effect was observed in the mid-dose group, in which four cagemates died on day 185 of the 2-year studies. There was no correlation between the tier of the rack where the affected cages were located and the occurrence of these episodes, and no apparent association between mortality and caging protocols was noted in the low-dose group or in the vehicle controls. Cage-associated mortality effects were not observed in dosed or vehicle control female rats.

On day 185 of the 2-year rat studies, a building-wide environmental systems failure resulted in temperatures up to 27° C (81° F) and relative humidities up to 94% in the animal rooms for several hours. All female rats and all mice in the pentachloroanisole studies and all other animals housed in the building survived this incident. However, seven male rats from the mid- and high-dose groups were found dead the next morning and were classified as accidental deaths (Table 5). Of these animals, four mid-dose and two high-dose males were cagemates. All mid- and high-dose male rats found dead had gross and histopathologic lesions that were consistent with hyperthermia induced or exacerbated by adverse environmental conditions. Because pentachloroanisole administration may have rendered these animals especially susceptible to heat stress, deaths were considered indirectly related to treatment.

Survival of high-dose females (88%) was greater than the vehicle controls and the low-dose females (Table 7 and Figure 3), and exceeded the historical survival rate of 494/820 (60.2%, range 46%-68%) for control female rats in recent NTP corn oil gavage studies. This survival pattern may have been related to the lower incidences of mammary gland fibroadenomas and mononuclear cell leukemia (Table B1) which frequently result in early death or moribund sacrifice. The reason for the decreased incidences of these neoplasms is uncertain but may have been related to decreased mean body weights of high-dose females.

Body Weights, Organ Weights, and Clinical Findings

Final mean body weights of mid- and high-dose (based on 15 animals) male rats were 7% and 10% lower than that of the vehicle control (Table 6 and Figure 3). The final mean body weight of high-dose female rats was 11% lower than that of the vehicle controls (Table 7 and Figure 3).

At the 9-month interim evaluation, relative kidney, brain, and liver weights of rats administered 20 or 40 mg/kg were significantly greater than those of the vehicle controls, apparently due primarily to the lower body weights (Table F2). At the 15-month interim evaluation, relative kidney and liver weights of 40 mg/kg males were significantly greater than those of the vehicle controls. Absolute and relative kidney and liver weights were significantly increased in dosed females, with the exception of the absolute liver weights of the mid-dose females (Table F3).

Clinical findings during the 2-year studies attributed to pentachloroanisole administration in dosed males included reddened scrotal skin and wet fur around the mouth and neck due to gasping and excessive salivation. These findings, consistent with hyperthermia, were often noted several hours after dosing. Affected animals that survived overnight appeared normal the following morning. A few high-dose males that died before the end of the study underwent rigor mortis within 5 to 30 minutes after death.

During the designated observation period (weeks 21 to 39) for the 9-month interim evaluation, the mean rectal temperature of high-dose male rats was significantly greater ($P \leq 0.05$; Dunnett's test) than that of the vehicle controls (vehicle control, 36.2° C; low-dose, 36.4° C; mid-dose, 36.5° C; high-dose, 36.7° C). During the designated observation period for the 15-month interim evaluation, mean rectal temperatures of males displaying clinical findings consistent with hyperthermia were 37.8° C (based on two

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

Week on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	10 mg/kg Av. Wt. (g)	10 mg/kg Wt. (% of controls)	10 mg/kg No. of Survivors	20 mg/kg Av. Wt. (g)	20 mg/kg Wt. (% of controls)	20 mg/kg No. of Survivors	40 mg/kg Av. Wt. (g)	40 mg/kg Wt. (% of controls)	40 mg/kg No. of Survivors
1	146	70	142	97	70	140	96	70	143	97	70
2	167	70	188	113	70	184	110	70	163	98	70
3	219	70	222	101	70	215	98	70	204	93	70
4	246	70	248	101	70	239	97	70	234	95	70
5	266	70	268	101	70	259	97	70	253	95	70
6	281	70	283	101	70	272	97	70	267	95	70
7	298	70	299	100	70	290	97	70	278	93	70
8	312	70	311	100	70	303	97	70	292	94	70
9	323	70	321	100	70	313	97	70	302	94	70
10	335	70	333	99	70	324	97	70	311	93	64
11	346	70	342	99	70	332	96	70	318	92	64
12	355	70	348	98	70	339	96	70	320	90	64
13	362	70	356	98	70	346	96	70	322	89	64
17	384	70	379	99	70	363	95	70	339	88	50
21	406	70	398	98	70	388	96	70	366	90	50
25	430	70	420	98	70	407	95	70	377	88	50
29	443	70	434	98	70	418	94	65	393	89	48
33	459	69	447	97	70	430	94	65	404	88	46
37	474	69	463	98	70	444	94	65	414	87	43
41[a]	488	59	474	97	60	457	94	54	426	87	33
45	498	59	483	97	60	459	92	54	428	86	33
49	499	59	480	96	60	464	93	54	428	86	33
53	509	59	491	96	59	468	92	54	436	86	33
57	510	59	500	98	59	473	93	54	440	86	33
61	511	59	496	97	59	475	93	54	444	87	32
65[a]	513	53	504	98	48	478	93	47	439	86	29
69	516	49	501	97	48	469	91	45	444	86	26
73	525	48	499	95	47	471	90	42	450	86	25
77	519	47	497	96	43	467	90	41	445	86	24
81	513	47	488	95	43	462	90	41	445	87	23
85	509	46	486	96	38	463	91	39	453	89	22
89	508	42	478	94	35	458	90	39	448	88	22
93	494	41	468	95	29	451	91	37	445	90	20
97	485	38	464	96	27	439	91	36	440	91	20
101	468	29	453	97	23	435	93	28	421	90	15
Terminal sacrifice		24			20			24			14
Mean for weeks											
1-13	281		282	100		274	98		262	93	
14-52	453		442	98		426	94		397	88	
53-101	506		487	96		462	91		442	87	

[a] Interim evaluation occurred during this week.

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

Week on Study	Vehicle Control		20 mg/kg			40 mg/kg		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
1	110	70	111	102	70	110	100	70
2	131	70	132	101	70	130	100	70
3	146	70	146	100	70	144	99	70
4	157	70	157	100	70	152	97	70
5	167	70	165	99	70	161	96	70
6	173	70	170	98	70	165	96	70
7	181	70	176	98	70	169	93	70
8	185	70	179	97	70	175	95	70
9	188	70	180	96	70	179	95	70
10	194	70	190	98	70	183	95	70
11	198	70	194	98	70	185	94	70
12	203	70	197	97	70	189	93	70
13	205	70	198	97	70	191	93	70
17	213	70	206	97	70	198	93	70
21	220	70	213	97	70	202	92	70
25	228	70	221	97	70	213	93	70
29	234	70	227	97	70	217	93	70
33	239	69	232	97	70	225	94	70
37	247	69	238	96	70	225	91	70
41[a]	251	59	248	99	60	234	93	60
45	258	59	253	98	60	236	91	60
49	269	59	262	97	59	242	90	60
53	276	58	271	98	58	243	88	60
57	288	58	280	97	58	250	87	60
61	294	57	288	98	58	256	87	60
65[a]	306	50	297	97	48	261	86	56
69	317	46	306	97	48	268	85	50
73	323	46	309	96	48	276	86	50
77	329	44	316	96	48	276	84	49
81	331	44	318	96	47	286	86	49
85	332	40	320	96	46	290	87	48
89	337	38	322	96	45	295	88	48
93	334	36	325	97	43	300	90	47
97	334	35	330	99	41	302	90	47
101	338	32	331	98	37	301	89	47
Terminal sacrifice		29			35			44
Mean for weeks								
1-13	172		169	98		164	95	
14-52	240		233	97		221	92	
53-101	318		309	97		277	87	

[a] Interim evaluation occurred during this week.

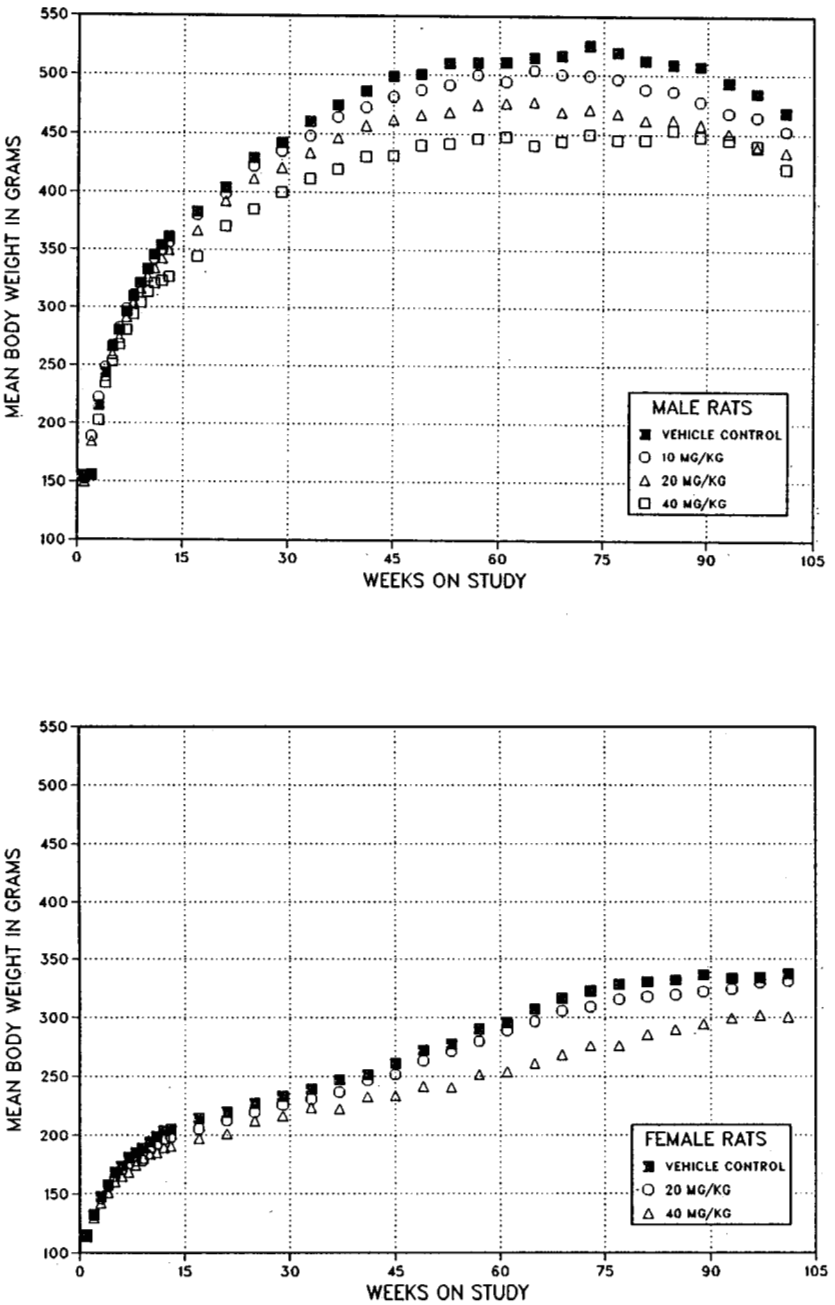

FIGURE 3
Growth Curves for Male and Female Rats Administered Pentachloroanisole by Gavage for 2 Years

measurements from two animals) in the mid-dose group and 38.1° C (based on 10 measurements from 7 animals) in the high-dose group. During the observation period in the 2-year studies, mean rectal temperatures of male rats displaying clinical findings of hyperthermia were 36.8° C (based on two measurements from two animals) for the mid-dose group and 38.2° C (based on 22 measurements from 17 animals) for the high-dose group.

Gross observations noted at necropsy in mid- and high-dose males that died before week 65 included congested lymph nodes, meninges, thymus, and lungs. These changes usually corresponded with microscopically observed congestion, hemorrhage, and/or edema. Collectively, these lesions were considered agonal changes consistent with death from hyperthermia. Generalized severe autolysis, possibly exacerbated by hyperthermia, was also noted in most tissues from these animals.

Hematology and Clinical Chemistry

There were no biologically significant differences in hematology or clinical chemistry parameters in dosed rats at the 9- or 15-month interim evaluation (Tables G2 and G3). Qualitative evaluation of liver porphyrin using 350 nm (ultraviolet) light was negative.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the adrenal gland, brain, kidney, lungs, lymph node, mammary gland, nose, pancreas, testes, thymus, and uterus in rats.

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 Appendixes A for male and B for female rats.

Adrenal Gland: At the 15-month interim evaluation, one high-dose female had a benign adrenal medulla pheochromocytoma and another high-dose female had adrenal medulla hyperplasia. Benign pheochromocytomas of the adrenal medulla occurred with significant positive trend in dosed male rats in the 2-year studies, and the incidences in the mid- and high-dose groups were significantly greater than that of the controls (Table 8). Malignant pheochromocytomas occurred in several control, low-dose, and mid-dose males but not in high-dose male rats. The incidence of pheochromocytomas in the high-dose group was lower than that of the mid-dose group, apparently because of the chemical-related decreased survival of the high-dose group. The historical incidence of benign and malignant pheochromocytomas (combined) in control male rats from recent NTP corn oil gavage studies is 255/804 (31.7%) with a range of 10%-44% (Table A4).

In contrast to the pheochromocytomas, the incidence of focal hyperplasia of the medulla was decreased in dosed male rats. The apparent dose-related decrease was not statistically significant by logistic regression analyses, when survival differences were taken into account (effective hyperplasia rates: vehicle control, 23/48; low-dose, 26/47; mid-dose, 16/41; high-dose, 9/24). In many studies increased incidences of endocrine neoplasms are accompanied by increased incidences of hyperplasia. However, in this study the presence of large pheochromocytomas may have obscured smaller foci of hyperplasia. This is supported by the observations that seven hyperplasias in the high-dose group were seen in rats without adrenal pheochromocytomas, only two of the high-dose males had pheochromocytomas, and none of the nine males with multiple pheochromocytomas had focal hyperplasia.

There was a marginal increase in the incidence of benign pheochromocytomas in high-dose females (Table 8). No malignant pheochromocytomas were observed in dosed or control groups. Incidences of adrenal medulla hyperplasia were also increased in dosed female rats.

The increased incidence of benign pheochromocytomas in high-dose females was not significant, reflecting in part that survival in this group (88%) was quite high compared to survival rates for the concurrent vehicle controls (58%) and the historical controls (60.2%; range 46%-74%). Because of the increased survival, more females in the high-dose group were at risk for neoplasm development compared to other groups with lower survival rates. Therefore, whether the marginal increases in benign

TABLE 8
Incidences of Adrenal Medulla Proliferative Lesions in Rats in the 2-Year Gavage Studies of Pentachloroanisole

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
Hyperplasia				
Overall rates[a]	23/50 (46%)	26/50 (52%)	16/50 (32%)	9/48 (19%)
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates	12/50 (24%)	17/50 (34%)	23/50 (46%)	15/48 (31%)
Terminal rates[b]	6/24 (25%)	10/20 (50%)	16/24 (67%)	8/14 (57%)
First incidence (days)	527	520	684	548
Logistic regression tests[c]	P=0.001	P=0.070	P=0.006	P=0.004
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rates	3/50 (6%)	2/50 (4%)	4/50 (8%)	0/48 (0%)
Terminal rates	0/24 (0%)	1/20 (5%)	2/24 (8%)	0/14 (0%)
First incidence (days)	624	626	704	–[d]
Logistic regression tests	P=0.292N	P=0.509N	P=0.457	P=0.218N
Adrenal Medulla: Benign and Malignant Pheochromocytoma[e]				
Overall rates	15/50 (30%)	18/50 (36%)	25/50 (50%)	15/48 (31%)
Terminal rates	6/24 (25%)	11/20 (55%)	17/24 (71%)	8/14 (57%)
First incidence (days)	527	520	684	548
Logistic regression tests	P=0.005	P=0.156	P=0.010	P=0.021
Female				
Hyperplasia				
Overall rates	10/50 (20%)		18/50 (36%)	25/50 (50%)**
Adrenal Medulla: Benign Pheochromocytoma[f]				
Overall rates	3/50 (6%)		7/50 (14%)	9/50 (18%)
Terminal rates	2/29 (7%)		6/35 (17%)	7/44 (16%)
First incidence (days)	718		673	712
Logistic regression tests	P=0.135		P=0.232	P=0.170

** P<0.01 by logistic regression test
[a] Number of lesion-bearing animals/number of animals with tissues examined microscopically
[b] Observed incidence at terminal kill
[c] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard neoplasms in animals dying prior to terminal kill as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[d] Not applicable; no neoplasms in animal group
[e] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 255/804 (31.7% ± 8.9%); range 10%-44%
[f] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 41/802 (5.1% ± 2.7%); range 0%-10%

pheochromocytomas in high-dose female rats was directly related to pentachloroanisole administration is uncertain.

Proliferative lesions of the adrenal medulla form a morphologic continuum (Plates 1-4). Focal hyperplasia consisted of aggregates of cells with minimally altered cellular arrangement and cytologic features. The affected cells often blended with the surrounding normal parenchyma with minimal or no compression. The cells were sometimes larger than normal cells with a round vesicular nucleus or smaller than normal cells with a hyperchromatic nucleus. Benign pheochromocytomas were well delineated masses which distorted the medulla or extended into the cortex. They were distinguished from hyperplasia by their size, altered architecture (growth pattern), and/or cytologic appearance. The neoplastic cells were arranged in variably sized aggregates, large solid sheets, or trabecular cords several cell layers thick. As in focal hyperplasia, the cells were often larger or smaller than normal cells; generally, the degree of cytologic anaplasia or atypia increased as the lesions increased in size. Because of the morphologic continuum, pheochromocytomas that extended through the capsule were designated as malignant (Plate 3).

Pigmentation: At the 9-month interim evaluation, three high-dose males and eight high-dose females had olfactory epithelial pigment similar to that observed in animals at the end of the 2-year studies.

Treatment-related increased incidences of minimal to mild pigmentation occurred in the 2-year studies in renal tubule epithelium, olfactory epithelium, and hepatocytes of rats, especially females (Table 9). The pigment was observed in scattered individual cells. In general, the severity increased slightly with dose. The decreased incidences of pigmentation in some organs

TABLE 9
Incidences of Pigmentation in Selected Organs of Rats in the 2-Year Gavage Studies of Pentachloroanisole

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
n	50	50	50	50
Kidney				
Renal tubule	1	23** (1.3)[a]	22** (1.8)	16** (2.1)
Nose				
Olfactory epithelium	0	29** (1.0)	40** (1.2)	25** (1.8)
Liver				
Hepatocyte	0	0	1 (1.0)	4* (1.0)
Female				
n	50		50	50
Kidney				
Renal tubule	0		43** (1.9)	45** (2.2)
Nose				
Olfactory epithelium	0[b]		46** (1.4)	50** (2.0)
Liver				
Hepatocyte	0		18** (1.3)	24** (1.0)

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
** $P \leq 0.01$
[a] Severity grades: 1=minimal; 2=mild; 3=moderate; 4=marked
[b] n=49

of high-dose males were attributed to increased early mortality. The pigment consisted of coarse, golden brown to dark brown, intracytoplasmic granules. The pigment granules did not contain iron, bile, or PAS-positive material (periodic acid-Schiff), as revealed by appropriate staining methods. The exact identity of the pigment was not determined. Pigmentation was considered related to pentachloroanisole administration in both sexes.

Pancreas: Acinar cell adenomas of the pancreas were observed in 12 control males, one low-dose male, and one mid-dose male; none were observed in the high-dose males (Table A3). Acinar cell adenomas occurred with a significant negative trend and the incidence in each of the dose groups was significantly lower than that of controls by pairwise comparisons. The historical incidence of this lesion in control male rats from recent NTP studies is 57/815 (7.0%, range 0%-32%). The chemical-related decrease in incidence of adenomas was accompanied by a similar decrease in the incidence of focal hyperplasia (control, 19/49; low-dose, 17/49; mid-dose, 8/49; high-dose, 1/50).

Mammary gland: The incidences of mammary gland fibroadenomas occurred with a significant negative trend in female rats (Table B3). The incidence of fibroadenomas in the high-dose group (14%) was significantly lower than that of concurrent controls (32%) and below the historical range, 18%-56%, observed in control female rats in recent NTP studies. This finding may be related to the significant decrease in mean body weights of these rats. Reductions in the incidence of mammary gland neoplasms associated with reductions in body weight have been observed in other NTP studies.

Uterus: Uterine stromal polyps and stromal sarcomas (combined) also occurred with a significant negative trend in female rats, and the incidence in the high-dose group (14%) was significantly lower than that of controls (30%) (Table B3). In contrast to the mammary gland fibroadenomas, the incidence of stromal neoplasms in the high-dose females was not lower than the lowest historical incidence seen in control female rats in recent NTP studies (stromal polyps: 167/820, 20.4%, range 4%-32%; stromal sarcoma: 12/820, 1.5%, range 0%-4%; stromal polyps and sarcomas combined: 177/820, 21.6%, range 4%-36%).

Miscellaneous lesions: The incidences of mild to moderate congestion and/or hemorrhage of lungs, thymus, brain (meninges), scrotal skin, adrenal cortex, and occasionally various lymph nodes increased almost exclusively in mid- and high-dose males that died before the end of the studies (Table A5). Virtually all of these rats had corresponding gross observations. Most cases of liver centrilobular necrosis occurred in these animals and probably resulted from ischemia subsequent to circulatory collapse. These changes may have been related to pentachloroanisole-induced hyperthermia. Although not a lesion, generalized severe autolysis was also noted in tissues of many of these animals. The early onset and extent of autolysis may have been exacerbated by hyperthermia.

Dosed male rats, especially those in the high-dose group, had decreased incidences of several neoplasms commonly seen in aging F344/N rats including mononuclear cell leukemia, testicular interstitial cell adenomas, and neoplasms of the preputial gland, pituitary pars distalis, thyroid C-cell, and mammary gland (Table A1). Incidences of several aging-associated nonneoplastic lesions such as nephropathy were also decreased in dosed males (Table A5). These findings were attributed to the high early mortality which resulted in fewer aged animals at risk for development of such lesions. The decreased incidences were not significant by survival-adjusted analysis and thus were considered only indirectly related to pentachloroanisole administration.

MICE

16-Day Studies

All mice administered 250 mg/kg body weight or greater died; four males and one female receiving 175 mg/kg also died (Table 10), and these deaths were considered directly related to chemical administration. Most of these mice died on day 2 after receiving only one dose; three deaths were attributed to gavage accidents.

Because of the high early mortality, valid comparisons of body weight gain and mean body weight could not be made for males administered greater than 100 mg/kg or for females administered greater than 175 mg/kg. No biologically significant changes in body weight gains and final mean body weights were noted in the 100 mg/kg male group or the 175 mg/kg female group. The only clinical finding related to pentachloroanisole treatment was inactivity similar to that described for rats in the 16-day studies. No treatment-related gross observations were noted at necropsy.

TABLE 10
Survival and Mean Body Weights of Mice in the 16-Day Gavage Studies of Pentachloroanisole

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	23.8 ± 0.6	27.2 ± 0.7	3.4 ± 0.2	
100	4/5[c]	24.4 ± 0.5	28.3 ± 1.1	3.8 ± 0.5	104
175	0/5[d]	24.0 ± 0.6	–	–	–
250	0/5[e]	23.4 ± 0.4	–	–	–
325	0/5[f]	23.2 ± 0.4	–	–	–
400	0/5[e]	23.8 ± 0.4	–	–	–
Female					
0	4/5[g]	20.0 ± 0.5	23.0 ± 0.0	2.8 ± 0.5	
100	5/5	20.2 ± 0.6	22.6 ± 0.4	2.4 ± 0.2	98
175	4/5[e]	20.8 ± 0.5	23.5 ± 0.3	2.5 ± 0.7	98
250	0/5[h]	19.6 ± 0.5	–	–	–
325	0/5[e]	20.4 ± 0.5	–	–	–
400	0/5[e]	20.2 ± 0.6	–	–	–

[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group are not significant by Williams' or Dunnett's test. No data were calculated for groups with 100% mortality.
[c] Day of death: 4, due to improper gavage technique
[d] Day of death: 2, 2, 2, 3, 4; death on day 4 due to improper gavage technique
[e] Day of death: all deaths occurred on day 2
[f] Day of death: 2, 2, 2, 2, 3
[g] Day of death: 3, due to improper gavage technique
[h] Day of death: 2, 2, 2, 2, 9

13-Week Studies

All males administered 140 and 180 mg/kg pentachloroanisole died, and nine males administered 120 mg/kg died. Six females administered 180 mg/kg died (Table 11). Most deaths occurred during week 1; early deaths and moribund sacrifices were considered directly related to pentachloroanisole administration.

Because of the high early mortality, valid comparisons of final mean body weights and body weight gains could not be made for males administered 120 mg/kg or greater or for females receiving 180 mg/kg. The mean body weights and body weight gains in male mice from the 40 and 80 mg/kg groups were not significantly different from those of the vehicle controls (Table 11). Body weight gains of female mice in the 40 to 120 mg/kg groups were significantly greater than those of the vehicle controls. The mean body weights of all dosed groups were similar to that of the controls.

Valid comparisons of absolute and relative organ weights could not be made for males administered 120 mg/kg or greater or for females administered 180 mg/kg (Table F4). Absolute and relative liver weights of males receiving 80 mg/kg were significantly greater than those of the controls; relative kidney weights of males administered 40 or 80 mg/kg were also significantly increased. In females, absolute and relative liver weights were significantly increased in all dosed groups and absolute and relative kidney weights were increased in the 80, 120, and 140 mg/kg groups. No other biologically significant changes in organ weights or in hematology or clinical chemistry parameters occurred in dosed mice (Tables F4 and G4).

All mice except those in the 40 mg/kg groups exhibited a behavioral pattern of temporary inactivity, recumbency, and separation, similar to that described for rats in the 16-day and 13-week studies. Most

TABLE 11
Survival and Mean Body Weights of Mice in the 13-Week Gavage Studies of Pentachloroanisole

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	24.1 ± 0.2	34.8 ± 0.8	10.7 ± 0.6	
40	10/10	23.5 ± 0.5	34.5 ± 0.8	11.0 ± 0.6	99
80	10/10	23.5 ± 0.4	34.6 ± 0.4	11.1 ± 0.3	99
120	1/10[c]	23.8 ± 0.4	32.0	8.0	92
140	0/10[d]	23.6 ± 0.4	–	–	–
180	0/10[e]	23.9 ± 0.5	–	–	–
Female					
0	10/10	19.2 ± 0.2	25.1 ± 0.3	5.9 ± 0.3	
40	10/10	18.7 ± 0.3	25.7 ± 0.4	7.0 ± 0.4*	102
80	10/10	18.9 ± 0.4	26.0 ± 0.3	7.1 ± 0.3*	104
120	10/10	18.9 ± 0.3	25.9 ± 0.3	7.0 ± 0.3*	103
140	10/10	19.3 ± 0.2	26.3 ± 0.3*	7.0 ± 0.3*	105
180	4/10[e]	19.1 ± 0.3	26.0 ± 0.4	7.0 ± 0.6	104

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No data were calculated for groups with 100% mortality.
[c] Week of death: 2, 3, 3, 3, 4, 4, 4, 6, 10; no standard error calculated due to high mortality in this group
[d] Week of death: 1, 1, 1, 1, 2, 3, 3, 3, 3, 4
[e] Week of death: all occurred during week 1

deaths occurred at night, but several males in the 120 and 140 mg/kg groups that survived overnight displayed inactivity, irregular or deep respiration, ataxia, and/or cyanotic skin immediately before being killed moribund. Two males from each of the 120 and 140 mg/kg groups underwent rigor mortis within 5 minutes after being killed moribund. No treatment-related gross observations were noted at necropsy. Several treatment-associated microscopic lesions were attributed to shock or agonal changes including pulmonary congestion and edema in males administered 80 mg/kg or greater and in females administered 140 or 180 mg/kg. Lymph node and thymic lymphoid depletion and adrenal congestion in males receiving 120 mg/kg pentachloroanisole or greater were also noted.

The incidences of several liver lesions were increased in dosed mice, especially males (Table 12). Severity of the liver lesions in the 40 to 120 mg/kg groups ranged from minimal to mild and generally increased with dose. Hepatocellular cytomegaly and karyomegaly occurred primarily in the centrilobular and midzonal regions. Cytomegaly consisted of enlarged hepatocytes with abundant cytoplasm, while karyomegaly was characterized by large, vesicular nuclei. Pigment in hepatocytes or Kupffer cells of dosed male mice was characterized by cytoplasmic accumulation of yellow-brown granules of undetermined identity; these granules did not contain iron, bile, or PAS-positive material, as revealed by appropriate staining procedures. These liver lesions were considered to be related to pentachloroanisole administration. The decreased incidence or absence of some of these lesions in the 140 and 180 mg/kg groups was attributed to the high early mortality. Decreased severity of some changes in these groups was probably related to the decreased time for lesion progression.

Based on the low survival in the 16-day and 13-week studies and the occurrence of potentially progressive toxic liver lesions in the 13-week studies, the dose levels of pentachloroanisole selected for administration by gavage to male and female mice for the 2-year studies were 0, 20, and 40 mg/kg.

TABLE 12
Incidences of Liver Lesions in Mice in the 13-Week Gavage Studies of Pentachloroanisole

	Vehicle Control	40 mg/kg	80 mg/kg	120 mg/kg	140 mg/kg	180 mg/kg
Male						
n	10	10	10	10	10	10
Hepatocyte, centrilobular/midzonal						
Cytomegaly	0	10** (1.7)[a]	10** (3.0)	2 (2.5)	0	0
Karyomegaly	0	8** (1.1)	10** (2.3)	9** (3.5)	5* (1.2)	0
Pigment	0	4* (1.3)	8** (1.6)	8** (1.8)	4* (1.5)	0
Kupffer cell						
Pigment	0	2 (1.5)	8 (1.7)	3 (2.3)	0	0
Female						
n	10	10	10	10	10	10
Hepatocyte, centrilobular/midzonal						
Cytomegaly	0	0	0	0	4* (2.0)	3 (1.7)
Karyomegaly	0	0	6** (1.0)	9** (1.1)	9** (1.6)	4* (1.8)

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test
** $P \leq 0.01$
[a] Severity grades: 1=minimal; 2=mild; 3=moderate; 4=marked

2-Year Studies

Survival

Estimates of survival probabilities for male and female mice administered pentachloroanisole by gavage for 2 years are presented in Table 13 and in Kaplan-Meier survival curves (Figure 4). The survival of high-dose female mice was significantly lower than that of the vehicle controls due to ovarian abscesses or morbidity from undetermined causes (Table D5). Females alive at 18 months included 76% of the controls, 68% of the low-dose, and 64% of the high-dose group.

TABLE 13
Survival of Mice in the 2-Year Gavage Studies of Pentachloroanisole

	Vehicle Control	20 mg/kg	40 mg/kg
Male			
Animals initially in study	70	70	70
9-Month interim evaluation[a]	10	10	10
15-Month interim evaluation[b]	10	10	7
Natural deaths	2	2	0
Moribund	17	20	22
Accidental deaths[c]	1	1	0
Animals surviving to study termination	30	27	28[d]
Percent probability of survival at end of study[e]	61	55	56
Mean survival days[f]	591	613	597
Survival analysis[g]	P=0.607	P=0.936	P=0.682
Female			
Animals initially in study	70	70	70
9-Month interim evaluation[a]	10	10	10
15-Month interim evaluation[b]	10	10	10
Natural deaths	8	6	8
Moribund	17	18	29
Accidental deaths[c]	1	1	0
Animals surviving to study termination	24	25	16
Percent probability of survival at end of study[e]	51	52	31
Mean survival days[f]	552	541	527
Survival analysis[g]	P=0.035	P=0.966	P=0.042

[a] Censored from survival analyses; one 20 mg/kg female died prior to the 9-month interim evaluation
[b] Censored from survival analysis; three 40 mg/kg females died prior to the 15-month interim evaluation
[c] Censored from survival analysis
[d] Includes one animal that died during the last week of the study
[e] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths and interim evaluations.
[f] Mean of all deaths (uncensored, censored, terminal sacrifice)
[g] 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 dosed columns.

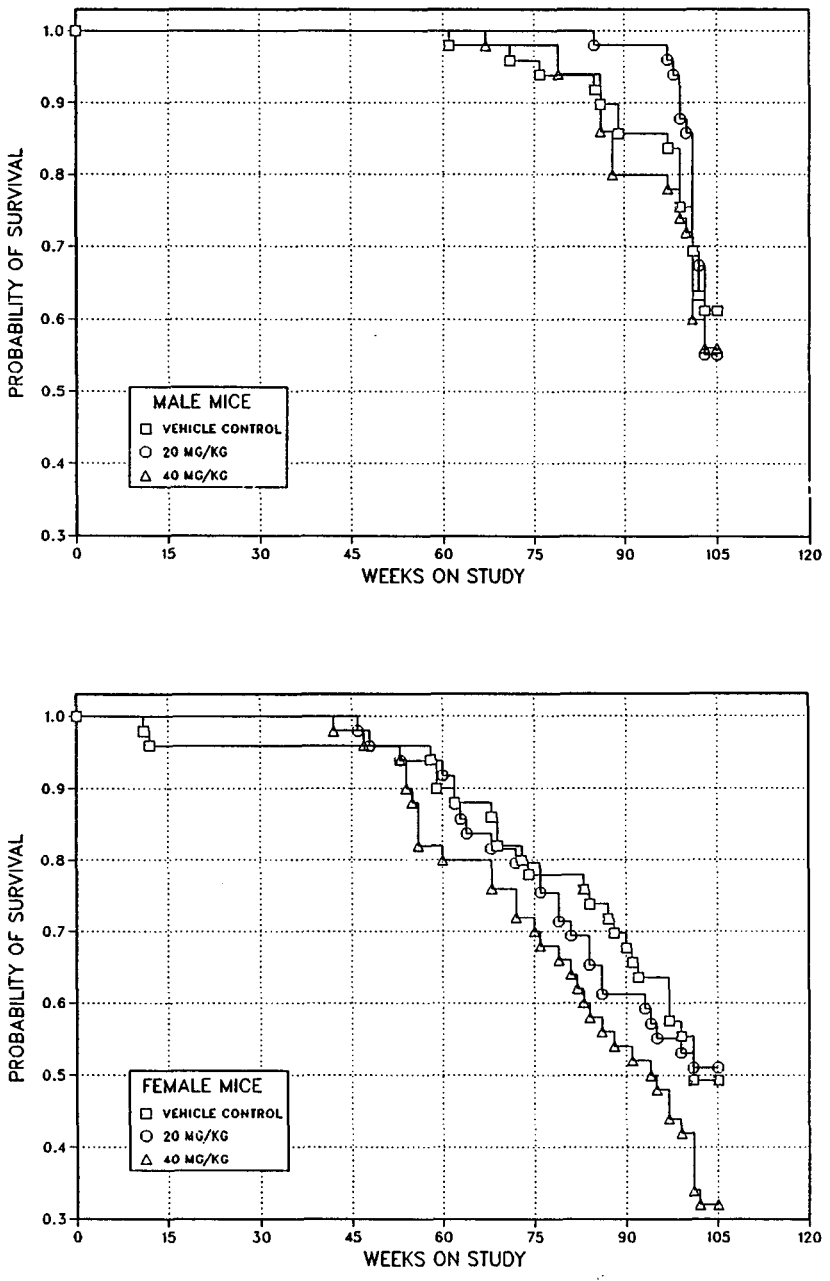

FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered Pentachloroanisole by Gavage for 2 Years

Body Weights, Organ Weights, and Clinical Findings

At the 9-month interim evaluation, absolute and relative liver weights of the high-dose females and relative liver weights of high-dose males were significantly greater that those of the vehicle controls (Table F5). Body weights of high-dose male mice were lower than the vehicle controls throughout the second year; final mean body weights of low- and high-dose male mice were 11% and 17% lower than the body weights of the vehicle controls (Figure 5 and Table 14). No significant differences in final mean body weights were noted in dosed female mice (Table 15). No treatment-related clinical findings were observed for either sex.

Hematology and Clinical Chemistry

There were no biologically significant differences in hematology and clinical chemistry parameters in dosed mice (Tables F5 and G5) at the 9-month interim evaluation. Qualitative evaluation of liver for porphyrin under 350 nm (ultraviolet) light was negative. At the 15-month interim evaluation, serum levels of alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase were greater in dosed male mice than in the vehicle controls. No other biologically significant differences in hematology or clinical chemistry parameters occurred in dosed mice (Table G6). Qualitative evaluation of liver porphyrin under 350 nm (ultraviolet) light was negative.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the adrenal gland, bone, liver, nose, and ovary in mice.

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 Appendixes C for male and D for female mice.

All Organs: The incidence of malignant neoplasms arising at any site in high-dose male mice was significantly greater than that of the controls (Table C3). The increased incidence of malignant neoplasms was due primarily to a significant increase in the incidence of hemangiosarcoma of the liver. Marginal, nonsignificant increases in malignant lymphomas (all types) and hepatocellular carcinomas also contributed to the overall significant increase in malignant neoplasms in the high-dose males.

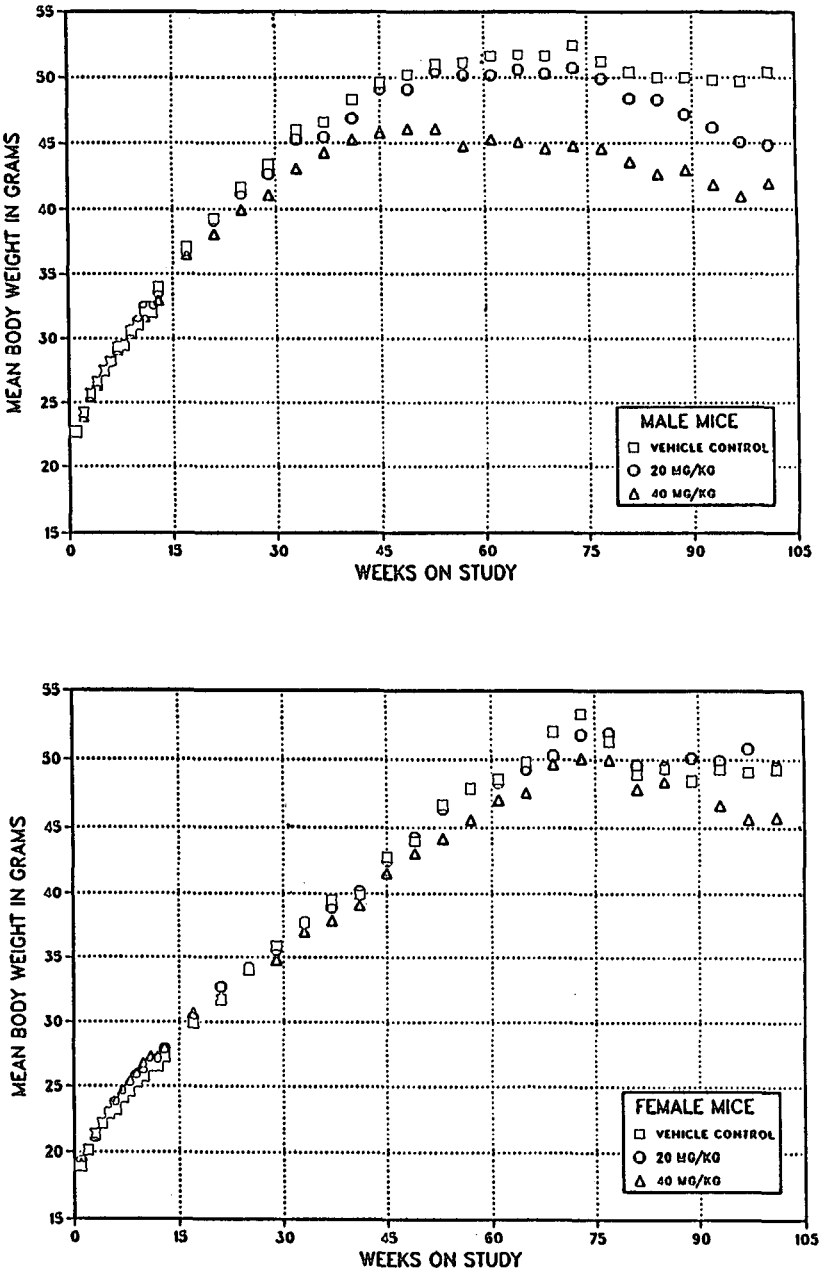

FIGURE 5
Growth Curves for Male and Female Mice Administered Pentachloroanisole by Gavage for 2 Years

TABLE 14
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Pentachloroanisole

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control Number of Survivors	20 mg/kg Av. Wt. (g)	20 mg/kg Wt. (% of controls)	20 mg/kg Number of Survivors	40 mg/kg Av. Wt. (g)	40 mg/kg Wt. (% of controls)	40 mg/kg Number of Survivors
1	22.4	70	22.4	100	70	22.1	99	70
2	24.1	69	24.3	101	70	23.9	99	70
3	25.5	69	25.6	100	70	25.3	99	70
4	26.4	69	26.5	100	70	26.3	100	70
5	27.4	69	27.7	101	70	27.4	100	70
6	28.1	69	28.3	101	70	28.2	100	70
7	29.3	69	29.6	101	70	29.1	99	70
8	29.5	69	29.9	101	70	29.6	100	70
9	30.7	69	31.2	102	70	30.5	99	70
10	31.3	69	31.9	102	70	31.4	100	70
11	32.6	69	33.0	101	70	32.0	98	70
12	32.6	69	33.1	102	70	32.6	100	70
13	34.3	69	34.2	100	70	33.4	97	70
17	37.2	69	37.3	100	70	36.8	99	70
21	39.3	69	39.7	101	70	38.3	98	70
25	41.9	69	41.9	100	70	40.3	96	70
29	43.4	69	43.3	100	70	41.5	96	70
33	45.9	69	45.8	100	70	43.4	95	70
37	46.4	69	46.1	99	70	44.2	95	70
41[a]	48.2	59	47.2	98	60	45.6	95	60
45	49.6	59	49.1	99	60	46.3	93	60
49	50.0	59	49.2	98	60	46.6	93	60
53	51.0	59	50.7	99	60	46.6	91	60
57	51.1	59	50.3	98	60	45.4	89	60
61	51.6	58	50.4	98	60	45.9	89	60
65[a]	51.7	48	50.6	98	50	45.1	87	50
69	51.6	48	50.3	98	50	44.6	86	49
73	52.4	47	50.7	97	50	44.8	86	49
77	51.2	46	49.9	98	50	44.6	87	49
81	50.4	46	48.4	96	50	43.6	87	47
85	50.0	45	48.3	97	50	42.7	85	47
89	50.0	42	47.2	94	49	43.0	86	40
93	49.8	42	46.2	93	49	41.9	84	40
97	49.7	41	45.1	91	48	41.0	83	40
101	50.4	35	44.9	89	36	42.0	83	33
Terminal sacrifice		30			27			28
Mean for weeks								
1-13	28.8		29.1	101		28.6	99	
14-52	44.7		44.4	99		42.6	95	
53-101	50.8		48.7	96		43.9	86	

[a] Interim evaluation occurred during this week.

TABLE 15
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Pentachloroanisole

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control Number of Survivors	20 mg/kg Av. Wt. (g)	20 mg/kg Wt. (% of controls)	20 mg/kg Number of Survivors	40 mg/kg Av. Wt. (g)	40 mg/kg Wt. (% of controls)	40 mg/kg Number of Survivors
1	18.9	70	18.9	100	70	18.7	99	70
2	20.0	70	19.9	100	69	19.9	100	70
3	21.1	70	20.9	99	69	21.0	100	70
4	22.1	70	22.1	100	69	21.9	99	70
5	22.8	70	22.8	100	69	22.6	99	70
6	23.0	70	23.5	102	69	23.6	103	70
7	23.9	70	24.1	101	69	24.5	103	70
8	24.5	70	24.7	101	69	25.2	103	70
9	25.3	70	25.5	101	69	25.8	102	70
10	25.8	70	25.9	100	69	26.8	104	70
11	26.6	69	26.6	100	69	27.3	103	70
12	26.7	69	27.1	102	69	27.3	102	70
13	27.5	68	27.9	102	69	28.1	102	70
17	30.2	68	30.3	100	69	30.7	102	70
21	32.1	68	32.6	102	68	32.2	100	70
25	34.4	68	34.1	99	68	34.2	99	70
29	36.1	68	35.5	98	68	34.7	96	70
33	37.7	68	37.6	100	68	37.2	99	70
37	39.4	68	38.5	98	68	38.0	96	70
41[a]	39.8	58	39.6	100	59	39.3	99	60
45	42.7	58	42.0	98	59	41.9	98	58
49	44.0	58	43.9	100	57	43.5	99	57
53	46.7	58	45.9	98	56	44.8	96	56
57	48.0	58	47.6	99	56	45.9	96	48
61	48.7	55	48.1	99	55	47.5	98	47
65[a]	49.8	44	49.3	99	41	47.6	96	40
69	52.0	41	50.3	97	40	49.7	96	38
73	53.4	40	51.8	97	39	50.1	94	36
77	51.3	39	51.9	101	37	50.0	98	34
81	48.9	38	49.6	101	34	47.9	98	32
85	49.3	36	49.5	100	32	48.4	98	29
89	48.5	34	50.1	103	30	48.4	100	27
93	49.3	31	49.9	101	29	46.7	95	26
97	49.1	28	50.8	104	27	45.7	93	24
101	49.3	25	49.5	100	25	45.8	93	17
Terminal sacrifice		24			25			16
Mean for weeks								
1-13	23.7		23.8	100		24.1	102	
14-52	37.4		37.1	99		36.9	99	
53-101	49.6		49.6	100		47.6	96	

[a] Interim evaluation occurred during this week.

Adrenal gland: Benign pheochromocytomas occurred in four low- and seven high-dose male mice; none was observed in control mice (Tables 16 and C3). Benign pheochromocytomas occurred with a significant positive trend, and the incidence in the high-dose males was significantly greater than that of controls. Moreover, the incidence of benign pheochromocytoma in high-dose males exceeded the historical incidence of such neoplasms (17/682, 2.5%; range 0%-4%;) (Table C4a) observed in control male mice in recent NTP studies. No malignant pheochromocytomas were observed in dosed or control groups. Diffuse hypertrophy of medullary cells and focal hyperplasia also occurred at high incidences in dosed male mice, but not in controls (Table 16). Hypertrophy was characterized by diffuse enlargement of medullary cells. Focal hyperplasia and pheochromocytoma formed a morphologic continuum similar to that observed in rats.

In contrast, a pheochromocytoma was seen in only one low-dose female, and none was seen in the high-dose or control groups (Table D1). Hypertrophy and hyperplasia were also not observed in females.

TABLE 16
Incidences of Adrenal Medulla Proliferative Lesions in Male Mice in the 2-Year Gavage Study of Pentachloroanisole

	Vehicle Control	20 mg/kg	40 mg/kg
Hyperplasia	0/50	13/50**	29/48**
Hypertrophy	0/50	3/50	36/48**
Benign Pheochromocytoma[a]			
Overall rates[b]	0/50 (0%)	4/50 (8%)	7/48 (15%)
Terminal rates[c]	0/30 (0%)	1/27 (4%)	5/27 (19%)
First incidence (days)	–[e]	691	691
Logistic regression tests[d]	P=0.004	P=0.069	P=0.007

** P<0.01 by logistic regression test
[a] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 17/682 (2.5% ± 1.6%); range 0%-4%
[b] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissues examined microscopically
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard tumors in animals dying prior to terminal kill as nonfatal.
[e] Not applicable; no neoplasms in dose group

Liver: Treatment-related liver lesions were considered to be the advanced stages of the alterations seen initially in the 13-week studies. Centrilobular hepatocellular cytomegaly with degeneration and/or necrosis of scattered individual hepatocytes, and pigment accumulation in hepatocytes and Kupffer cells occurred in dosed mice of each sex (Table 17). However, the incidences in males were greater than that in females. At the 15-month interim evaluation, absolute and relative liver weights were marginally increased in dosed male mice and were significantly increased in dosed females (Table F6). Treatment-related liver lesions were considered to be progressive stages of the pathologic processes as seen in the 13-week studies and 9-month interim evaluations. Centrilobular hepatocellular cytomegaly, degeneration and necrosis, and pigment accumulation in hepatocytes and Kupffer cells occurred in dosed male and female mice. However, incidence and severity were greater in males.

Hemangiosarcomas of the liver (Plate 5) occurred with a significant positive trend in dosed male mice, and the incidence in the high-dose group was significantly greater than that of controls by pairwise comparisons (Tables 17 and C3). Moreover, the incidence of hemangiosarcomas of the liver in high-dose males exceeds the historical range, 0%-6% (Table C4d), in control male mice from recent NTP studies. Angiectasis, a possible precursor of vascular neoplasms, was observed in one control and three low-dose males; none was seen in the high-dose group. In contrast to the incidence of hemangioma or hemangiosarcoma in the liver, the incidence of hemangioma or hemangiosarcoma (combined) occurring at any site was also marginally increased, but neither the trend nor the pairwise comparison was significant (Table C3).

Several nonneoplastic liver lesions occurred at higher incidences in dosed male and female mice, especially in males (Table 17). These lesions were similar to those seen in the 13-week study and in the interim evaluations. Several hepatocellular changes diagnosed separately in the 13-week study and in the interim evaluations were defined as cytologic alterations. Cytologic alteration was characterized by centrilobular cytomegaly (enlarged hepatocytes with abundant, finely granular eosinophilic cytoplasm), karyomegaly (enlarged nuclei with prominent chromatin clumping), degeneration and necrosis (cytoplasmic vacuolation or shrinkage, karyorrhexis and karyolysis of individual cells), multinucleated giant cell formation, and rarely erythrophagocytosis (Plates 6, 7, and 8). Hyperplasia of intrahepatic bile ducts and ductules was also observed and consisted of the proliferation of immature epithelial cells arranged in small aggregates, ductular structures, or as individual cells in the portal tracts and periportal hepatic parenchyma. Scattered Kupffer cells and, to a lesser extent hepatocytes, contained fine, yellow-brown granular pigment. Subacute inflammation, characterized by scattered infiltrates of mononuclear inflammatory cells and occasionally neutrophils, was also observed in dosed mice. The severity of these lesions increased slightly with dose, especially in males (Table 17).

Hepatocellular mixed cell foci (single or multiple combined) occurred with a significant, dose-related positive trend in male mice, and the incidence in the high-dose group was significantly greater than that in the controls. Although the incidence of clear cell foci also occurred at a slightly higher incidence in high-dose males, the incidences of basophilic or eosinophilic foci in high-dose male mice were significantly lower than in the controls. The biological significance of these findings is uncertain. Hepatocellular foci (eosinophilic, basophilic, clear cell, or mixed) are distinguished from normal parenchyma primarily on the basis of cytoplasmic staining properties, but they may also exhibit slight alteration in the arrangement of the hepatic plates. Foci are considered preneoplastic lesions and form a morphologic continuum with hepatocellular adenoma and hepatocellular carcinoma. The incidence of hepatocellular neoplasms was not increased in dosed male mice (Tables C1 and C3).

Ovary: The incidence of ovarian abscesses was marginally increased in dosed female mice (control, 12/45; low-dose, 14/36; high-dose, 18/50) (Table D5). Incidences of associated reactive changes, such as bone marrow hypercellularity in low-and high-dose females and splenic hematopoietic cell proliferation in high-dose females, were also increased (Table D5). Ovarian abscesses are usually fatal lesions (Rao *et al.*, 1987), and only a few females with ovarian abscesses survived until the end of the study (1/12; 1/14; 1/18).

TABLE 17
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Gavage Studies of Pentachloroanisole

	Vehicle Control	20 mg/kg	40 mg/kg
Male			
9-Month Interim Evaluation			
n	10	10	10
Hepatocyte, centrilobular			
Cytomegaly	0	10** (3.0)[a]	10** (3.0)
Degeneration	0	10** (1.0)	10** (1.0)
Necrosis	0	10** (1.0)	10** (1.0)
Hepatocyte/Kupffer cell, centrilobular			
Pigmentation	0	0	10** (1.0)
15-Month Interim Evaluation			
n	10	10	10
Hepatocyte, centrilobular			
Cytomegaly	0	10** (3.0)	10** (3.0)
Degeneration	0	10** (2.4)	10** (3.0)
Necrosis	0	10** (2.0)	10** (3.0)
Hepatocyte/Kupffer cell, centrilobular			
Pigmentation	0	10** (1.0)	10** (1.9)
2-Year Study			
n	50	50	50
Hepatocyte, centrilobular			
Cytologic alteration	0	50** (3.1)	50** (3.1)
Kupffer cell			
Pigmentation	1 (1.0)	50** (2.9)	50** (3.0)
Biliary tract hyperplasia	0	47** (1.7)	48** (2.1)
Inflammation, subacute	0	49** (2.0)	49** (2.1)
Mixed cell foci	9	15	27**
Hemangiosarcoma[b]			
Overall rates[c]	2/50 (4%)	8/50 (16%)	10/50 (20%)
Terminal rates[d]	0/30 (0%)	1/27 (4%)	6/28 (21%)
First incidence (days)	701	682	612
Logistic regression tests[e]	P=0.013	P=0.051	P=0.015

TABLE 17
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Gavage Studies of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Female			
9-Month Interim Evaluation			
n	10	9	10
Hepatocyte, centrilobular			
Cytomegaly	0	9** (2.0)	10** (3.0)
Degeneration	0	3 (1.0)	10** (1.0)
Necrosis	0	1 (1.0)	9** (1.0)
Hepatocyte/Kupffer cell, centrilobular			
Pigmentation	0	0	7** (1.0)
15-Month Interim Evaluation			
n	10	10	10
Hepatocyte, centrilobular			
Cytomegaly	0	10** (1.6)	7** (2.7)
Degeneration	0	0	7** (1.3)
Necrosis	0	0	7** (1.4)
Hepatocyte/Kupffer cell, centrilobular			
Pigmentation	0	6** (1.0)	7** (1.1)
2-Year Study			
n	50	50	50
Hepatocyte, centrilobular			
Cytologic alteration	1 (2.0)	34** (1.9)	39** (2.4)
Kupffer cell			
Pigmentation	0	37** (1.6)	48** (2.4)
Biliary tract hyperplasia	1 (1.0)	16** (1.2)	30** (1.9)
Inflammation, subacute	1 (1.0)	28** (1.5)	32** (2.0)

** Significantly different (P≤0.01) from the control group by the logistic regression test
[a] Severity grades: 1=minimal; 2=mild; 3=moderate; 4=marked
[b] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 15/699 (2.1% ± 2.1%); range 0%-6%
[c] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissues examined microscopically
[d] Observed incidence at terminal kill
[e] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards tumors in animals dying prior to terminal kill as nonfatal.

Although the increased incidence of ovarian abscesses in the dosed groups was not statistically significant by life table analysis, these lesions tended to occur earlier in dosed animals. For example, 16/17 high-dose females dying prior to 80 weeks had ovarian abscesses compared with only 6/12 controls. It is likely that this lesion was primarily responsible for the marginally reduced survival observed in high-dose female mice.

Malignant lymphoma: The incidence of malignant lymphomas (all types) was marginally increased in high-dose female mice (Table 18). Because the incidences of these lesions in the present studies were well within historical ranges of controls and were only marginally significant, they were not considered to be related to pentachloroanisole administration.

Osteosarcoma: Osteosarcoma of the bone occurred in two low-dose male mice (Table C1). The historical incidence of this neoplasm in control male mice from recent NTP corn oil gavage studies was 1/700 (0.1%, range 0%-2%). The incidence of these two neoplasms was not significant or dose-related, and therefore was not considered related to pentachloroanisole administration.

Nose: Dose-related increased incidences of nonneoplastic nasal lesions (suppurative inflammation and foreign bodies) were noted in male mice (Table C5) and, to a greater extent, in female mice (Table D5). Foreign bodies were slightly refractile, translucent, pale yellow globules, which may have formed during intranasal instillation from the reflux or regurgitation of corn oil and which caused a secondary suppurative inflammation. The increased incidences in dosed animals may have been due to possible local irritation by pentachloroanisole and/or higher rates of reflux and regurgitation in these dosed animals, thus, a direct relationship to systemic pentachloroanisole toxicity was uncertain.

TABLE 18
Incidences of Malignant Lymphomas in Female Mice in the 2-Year Gavage Study of Pentachloroanisole[a]

	Vehicle Control	20 mg/kg	40 mg/kg
Overall rates[b]	7/50 (4%)	9/50 (16%)	12/50 (20%)
Terminal rates[c]	5/24 (0%)	1/27 (4%)	6/28 (21%)
First incidence (days)	674	472	583
Life table test[d]	P=0.033	P=0.391	P=0.036
Logistic regression test[d]	P=0.057	P=0.360	P=0.049

[a] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 155/698 (22.2% ± 8.3%); range 0%-40%
[b] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissues examined microscopically
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.

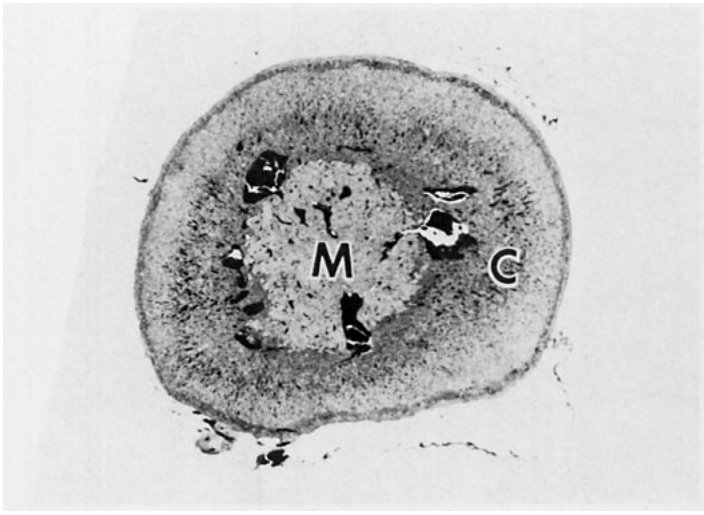

PLATE 1
Adrenal Gland: Normal cross-sectional width ratio of cortex (C) to medulla (M) in a vehicle control male rat from the 2-year gavage study of pentachloroanisole. H&E ×45

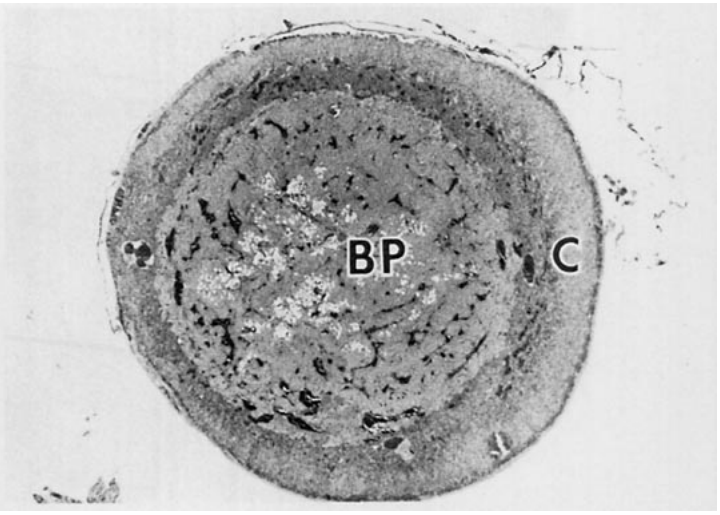

PLATE 2
Adrenal Gland: Compression by expansile benign pheochromocytoma (BP) narrows width of adjacent cortex (C) in a male rat given 10 mg/kg pentachloroanisole in the 2-year gavage study. H&E ×45

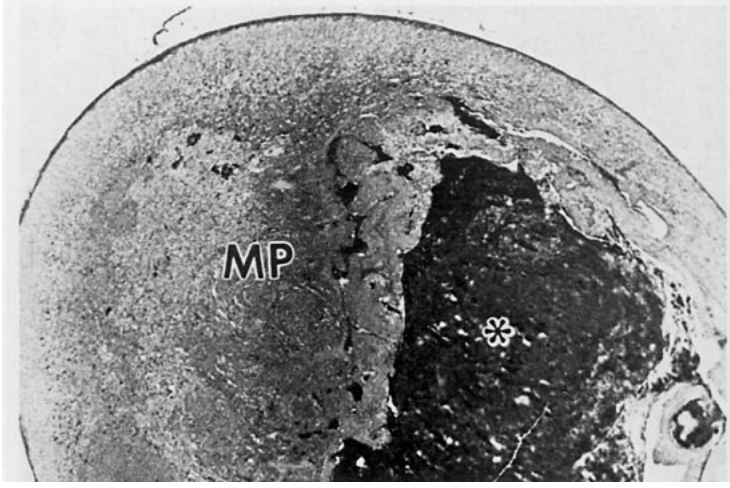

PLATE 3
Adrenal Gland: Malignant pheochromocytoma (MP) obliterates cortex and causes massive enlargement of the adrenal gland. Focal hemorrhage (asterisk) is also present in this male rat given 10 mg/kg pentachloroanisole in the 2-year gavage study. H&E ×45

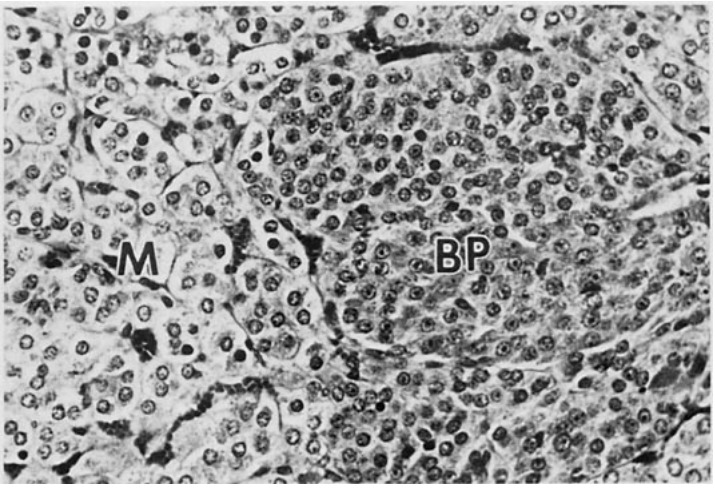

PLATE 4
Adrenal Gland: Higher magnification of benign pheochromocytoma (BP) in a male rat given 20 mg/kg pentachloroanisole in the 2-year gavage study. Note the increased cellular density compared to the adjacent normal medulla (M). H&E ×240

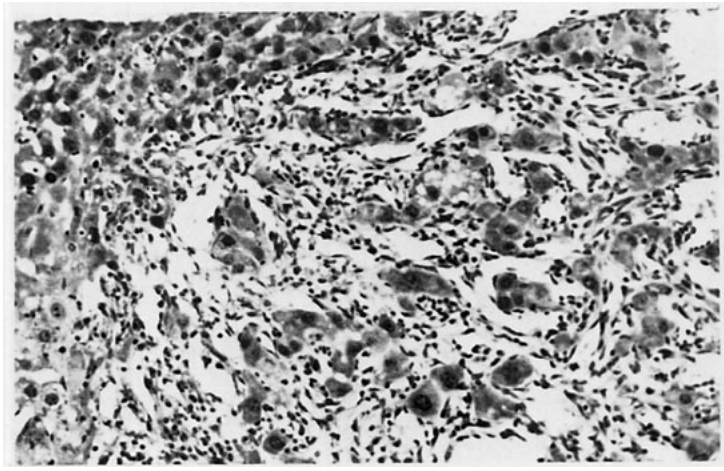

PLATE 5
Liver: Hemangiosarcoma in a male mouse given 20 mg/kg pentachloroanisole in the 2-year gavage study. H&E ×150

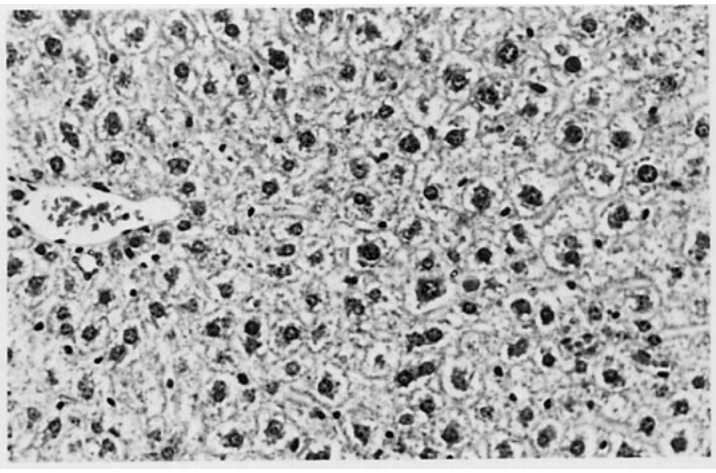

PLATE 6
Liver: Normal hepatic parenchyma from a vehicle control male mouse from the 2-year gavage study of pentachloroanisole. H&E ×240

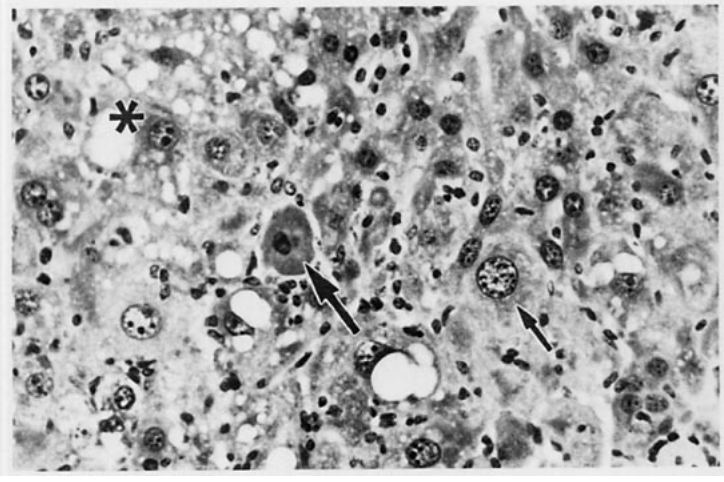

PLATE 7
Liver: Enlarged (cytomegalic) hepatocytes exhibit large (karyomegalic) nuclei (small arrow). Hepatocellular vacuolization (asterisk) and individual cell necrosis (large arrow) are also present in a male mouse given 20 mg/kg pentachloroanisole in the 2-year gavage study. H&E ×240

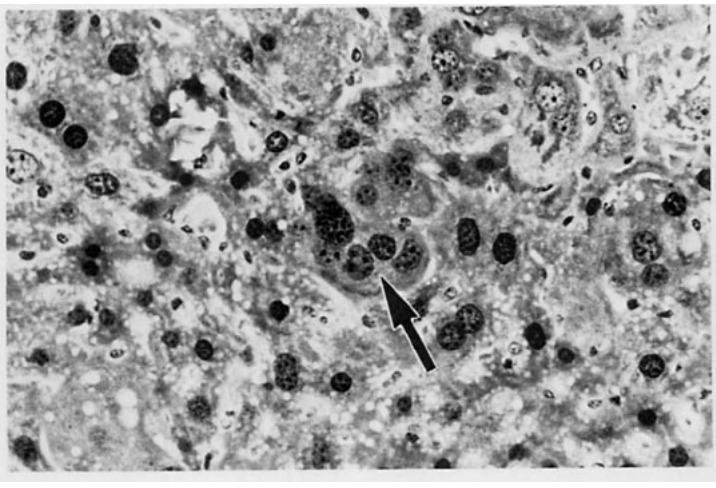

PLATE 8
Liver: Hepatocellular multinucleated giant cell (arrow) from a male mouse given 40 mg/kg pentachloroanisole in the 2-year gavage study. H&E ×240

GENETIC TOXICOLOGY

Pentachloroanisole (10-10,000 μg/plate) was tested for induction of gene mutations in four strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1; Mortelmans *et al.*, 1986). No mutagenic activity was observed in strain TA100 or TA1535 with or without S9, but positive responses were obtained with strains TA98 and TA1537 without S9; no increase in mutagenic colonies occurred in these strains with S9. Precipitation occurred at 1,000 μg/plate and higher concentrations. In the mouse lymphoma assay, pentachloroanisole induced trifluorothymidine resistance in L5178Y cells over a concentration range of 18.75 to 500 μg/mL with Aroclor 1254-induced male F344/N rat liver S9; without S9, the responses were weak, not dose related, and inconsistent (Table E2; McGregor *et al.*, 1987). Precipitation also occurred in this assay at about the 125 μg/mL dose level, and this may have been a factor in the lack of a clear dose-response relationship for all but one of the positive trials. In cytogenetic tests with Chinese hamster ovary cells, pentachloroanisole induced sister chromatid exchanges (Table E3), but not chromosomal aberrations (Table E4), with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9. A delayed harvest protocol was required in the sister chromatid exchange test to offset pentachloroanisole-induced cell cycle delay and allow detection of the positive responses. Delayed harvest was also used for the chromosomal aberrations test to offset the cytotoxicity induced by pentachloroanisole. Precipitation occurred in the sister chromatid exchange and chromosomal aberration tests at pentachloroanisole concentrations of 35 μg/mL and higher.

TOXICOKINETICS

After intravenous administration, pentachloroanisole was found to be rapidly eliminated in both male and female rats and mice (Figure H1) with no major differences between sexes. The elimination of pentachloroanisole can be described by a classical two-compartment model with first-order elimination kinetics. The terminal elimination half-lives in rats and mice were about 1.2 and 1.0 hours, respectively. The calculated plasma clearance was 6.07 L/kg-hr for male rats, 5.61 L/kg-hr for female rats, 8.45 L/kg-hr for male mice, and 10.2 L/kg-hr for female mice. The calculated volume of the central compartment was about 2.41 L/kg for male rats, 2.01 L/kg for female rats, 2.05 L/kg for male mice, and 4.5 L/kg for female mice. High concentrations of pentachlorophenol were observed immediately after the administration of pentachloroanisole in each species and sex. The terminal half-life of pentachlorophenol in both rats and mice was estimated at about 8 hours.

After gavage administration, pentachloroanisole concentrations were found to be lower than those of pentachlorophenol by two to three orders of magnitude in both rats (Figure H2) and mice (Figure H3). For male and female rats and mice the area under the concentration-versus-time curve of pentachloroanisole increased with dose but the dose proportionality was lost above 20 mg/kg (Figure H4). Dose proportionality was seen in all dose groups for the maximum concentration of pentachloroanisole achieved after gavage administration for male and female rats and mice. The variation of C_{max} at each dose group was also high (Figure H5). The area under the concentration-versus-time curve of pentachlorophenol and C_{max} values increased with pentachloroanisole dosage and appeared to be proportional to dose for rats and mice. The area under the concentration-versus-time curve was sex dependent in rats only. The terminal half-life of pentachlorophenol in both rats and mice was estimated to be 5 to 9 hours. This terminal half-life showed no sex-related difference in mice, but was longer for female rats than for male rats.

The bioavailability of pentachloroanisole was found to be low, but it increased with dose. These estimates were based on the dosage normalized area under the concentration-versus-time curve of pentachloroanisole and of pentachlorophenol (H1 and H2).

DISCUSSION AND CONCLUSIONS

Pentachloroanisole is a chlorinated aromatic compound that is widely distributed at low levels in the environment and in foods. Formation of pentachloroanisole may result from degradation of pentachlorophenol, pentachloronitrobenzene, and other structurally related, environmentally ubiquitous, aromatic compounds, many of which are known rodent toxins or carcinogens (NTP, 1982, 1989; Safe, 1984; Silberhorn *et al.*, 1990). For these reasons, and because no information on its toxicity or carcinogenicity in rodents was available, pentachloroanisole was selected for study in F344/N rats and B6C3F$_1$ mice.

Because human exposure to pentachloroanisole would most likely occur from low-level contamination of drinking water and food, the oral route of administration was chosen for these studies. Corn oil was selected as the vehicle for gavage administration because pentachloroanisole is poorly soluble in water and unstable in rodent feed.

Pentachloroanisole differs from pentachlorophenol by a single methyl substitution. The *o*-methylation of pentachlorophenol by microorganisms is considered a major source of environmental pentachloroanisole (Cserjesi and Johnson, 1972). However, in vertebrates, including rats, mice, and humans, pentachlorophenol is metabolized almost entirely to glucuronide and sulfate conjugates, tetrachloroquinone, or less substituted chlorophenols. Pentachloroanisole, if produced at all, is a minor metabolite (Jakobson and Yllner, 1971; Akitake and Kobayashi, 1975; Bose and Fujiwara, 1978; Kobayashi, 1978; Lu *et al.*, 1978; Firestone *et al.*, 1979; Ahlborg and Thunberg, 1980; Crosby *et al.*, 1981; Renner and Mücke, 1986).

In contrast, pentachloroanisole is readily demethylated to pentachlorophenol *in vitro* by porcine hepatic microsomes (Agins *et al.*, 1982; Agins, 1984) and *in vivo* by rainbow trout (Glickman *et al.*, 1977; Lech *et al.*, 1978). Female mice have also been shown to metabolize pentachloroanisole almost entirely to pentachlorophenol or a pentachlorophenol conjugate (Vodicnik *et al.*, 1980).

Several toxic effects, such as tachypnea, central nervous system depression, rapid onset of rigor mortis, and hyperthermia seen in these studies have been previously associated with pentachlorophenol exposure in laboratory and domestic animals and in humans (Deichmann, 1943; Blevins, 1965; Chapman and Robson, 1965; WHO, 1987). Pentachlorophenol-mediated hyperthermia results directly from uncoupling of oxidative phosphorylation (Buffa *et al.*, 1963; Weinbach and Garbus, 1965; WHO, 1987); the other clinical findings are probably secondary. Proliferative lesions of the adrenal medulla have been observed in pentachlorophenol-treated B6C3F$_1$ mice (NTP, 1989) but not in Sprague-Dawley rats (Schwetz *et al.*, 1978). *In vivo* conversion of pentachloroanisole to pentachlorophenol could have occurred in the present studies and might account for some of the findings, but definitive proof could only be provided by metabolism studies.

In the 16-day studies, high early mortality, clinical toxicity, and treatment-related gross observations were noted in rats and mice administered greater than 100 mg/kg pentachloroanisole. In the 13-week studies, most rats and male mice receiving doses of 80 mg/kg or greater died before the end of the studies; survival of female mice was decreased only in the 180 mg/kg group. Clinical findings of toxicity, such as inactivity and dyspnea, were noted in rats and mice receiving from 80 to 180 mg/kg. Chemical-related liver lesions were also observed in dosed rats and mice in the 13-week studies.

Based on these results, doses selected for the 2-year studies were 0, 20, or 40 mg/kg pentachloroanisole. Male rats exhibited the greatest mortality and highest incidence of toxic lesions in the 16-day studies and 13-week studies, and were thus considered to be more sensitive to pentachloroanisole toxicity. Therefore, an additional male rat dose group of 10 mg/kg was included to ensure study adequacy if the maximum tolerated dose was exceeded.

In fact, survival of high-dose male rats was significantly decreased at the end of the 2-year studies

because of numerous early deaths (36/50); most of these deaths (20/36) occurred at or before week 16. Because of high early mortality, incidences of several of the chemical-related neoplasms and nonneoplastic lesions peaked in the mid-dose group and decreased in the high-dose group. High-dose male rats also had decreased incidences of many spontaneous aging-related neoplasms and nonneoplastic lesions due to the lower survival. These were thus only secondarily related to chemical administration.

The deaths of male rats in the 16-day studies and 13-week studies and many early and accidental deaths of the mid- and high-dose male rats in the 2-year studies may have been related to pentachloroanisole-induced hyperthermia. The cause of the significant temporal association of cagemate mortality in these groups is unknown but may have also been hyperthermia-related. Individuals susceptible to hyperthermia may have elevated the ambient cage temperatures, which could have precipitated a "chain-reaction" of hyperthermia among cagemates. The mice were individually housed in polycarbonate cages fitted with disposable fiber filters which may have restricted heat dissipation. There was no evidence that other factors contributed to the cage-related pattern of mortality. Clinical findings consistent with hyperthermia, such as inactivity, wet fur around the mouth and neck, and reddened scrotal skin, were observed in many rats in these higher dose groups. The gross and microscopic findings of generalized congestion, hemorrhage, and edema seen in most of these rats were also consistent with hyperthermia (Jones and Hunt, 1983); other life-threatening lesions were not present. Several high-dose males in the 2-year study exhibiting clinical findings of hyperthermia also had elevated rectal temperatures. Slight, but significant, elevation of mean rectal temperature was also noted in high-dose male rats from the 9-month interim evaluations, even though these animals seemed otherwise normal.

In contrast, female rats and male and female mice had mortality patterns, clinical toxicity, and lesions similar to those seen in male rats only when given high doses of pentachloroanisole in the 16-day and 13-week studies. Although the comparatively greater sensitivity of male rats to pentachloroanisole is obvious, the underlying mechanisms are unknown.

The onset and duration of clinical findings followed an unusual course in affected rats and mice. Clinical findings became evident shortly after dosing, persisted for several hours, and gradually decreased until the survivors appeared normal at the next dosing period. In previous studies, pentachloroanisole and pentachlorophenol were shown to be rapidly metabolized and excreted by rats and mice (Jakobson and Yllner, 1971; Braun *et al.*, 1979; Vodicnik *et al.*, 1980). Thus, the clinical toxicity in these studies may have temporarily paralleled steep absorption, metabolism, and excretion curves of pentachloroanisole and other metabolites, such as pentachlorophenol.

In the 2-year studies, the incidences of proliferative lesions in the adrenal medulla were significantly greater in dosed male rats and male mice. In both species, proliferative lesions constituted a morphologic continuum ranging from hyperplasia (small, non-compressive foci of increased cellularity), to benign pheochromocytomas (discrete, compressive nodules of well-differentiated cells), to malignant pheochromocytomas (large masses with invasion through the glandular capsule). Hypertrophy, which occurred in dosed male mice, denoted a diffuse hyperplasia in which both the number and size of medullary cells were increased.

In male rats, increased incidences of combined benign and malignant pheochromocytomas were noted; after adjusting for high early mortality and low survival, the pheochromocytoma incidence in the high-dose group was significantly greater than in the vehicle controls. The negative trend in adrenal medullary hyperplasia may have been related to the presence of numerous large pheochromocytomas, which may have obscured small hyperplastic foci in the adrenal glands of mid- and high-dose male rats that died early. In high-dose male mice, the incidences of benign pheochromocytomas were significantly increased and exceeded the historical control range and were accompanied by increases in hyperplasia and hypertrophy. Thus, pheochromocytomas were considered directly related to pentachloroanisole administration in male rats and male mice.

In contrast, dosed female rats clearly exhibited increased incidences of adrenal medullary hyperplasia. The slight increase in benign pheochromocytomas in high-dose female rats exceeded the range of the historical controls, but the survival rate of high-dose females was greater than that of concurrent and historical controls. Therefore, it is uncertain if the increase in benign pheochromocytomas in dosed

female rats was entirely related to pentachloroanisole administration. No significant trends in the incidences of adrenal medulla proliferative lesions were noted in dosed female mice.

In other NTP studies, pentachlorophenol administration has also been associated with adrenal medullary neoplasia. Positive trends for benign and malignant pheochromocytomas and medullary hyperplasia were seen in male and female $B6C3F_1$ mice fed purified pentachlorophenol and in male mice fed technical grade pentachlorophenol (NTP, 1989). However, the incidence of adrenal medulla neoplasms was not increased in male or female Sprague-Dawley rats fed 1.0 to 30 mg pentachlorophenol/kg body weight for up to 2 years (Schwetz *et al.*, 1978).

Chemical-related, predominantly site-specific, increases in the incidences of vascular endothelial neoplasms (hemangiosarcomas and hemangiomas) have been previously noted in the hearts of male and female mice exposed to 1,3-butadiene (NTP, 1984; NTP, 1993), the livers and spleens of male mice exposed to *p*-chloroaniline (NCI, 1979), the spleens of male and female rats exposed to cupferron (NCI, 1978), and the livers of humans exposed to vinyl chloride (IARC, 1979b). Thus, analysis of site-specific incidences of these neoplasms is appropriate.

In these studies, the incidences of liver hemangiosarcomas were significantly increased in dosed male mice and exceeded the recent historical control range for male mice. These neoplasms were considered directly related to pentachloroanisole administration. Increased incidences of liver hemangiosarcomas were also seen in male and female mice given purified and technical grade pentachlorophenol in the diet (NTP, 1989).

Several nonneoplastic hepatocellular lesions in dosed mice were considered features of a progressive pathologic process. Hepatocellular cytomegaly, karyomegaly, and pigmentation first appeared in the 13-week studies and were later noted in the 2-year studies. More advanced stages of the pathologic process in the 2-year studies also featured hepatocellular necrosis and degeneration, multinucleated giant cell formation, and erythrophagocytosis. These hepatocellular changes were considered directly related to pentachloroanisole administration. The elevations in serum aminotransferases and sorbitol dehydrogenase seen in dosed male mice in the 15-month interim evaluations were considered to be compatible with the hepatocellular lesions (Loeb, 1989). Other liver lesions, such as Kupffer cell pigmentation, biliary tract hyperplasia, and subacute inflammation, were seen almost exclusively in the 2-year studies, and may have been reactive changes secondary to the hepatocellular lesions.

Collectively, the nonneoplastic liver lesions in these studies resembled lesions previously reported in rats (Kimbrough and Linder, 1978) and mice (NTP, 1989) administered pentachlorophenol in feed. Similar hepatotoxic lesions are also well-documented effects of exposure to many other chlorinated hydrocarbons in rats, mice, and several other species (Safe, 1984; Kuiper-Goodman and Grant, 1986; Birnbaum *et al.*, 1990; NTP, 1991a,b) and may be related to alteration in nuclear DNA activity and smooth endoplasmic reticulum proliferation in affected hepatocytes (Safe, 1984). Similar pathogenic mechanisms may have resulted in the hepatotoxic lesions in mice in the present studies. Increased incidences of hepatocellular mixed cell foci in dosed male mice may have been chemical related. Similar hepatocellular proliferative lesions have previously been associated with exposure to pentachlorophenol (NTP, 1989) and several other chlorinated hydrocarbons (Safe, 1984; Silberhorn *et al.*, 1990).

In the 13-week studies, the liver lesions noted in dosed rats were morphologically distinct from those occurring in mice. In mice, changes indicative of sublethal, progressive hepatotoxicity, such as cytomegaly and karyomegaly, were predominant; in rats, hepatocellular necrosis was more pronounced. These findings suggest that the rat liver lesions may have been a peracute manifestation of toxicity associated with large doses of pentachloroanisole.

Because many affected rats in the 13-week studies died early due to hyperthermia, peracute hepatic ischemia resulting from terminal circulatory collapse may have also contributed to the development of the liver lesions. In the 2-year studies, a similar pathogenic mechanism in dosed male rats may have accounted for the increased incidences of hepatocellular centrilobular necrosis which occurred almost exclusively in animals that died early due to hyperthermia.

Several other nonneoplastic lesions in rats and mice occurred with positive trends but were considered to

be only secondarily related to pentachloroanisole administration. In addition to the pigmentation seen in livers of dosed mice, golden-brown intracytoplasmic pigment was observed in renal tubule epithelium, olfactory epithelium, and hepatocytes of dosed rats. Intracellular pigments, previously associated with chlorinated hydrocarbon exposure, generally fall into two classes: porphyrins and lipofuscin/ceroid.

Because of their porphyrinogenic properties, hexachlorobenzene and certain other chlorinated hydrocarbons often produce intracellular accumulations of porphyrin material in hepatocytes and other cells of dosed animals (Kimbrough, 1972; Safe, 1984; Kuiper-Goodman and Grant, 1986; NTP, 1991b). Often, female animals are more severely affected (San Martin de Viale *et al.*, 1970; Strik *et al.*, 1980; Kuiper-Goodman and Grant, 1986; NTP, 1991b), and rats may be more sensitive than mice (NTP, 1991b). In the present studies, all tests for hepatic porphyrins were negative, but methodological difficulties may have affected the results. Therefore, it is possible that the pigmented material in rat and mouse cells was composed of one or more porphyrins.

Lipofuscins and ceroid are cellular lipopigments that form due to autoxidation of unsaturated lipids. These pigments are seen in aging control rats and mice and in various pathologic conditions of many other species (Cheville, 1983). Lipofuscin/ceroid has also been noted in hepatocytes and other cells of animals exposed to several chlorinated hydrocarbons (McConnell *et al.*, 1978). Because lipofuscin/ceroid variants are somewhat heterogeneous in chemical composition, reactivity with special stains may vary. The results from using special stains in these studies are therefore inconclusive.

In summary, results from the present studies and the literature do not conclusively support either of the two most likely differential diagnoses for the pigment or even indicate that the same material was present in both rats and mice. Additionally, the possibility that the pigment may have been composed of a third material, such as hemosiderin (Kimbrough, 1972), was not entirely eliminated.

Ovarian abscesses in mice are generally fatal lesions of bacterial etiology (Rao *et al.*, 1987). The incidence of these lesions increased marginally in dosed female mice; most affected animals died or were sacrificed moribund before the end of the studies. Thus, the decreased survival of dosed female mice was attributed to some extent to ovarian abscesses. Although no data are available for pentachloroanisole, the immunotoxic properties of pentachlorophenol (Kerkvliet *et al.*, 1982a,b; Holsapple *et al.*, 1984) and other chlorinated hydrocarbons (Kimbrough, 1972; Vos *et al.*, 1980; Safe, 1984) are well documented. Subtle treatment-related immunosuppression may have thus played a role in the pathogenesis of ovarian abscesses in these studies.

Suppurative inflammation and foreign bodies (compatible with corn oil) occurred with increased incidences in the noses of dosed male and female mice. These changes were probably related to intranasal instillation of corn oil containing pentachloroanisole due to reflux or regurgitation and were thus only secondarily related to pentachloroanisole administration. The changes seen in the present studies are apparently distinct from the olfactory epithelial metaplasia and inflammation observed in male and female mice administered pentachlorophenol in feed (NTP, 1989).

Although pentachloroanisole does not contain any molecular features which provide an alert to DNA reactivity (Ashby and Tennant, 1991), and the metabolites of pentachloroanisole are essentially negative in genotoxicity assays, pentachloroanisole gave positive results in three of the four NTP genetic toxicity studies. Pentachloroanisole was shown to be a direct-acting mutagen in frameshift strains of *S. typhimurium* but S9 activation was required for a positive response in the mouse lymphoma assay. Precipitation of pentachloranisole was evident at the effective concentrations in both these assays. Sister chromatid exchanges were induced in Chinese hamster ovary cells with and without S9; these positive responses in the SCE test were obtained only at doses that caused a delay in cell cycling time. The test results are still valid, however, because the mere observation of *in vitro* cytotoxicity is not sufficient to diminish the potential *in vivo* genotoxicity of a chemical; some *in vivo* genotoxins which are active at doses below those which produce observable animal toxicity are detected only at toxic concentrations *in vitro* (Scott *et al.*, 1991). Thus, the results of the genetic toxicity studies of pentachloroanisole are predictive of the results of the studies in rats and mice where benign neoplasms of the adrenal medulla were observed in male rats and mice and hemangiosarcomas of the liver were observed in male mice.

Gavage and intravenous toxicokinetic studies of pentachloroanisole showed no sex-related differences in either the bioavailability or in the peak plasma concentration of pentachloroanisole in rats or mice. The concentration of the metabolite, pentachlorophenol, was higher in female rats than in male rats after gavage administration and the sex-related difference in toxic and carcinogenic response to pentachloroanisole in rats and mice were observed. These findings cannot be attributed to the sex-related differences in systemic availability of pentachloroanisole or to the rate of metabolism of pentachloroanisole to pentachlorophenol.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of pentachloroanisole in male F344/N rats based on increased incidences of benign pheochromocytomas of the adrenal medulla. There was *equivocal evidence of carcinogenic activity* of pentachloroanisole in female F344/N rats based on marginally increased incidences of benign pheochromocytomas of the adrenal medulla. There was *some evidence of carcinogenic activity* of pentachloroanisole in male $B6C3F_1$ mice based on increased incidences of benign pheochromocytomas of the adrenal medulla and hemangiosarcomas of the liver. There was *no evidence of carcinogenic activity* of pentachloroanisole in female $B6C3F_1$ mice given doses of 20 or 40 mg/kg.

Pentachloroanisole administration was associated with increased incidences of adrenal medulla hyperplasia in female rats and increased incidences of pigmentation in the renal tubule epithelium, olfactory epithelium, and hepatocytes of male and female rats. In addition, decreased incidences of pancreatic adenomas and focal hyperplasia in male rats and decreased incidences of mammary gland fibroadenomas and uterine stromal polyps and sarcomas (combined) in female rats were observed. Hyperthermia-related lesions in male rats receiving 20 or 40 mg/kg were considered indirectly related to pentachloroanisole administration.

Pentachloroanisole administration was associated with increased incidences of adrenal medulla hyperplasia and hypertrophy and hepatocellular mixed cell foci in male mice. In male and female mice, nonneoplastic liver lesions associated with pentachloroanisole administration included hepatocellular cytologic alteration, Kupffer cell pigmentation, biliary tract hyperplasia, and subacute inflammation.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF PENTACHLOROANISOLE

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

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	23	21	14	5
Natural deaths	3	9	12	31
Survivors				
Terminal sacrifice	24	20	24	14
Animals examined microscopically	70	70	70	70
Alimentary System				
Intestine large, cecum	(50)	(49)	(48)	(50)
Intestine large, colon	(50)	(50)	(49)	(49)
Intestine large, rectum	(50)	(50)	(49)	(47)
Intestine small, duodenum	(50)	(50)	(49)	(49)
Intestine small, ileum	(50)	(50)	(47)	(50)
Intestine small, jejunum	(50)	(50)	(47)	(50)
Adenoma		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, stomach		1 (2%)		
Hepatocellular adenoma		1 (2%)	1 (2%)	
Mesentery	(11)	(11)	(5)	(9)
Leiomyosarcoma, metastatic, spleen	1 (9%)			
Liposarcoma	1 (9%)			
Pancreas	(49)	(49)	(49)	(50)
Carcinoma, metastatic, stomach			1 (2%)	
Acinar cell, adenoma	12 (24%)	1 (2%)	1 (2%)	
Pharynx	(1)		(2)	(1)
Papilloma squamous	1 (100%)			1 (100%)
Squamous cell carcinoma			1 (50%)	
Salivary glands	(50)	(50)	(48)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Papilloma squamous	1 (2%)			
Stomach, glandular	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)	1 (2%)	
Tongue	(1)	(2)	(4)	(2)
Papilloma squamous		1 (50%)		1 (50%)
Squamous cell carcinoma			1 (25%)	
Cardiovascular System				
Heart	(50)	(50)	(49)	(50)
Schwannoma benign	3 (6%)	1 (2%)		
Endocrine System				
Adrenal gland, cortex	(49)	(50)	(50)	(50)
Adrenal gland, medulla	(50)	(50)	(50)	(48)
Pheochromocytoma malignant	3 (6%)	2 (4%)	3 (6%)	
Pheochromocytoma malignant, multiple			1 (2%)	
Pheochromocytoma benign	11 (22%)	12 (24%)	13 (26%)	6 (13%)
Pheochromocytoma benign, multiple	1 (2%)	5 (10%)	10 (20%)	9 (19%)
Islets, pancreatic	(49)	(49)	(49)	(50)
Adenoma	8 (16%)	2 (4%)	3 (6%)	6 (12%)
Carcinoma	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Endocrine System (continued)				
Parathyroid gland	(49)	(50)	(49)	(50)
Adenoma			1 (2%)	
Pituitary gland	(49)	(50)	(48)	(50)
Pars distalis, adenoma	16 (33%)	22 (44%)	14 (29%)	10 (20%)
Pars distalis, carcinoma	4 (8%)	1 (2%)	1 (2%)	
Pars nervosa, neoplasm NOS		1 (2%)		
Thyroid gland	(50)	(50)	(49)	(50)
C-cell, adenoma	12 (24%)	6 (12%)	7 (14%)	5 (10%)
C-cell, carcinoma	1 (2%)	1 (2%)		
Follicular cell, adenoma	1 (2%)		1 (2%)	
General Body System				
Tissue NOS	(3)			
Genital System				
Preputial gland	(50)	(48)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	5 (10%)	
Carcinoma	6 (12%)	2 (4%)	1 (2%)	1 (2%)
Prostate	(50)	(50)	(50)	(50)
Carcinoma, metastatic, stomach			1 (2%)	
Seminal vesicle	(50)	(50)	(49)	(50)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma	46 (92%)	45 (90%)	42 (84%)	24 (48%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Lymph node	(50)	(50)	(50)	(50)
Bronchial, carcinoma, metastatic, stomach			1 (2%)	
Mediastinal, carcinoma, metastatic, stomach			1 (2%)	
Lymph node, mandibular	(50)	(49)	(49)	(49)
Carcinoma, metastatic, thyroid gland	1 (2%)			
Lymph node, mesenteric	(50)	(50)	(49)	(48)
Spleen	(50)	(49)	(50)	(50)
Carcinoma, metastatic, stomach			1 (2%)	
Leiomyosarcoma	1 (2%)			
Thymus	(46)	(47)	(47)	(47)
Integumentary System				
Mammary gland	(48)	(49)	(50)	(47)
Carcinoma	1 (2%)			
Fibroadenoma	6 (13%)	9 (18%)	2 (4%)	1 (2%)
Skin	(50)	(49)	(50)	(50)
Basal cell carcinoma	2 (4%)			2 (4%)
Carcinosarcoma	1 (2%)			
Keratoacanthoma	1 (2%)	1 (2%)		
Papilloma squamous	1 (2%)		1 (2%)	
Squamous cell carcinoma			2 (4%)	
Trichoepithelioma		1 (2%)		
Sebaceous gland, carcinoma	1 (2%)			
Subcutaneous tissue, fibroma	4 (8%)	1 (2%)		1 (2%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	1 (2%)	3 (6%)	
Subcutaneous tissue, myxosarcoma			1 (2%)	
Subcutaneous tissue, osteosarcoma				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, pharynx			1 (2%)	
Skeletal muscle		(1)		
Fibroma		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Carcinoma, metastatic, pituitary gland	1 (2%)			
Granular cell tumor benign		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	5 (10%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)			
Carcinoma, metastatic, stomach			1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (2%)			
Fibrosarcoma, metastatic, skin			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal gland	1 (2%)			
Mediastinum, hemangiosarcoma	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)			
Squamous cell carcinoma	1 (2%)	2 (4%)		
Special Senses System				
Zymbal's gland	(1)		(1)	
Squamous cell carcinoma			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	23 (46%)	22 (44%)	15 (30%)	8 (16%)
Mesothelioma benign			1 (2%)	
Mesothelioma malignant	3 (6%)	4 (8%)		1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	50	45	26
Total primary neoplasms	182	154	136	79
Total animals with benign neoplasms	49	49	45	26
Total benign neoplasms	127	117	104	66
Total animals with malignant neoplasms	39	33	28	11
Total malignant neoplasms	55	36	32	13
Total animals with metastatic neoplasms	4	1	3	
Total metastatic neoplasms	5	1	8	
Total animals with uncertain neoplasms benign or malignant		1		
Total uncertain neoplasms		1		

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control

Number of Days on Study	2 1 3	5 0 7	5 2 7	5 6 8	5 9 4	6 0 5	6 1 1	6 1 7	6 2 4	6 4 9	6 5 1	6 5 3	6 8 3	6 8 3	6 8 4	6 8 9	7 0 1	7 0 2	7 0 3	7 0 3	7 0 4	7 0 5	7 0 5	7 0 5	7 1 8
Carcass ID Number	0 7 1	0 5 1	0 2 1	0 7 2	0 3 1	0 8 1	0 3 2	0 2 2	0 6 1	0 9 1	0 4 1	0 5 2	0 9 2	1 0 1	1 1 1	0 2 4	0 8 2	2 3	0 8 3	1 0 2	0 1 2	0 4 2	0 7 3	0 7 4	0 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery							+		+						+	+					+	+		+	
Leiomyosarcoma, metastatic, spleen																X									
Liposarcoma															X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																						X			
Pharynx																									
Papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth					+																				
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant									X				X											X	
Pheochromocytoma benign			X							X				X								X			
Pheochromocytoma benign, multiple																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X							X						X				X			
Carcinoma																									

+: 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 Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	726	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	09 3	01 3	01 4	01 5	02 5	03 4	03 5	04 3	04 4	04 5	05 3	05 4	05 5	06 2	06 3	06 4	06 5	07 5	08 4	08 5	09 4	09 5	10 3	10 4	10 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+								+						+						+				11
Leiomyosarcoma, metastatic, spleen																										1
Liposarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell, adenoma	X				X			X			X	X	X	X			X		X		X		X			12
Pharynx																	+									1
Papilloma squamous																	X									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous													X													1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																				+						1
Tooth			+																							2
Cardiovascular System																										
Blood vessel										+						+		+				+				4
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign		X								X													X			3
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										3
Pheochromocytoma benign	X					X				X		X				X						X		X		11
Pheochromocytoma benign, multiple																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X															X			X					X		8
Carcinoma				X																						1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control
(continued)

Number of Days on Study	2 1 3	5 0 7	5 2 7	5 6 8	5 9 4	6 0 5	6 1 1	6 1 7	6 2 4	6 4 9	6 5 1	6 5 3	6 8 3	6 8 3	6 8 4	6 8 9	7 0 1	7 0 2	7 0 3	7 0 3	7 0 4	7 0 5	7 0 5	7 0 5	7 1 8
Carcass ID Number	0 7 1	0 5 1	0 2 1	0 7 2	0 3 1	0 8 1	0 3 2	0 2 2	0 6 1	0 9 1	0 4 1	0 5 2	0 9 2	1 0 1	1 1 1	1 2 4	1 2 2	1 2 3	1 3 3	1 0 2	1 1 2	1 4 2	1 7 3	1 7 4	1 3 3
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X		X		X	X													X
Pars distalis, carcinoma								X									X					X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X		X					X								X
C-cell, carcinoma																				X					
Follicular cell, adenoma																									
General Body System																									
Tissue NOS							+																		
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma		X															X	X	X	X					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																				X					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																X									
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma													X	X										X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																			X	X					
Carcinosarcoma																									
Keratoacanthoma																									
Papilloma squamous																									
Sebaceous gland, carcinoma																									
Subcutaneous tissue, fibroma													X												
Subcutaneous tissue, fibrosarcoma																		X							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 9 3	0 1 3	0 1 4	0 1 5	0 2 5	0 3 4	0 3 5	0 4 3	0 4 4	0 4 5	0 5 3	0 5 4	0 5 5	0 6 2	0 6 3	0 6 4	0 6 5	0 7 5	0 8 4	0 8 5	0 9 4	0 9 5	1 0 3	1 0 4	1 0 5	Total Tissues/ Tumors
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X				X	X	X			X	X				X				X			X		X		16
Pars distalis, carcinoma									X																	4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X	X	X				X					X			X				X		X		12
C-cell, carcinoma																										1
Follicular cell, adenoma																								X		1
General Body System																										
Tissue NOS					+		+																			3
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X								X		2
Carcinoma																				X						6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	46
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+		46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	48
Carcinoma									X																	1
Fibroadenoma	X						X													X						6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										2
Carcinosarcoma																									X	1
Keratoacanthoma				X																						1
Papilloma squamous		X																								1
Sebaceous gland, carcinoma						X																				1
Subcutaneous tissue, fibroma										X							X					X			4
Subcutaneous tissue, fibrosarcoma													X													2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control
(continued)

Number of Days on Study	2 1 3	5 0 7	5 2 7	5 6 8	5 9 4	6 0 5	6 1 1	6 1 7	6 2 4	6 4 9	6 5 1	6 5 3	6 8 3	6 8 3	6 8 4	6 8 9	7 0 1	7 0 2	7 0 3	7 0 3	7 0 4	7 0 5	7 0 5	7 0 5	7 1 8
Carcass ID Number	0 7 1	0 5 1	0 2 1	0 7 2	0 3 1	0 8 1	0 3 2	0 2 2	0 6 1	0 9 1	0 4 1	0 5 2	0 9 2	1 0 1	0 1 1	0 2 4	0 8 2	0 2 3	0 8 3	1 0 2	0 1 2	0 4 2	0 7 3	0 7 4	0 3 3
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																	X								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, thyroid gland																				X					
Pheochromocytoma malignant, metastatic, adrenal gland									X																
Mediastinum, hemangiosarcoma																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma			X																						
Squamous cell carcinoma														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+																					
Zymbal's gland					+																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra													+												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X	X	X	X	X			X										
Mesothelioma malignant									X								X				X				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 9 3	0 1 3	0 1 4	0 1 5	0 2 5	0 3 4	0 3 5	0 4 3	0 4 4	0 4 5	0 5 3	0 5 4	0 5 5	0 6 2	0 6 3	0 6 4	0 6 5	0 7 5	0 8 4	0 8 5	0 9 4	0 9 5	1 0 3	1 0 4	1 0 5	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma														X												1
Carcinoma, metastatic, thyroid gland																										1
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Mediastinum, hemangiosarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+																						2
Zymbal's gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																						+				2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X		X	X				X	X		X		X		X	X	X	X	X	X	X		X	23
Mesothelioma malignant																										3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 10 mg/kg

Number of Days on Study	4 3 5	4 3 7	4 8 8	5 2 0	5 2 1	5 2 9	5 3 5	5 6 8	5 7 0	5 7 2	5 7 7	5 7 8	5 9 8	6 0 4	6 1 3	6 2 5	6 2 6	6 2 7	6 3 4	6 4 0	6 4 9	6 4 9	6 6 7	6 7 8	6 8 4
Carcass ID Number	4 6 1	4 9 1	4 6 2	5 2 1	4 7 1	4 8 1	5 1 1	5 1 2	5 0 1	4 8 2	4 9 2	4 5 1	4 5 2	4 6 3	4 8 3	4 7 2	5 0 2	4 6 4	4 8 4	3 3 1	5 0 3	5 1 3	4 4 1	4 8 5	4 5 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, stomach		X																							
Hepatocellular adenoma																									
Mesentery				+				+								+	+	+						+	
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X																							
Tongue																									
Papilloma squamous																									
Tooth				+																					
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																	X								
Pheochromocytoma benign																	X								
Pheochromocytoma benign, multiple				X																				X	
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X			X	X		X	X				X				X			X	X	X	X	X
Pars distalis, carcinoma																									
Pars nervosa, neoplasm NOS				X																					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X																X					
C-cell, carcinoma																						X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 10 mg/kg
(continued)

Number of Days on Study	6 8 7	6 8 9	7 0 9	7 2 4	7 2 6	7 3 3	7 3 3	7 3 3	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	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	4 9 3	5 2 2	5 0 4	4 6 5	5 1 4	4 4 2	5 2 3	5 2 4	4 9 4	4 9 5	5 0 5	5 1 5	5 2 5	4 3 2	4 3 3	4 3 4	4 3 5	4 4 3	4 4 4	4 4 5	4 5 4	4 5 5	4 7 3	4 7 4	4 7 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, stomach																										1
Hepatocellular adenoma																		X								1
Mesentery		+									+		+				+			+						11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell, adenoma				X																						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Tongue			+				+																			2
Papilloma squamous			X																							1
Tooth																										1
Cardiovascular System																										
Blood vessel			+						+		+		+													4
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign											X															1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																			X							2
Pheochromocytoma benign		X		X	X	X								X						X	X	X	X	X	X	12
Pheochromocytoma benign, multiple			X							X						X										5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X																					2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X			X				X				X	X		X			X	X	X		22
Pars distalis, carcinoma																		X								1
Pars nervosa, neoplasm NOS																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X	X								X															X	6
C-cell, carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 10 mg/kg
(continued)

Number of Days on Study	4 3 5	4 3 7	4 8 8	5 2 0	5 2 1	5 2 9	5 3 5	5 6 8	5 7 0	5 7 2	5 7 7	5 7 8	5 9 8	6 0 4	6 1 3	6 2 5	6 2 6	6 2 7	6 3 4	6 4 0	6 4 9	6 6 9	6 7 7	6 8 8	6 8 4
Carcass ID Number	4 6 1	4 9 1	4 6 2	5 2 1	4 7 1	4 8 1	5 1 1	5 1 2	5 0 1	4 8 2	4 9 2	4 5 1	4 5 2	4 6 3	4 8 3	4 5 2	5 7 2	4 0 2	4 6 4	4 8 4	5 3 1	5 0 3	4 1 3	4 4 5	4 5 3
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoma												X													
Carcinoma											X		X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma				X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Trichoepithelioma															X										
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																				+					
Fibroma																				X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 10 mg/kg
(continued)

Number of Days on Study	6 8 7	6 8 9	7 0 9	7 2 4	7 2 6	7 3 3	7 3 3	7 3 3	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	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	4 9 3	5 2 2	5 0 4	4 6 5	5 1 4	4 4 2	5 2 3	5 2 4	4 9 4	4 9 5	5 0 5	5 1 5	5 2 5	4 3 2	4 3 3	4 3 4	4 3 5	4 4 3	4 4 4	4 4 5	4 5 4	4 5 5	4 7 3	4 7 4	4 7 5	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma																										2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	45
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Fibroadenoma		X		X		X	X	X	X						X		X						X			9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																									X	1
Trichoepithelioma																										1
Subcutaneous tissue, fibroma	X																									1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Fibroma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 10 mg/kg
(continued)

Number of Days on Study	4	4	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6
	3	3	8	2	2	2	3	6	7	7	7	7	9	0	1	2	2	2	3	4	4	4	6	7	8	
	5	7	8	0	1	9	5	8	0	2	7	8	8	4	3	5	6	7	4	0	9	9	7	8	4	
Carcass ID Number	4	4	4	5	4	4	5	5	5	4	4	4	4	4	4	4	5	4	4	4	5	5	4	4	4	
	6	9	6	2	7	8	1	1	0	8	9	5	5	6	8	7	0	6	8	3	0	1	4	8	5	
	1	1	2	1	1	1	1	2	1	2	2	1	2	3	3	2	2	4	4	1	3	3	1	5	3	
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Granular cell tumor benign					X																					
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																					X	X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Squamous cell carcinoma														X									X			
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Ear	+																									
Eye			+			+				+				+												
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear			X	X	X							X			X	X	X	X	X	X						
Mesothelioma malignant				X				X										X								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 10 mg/kg
(continued)

Number of Days on Study	6 8 7	6 8 9	7 0 9	7 2 4	7 2 6	7 3 3	7 3 3	7 3 3	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	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	4 9 3	5 2 2	5 0 4	4 6 5	5 1 4	4 4 2	5 2 3	5 2 4	4 9 4	4 9 4	5 0 5	5 1 5	5 2 5	4 3 2	4 3 3	4 3 4	4 3 5	4 4 3	4 4 4	4 4 5	4 5 4	4 5 5	4 7 3	4 7 4	4 7 5	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor benign																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X								X						X										5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear																										1
Eye											+							+	+							7
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X		X	X			X	X	X		X	X	X				X						22
Mesothelioma malignant		X																								4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg

Number of Days on Study	1 8 5	1 8 5	1 8 5	1 8 5	1 8 5	4 8 6	4 9 3	5 0 7	5 0 9	5 6 8	5 7 8	6 2 8	6 3 3	6 5 4	6 8 3	6 8 4	6 8 7	6 9 7	7 0 1	7 0 3	7 0 4	7 0 4	7 0 5	7 1 8	7 1 8
Carcass ID Number	2 9 1	2 9 2	2 9 3	2 9 4	3 8 1	3 5 1	3 0 1	3 8 2	3 2 1	3 0 2	3 5 2	3 0 3	3 5 3	3 3 2	3 3 3	3 6 1	3 3 1	3 7 1	3 4 1	3 1 1	3 2 2	3 6 2	2 9 5	3 0 4	3 3 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X									
Mesentery								+										+							
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, stomach											X														
Acinar cell, adenoma																									
Pharynx																		+							
Squamous cell carcinoma																		X							
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma											X														
Tongue								+											+						
Squamous cell carcinoma								X																	
Cardiovascular System																									
Blood vessel																							+		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								X	
Pheochromocytoma malignant, multiple																						X			
Pheochromocytoma benign																		X		X				X	
Pheochromocytoma benign, multiple																X	X				X				
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Pituitary gland	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X			X			X			X	X		
Pars distalis, carcinoma														X											
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X						X		
Follicular cell, adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg
(continued)

Number of Days on Study	7 1 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	
Carcass ID Number	3 8 3	3 0 5	3 1 2	3 1 3	3 1 4	3 1 5	3 2 3	3 2 4	3 2 5	3 4 2	3 3 5	3 4 3	3 4 4	3 4 5	3 5 4	3 5 5	3 6 3	3 6 4	3 6 5	3 7 2	3 7 3	3 7 4	3 7 5	3 8 4	3 8 5	Total Tissues/ Tumors	
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular adenoma																										1	
Mesentery	+																		+					+		5	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Carcinoma, metastatic, stomach																										1	
Acinar cell, adenoma																	X									1	
Pharynx	+																									2	
Squamous cell carcinoma																										1	
Salivary glands	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma																										1	
Tongue								+				M						+								4	
Squamous cell carcinoma																										1	
Cardiovascular System																												
Blood vessel								+					+			+							+			5	
Heart	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Endocrine System																												
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Pheochromocytoma malignant							X						X													3	
Pheochromocytoma malignant, multiple																										1	
Pheochromocytoma benign		X	X	X	X	X	X	X			X					X		X								13	
Pheochromocytoma benign, multiple	X									X				X			X		X	X	X					10	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma							X																X			3	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma																										1	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Pars distalis, adenoma		X		X					X					X		X			X	X	X			X		14	
Pars distalis, carcinoma																										1	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
C-cell, adenoma										X			X				X	X						X		7	
Follicular cell, adenoma	X																									1	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg
(continued)

Number of Days on Study	1 1 1 1 1 4 4 5 5 5 5 6 6 6 6 6 6 7 7 7 7 7 7 7 8 8 8 8 8 8 9 0 0 6 7 2 3 5 8 8 8 9 0 0 0 0 0 1 1 5 5 5 5 5 6 3 7 9 8 8 8 3 4 3 4 7 7 1 3 4 4 5 8 8
Carcass ID Number	2 2 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 2 3 3 9 9 9 9 8 5 0 8 2 0 5 0 5 3 3 6 3 7 4 1 2 6 9 0 3 1 2 3 4 1 1 1 2 1 2 2 3 3 2 3 1 1 1 1 1 2 2 5 4 4
General Body System	
None	
Genital System	
Epididymis	+ +
Preputial gland	+ +
Adenoma	
Carcinoma	
Prostate	+ +
Carcinoma, metastatic, stomach	X
Seminal vesicle	+ + + + + + + + + + M + + + + + + + + + + + + + +
Testes	+ +
Interstitial cell, adenoma	X X X X X X X X X X X X X X X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Bronchial, carcinoma, metastatic, stomach	X
Mediastinal, carcinoma, metastatic, stomach	X
Lymph node, mandibular	+ + + + + + M + + + + + + + + + + + + + + + + + +
Lymph node, mesenteric	+ + + + + + + + + + M + + + + + + + + + + + + + +
Spleen	+ +
Carcinoma, metastatic, stomach	X
Thymus	+ + + + + + + + + + + + + M + + + + + + + + + + M
Integumentary System	
Mammary gland	+ +
Fibroadenoma	X X
Skin	+ +
Papilloma squamous	
Squamous cell carcinoma	
Subcutaneous tissue, fibrosarcoma	X X
Subcutaneous tissue, myxosarcoma	X
Musculoskeletal System	
Bone	+ +
Squamous cell carcinoma, metastatic, pharynx	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	7 1 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	
Carcass ID Number	3 8 3	3 0 5	3 1 2	3 1 3	3 1 4	3 1 5	3 2 3	3 2 4	3 2 5	3 4 2	3 3 5	3 4 3	3 4 4	3 4 5	3 5 4	3 5 5	3 6 3	3 6 4	3 6 5	3 7 2	3 7 3	3 7 4	3 7 5	3 8 4	3 8 5		Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma								X			X	X		X				X								5
Carcinoma																	X									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, metastatic, stomach																											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
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		42
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Bronchial, carcinoma, metastatic, stomach																											1
Mediastinal, carcinoma, metastatic, stomach																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, metastatic, stomach																											1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Fibroadenoma																											2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Papilloma squamous							X																				1
Squamous cell carcinoma	X				X																						2
Subcutaneous tissue, fibrosarcoma															X												3
Subcutaneous tissue, myxosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Squamous cell carcinoma, metastatic, pharynx																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg
(continued)

Number of Days on Study	1 8 5	1 8 5	1 8 5	1 8 5	1 8 5	4 8 6	4 9 3	5 0 7	5 0 9	5 0 8	5 6 8	6 7 8	6 2 8	6 3 3	6 5 4	6 8 3	6 8 4	6 8 7	6 9 7	7 0 1	7 0 3	7 0 4	7 0 4	7 0 5	7 1 8	7 1 8
Carcass ID Number	2 9 1	2 9 2	2 9 3	2 9 4	3 8 1	3 5 1	3 0 1	3 8 2	3 2 1	3 0 2	3 5 2	3 0 3	3 5 3	3 3 3	3 3 2	3 3 3	3 6 1	3 3 1	3 7 1	4 1 1	1 1 1	2 2 2	2 6 2	2 9 5	3 0 4	3 3 4
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																							X			
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X		
Carcinoma, metastatic, stomach											X															
Fibrosarcoma, metastatic, skin																	X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																		+								
Eye															+											
Zymbal's gland										+																
Squamous cell carcinoma										X																
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X		X			X				X		X	X		X					
Mesothelioma benign																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	719	733	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	736	736	
Carcass ID Number	38 3	30 5	31 2	31 3	31 4	31 5	32 3	32 4	32 5	42 2	33 5	34 3	44 4	45 5	45 4	55 5	56 3	64 4	65 5	67 2	73 3	74 4	75 5	84 4	85 5	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																				X						2
Carcinoma, metastatic, stomach																										1
Fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye						+																				2
Zymbal's gland																										1
Squamous cell carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X							X						X		X	X		X			X		15
Mesothelioma benign	X																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg (continued)

Number of Days on Study	5 1 4	5 4 8	5 9 2	6 3 5	6 3 6	6 8 4	6 9 6	6 9 7	6 9 7	7 0 2	7 0 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 2	2 4 3	2 3 3	1 7 2	1 7 3	1 5 3	1 7 4	1 5 4	2 2 2	1 9 3	2 4 4	1 5 5	1 7 5	1 8 5	1 9 4	1 9 5	2 0 2	2 0 3	2 0 4	2 0 5	2 2 4	2 2 5	2 3 4	3 3 5	2 4 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																+					+	+		+		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																						+				1
Papilloma squamous																						X				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																		+				+				2
Papilloma squamous																		X								1
Cardiovascular System																										
Blood vessel															+	+	+		+			+				5
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign		X									X			X			X			X		X				6
Pheochromocytoma benign, multiple				X		X	X		X	X					X				X		X			X		9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X						X		X			X										X	X			6
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X	X		X	X		X			X								X		X	X	10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X			X	X				X				X												5
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	0 6 0	0 6 6	0 6 6	0 6 6	0 6 7	0 6 7	0 6 6	0 9 6	0 9 6	0 9 6	0 9 6	0 9 6	0 9 7	0 9 7	1 0 8	1 0 8	1 0 8	1 0 9	1 0 9	1 0 9	1 1 0	1 1 5	1 8 5	2 0 6	2 0 6	4 8 8
Carcass ID Number	1 5 1	1 6 1	1 6 2	1 6 3	1 6 4	1 6 5	1 8 1	1 8 2	1 8 3	1 8 4	2 2 1	1 7 1	2 0 1	2 1 1	2 1 2	2 1 3	2 1 4	2 4 1	2 4 2	2 1 5	1 9 1	1 9 2	2 3 1	2 3 2	2 2 3
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, osteosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	5 1 4	5 4 8	5 9 2	6 3 5	6 3 6	6 8 4	6 9 6	6 9 7	6 9 7	7 0 2	7 0 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 2	2 4 3	2 3 3	1 7 2	1 7 3	1 5 3	1 7 4	1 5 4	2 2 2	1 9 3	2 4 4	1 5 5	1 7 5	1 8 5	1 9 4	1 9 5	2 0 2	2 0 3	2 0 4	2 0 5	2 2 4	2 3 5	2 2 4	2 3 4	3 3 5	2 4 5	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma										X																	1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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		24
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	M	+	+	47
Integumentary System																											
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibroadenoma																										X	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma		X																	X								2
Subcutaneous tissue, fibroma								X																			1
Subcutaneous tissue, osteosarcoma											X																1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X					X															2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																				+			+				2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2	4
	6	6	6	6	6	6	9	9	9	9	9	9	9	0	0	0	0	0	0	1	8	8	0	0	8
	0	6	6	6	7	7	6	6	6	6	6	7	7	8	8	8	9	9	9	0	5	5	6	6	8
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	2	1	2	2	2	2	2	2	2	2	1	1	2	2	2
	5	6	6	6	6	6	8	8	8	8	2	7	0	1	1	1	1	4	4	1	9	9	3	3	2
	1	1	2	3	4	5	1	2	3	4	1	1	1	1	2	3	4	1	2	5	1	2	1	2	3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	5 1 4	5 4 8	5 9 2	6 3 5	6 3 6	6 8 4	6 9 6	6 9 7	6 9 7	7 0 2	7 0 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 2	2 4 3	2 3 3	1 7 2	1 7 3	1 5 3	1 7 4	1 5 4	1 2 2	2 9 3	1 4 4	2 4 5	1 5 5	1 7 5	1 8 5	1 9 4	1 9 5	2 0 2	2 0 3	2 0 4	2 0 5	2 2 4	2 2 5	2 3 4	2 3 5	2 4 5	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X				X	X		X	X		X	X					X								8
Mesothelioma malignant																						X				1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Pentachloroanisole

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	12/50 (24%)	17/50 (34%)	23/50 (46%)	15/48 (31%)
Adjusted rates[b]	37.4%	61.9%	73.6%	70.8%
Terminal rates[c]	6/24 (25%)	10/20 (50%)	16/24 (67%)	8/14 (57%)
First incidence (days)	527	520	684	548
Life table tests[d]	P=0.010	P=0.077	P=0.020	P=0.015
Logistic regression tests[d]	P=0.001	P=0.070	P=0.006	P=0.004
Cochran-Armitage test[d]	P=0.256			
Fisher exact test[d]		P=0.189	P=0.018	P=0.282
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rates	3/50 (6%)	2/50 (4%)	4/50 (8%)	0/48 (0%)
Adjusted rates	8.2%	7.8%	14.7%	0.0%
Terminal rates	0/24 (0%)	1/20 (5%)	2/24 (8%)	0/14 (0%)
First incidence (days)	624	626	704	–[e]
Life table tests	P=0.282N	P=0.603N	P=0.491	P=0.260N
Logistic regression tests	P=0.292N	P=0.509N	P=0.457	P=0.218N
Cochran-Armitage test	P=0.147N			
Fisher exact test		P=0.500N	P=0.500	P=0.129N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rates	15/50 (30%)	18/50 (36%)	25/50 (50%)	15/48 (31%)
Adjusted rates	42.6%	65.7%	77.7%	70.8%
Terminal rates	6/24 (25%)	11/20 (55%)	17/24 (71%)	8/14 (57%)
First incidence (days)	527	520	684	548
Life table tests	P=0.033	P=0.148	P=0.042	P=0.054
Logistic regression tests	P=0.005	P=0.156	P=0.010	P=0.021
Cochran-Armitage test	P=0.457			
Fisher exact test		P=0.335	P=0.033	P=0.534
Heart: Benign Schwannoma				
Overall rates	3/50 (6%)	1/50 (2%)	0/49 (0%)	0/50 (0%)
Adjusted rates	12.5%	5.0%	0.0%	0.0%
Terminal rates	3/24 (13%)	1/20 (5%)	0/23 (0%)	0/14 (0%)
First incidence (days)	729 (T)	729 (T)	–	–
Life table tests	P=0.066N	P=0.370N	P=0.126N	P=0.228N
Logistic regression tests	P=0.066N	P=0.370N	P=0.126N	P=0.228N
Cochran-Armitage test	P=0.043N			
Fisher exact test		P=0.309N	P=0.125N	P=0.121N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	1/50 (2%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rates	3.8%	19.5%	7.6%	12.0%
Terminal rates	0/24 (0%)	2/20 (10%)	1/24 (4%)	1/14 (7%)
First incidence (days)	718	649	705	696
Life table tests	P=0.395	P=0.059	P=0.500	P=0.305
Logistic regression tests	P=0.361	P=0.075	P=0.478	P=0.279
Cochran-Armitage test	P=0.544N			
Fisher exact test		P=0.102	P=0.500	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	2/50 (4%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rates	7.9%	19.5%	7.6%	12.0%
Terminal rates	1/24 (4%)	2/20 (10%)	1/24 (4%)	1/14 (7%)
First incidence (days)	718	649	705	696
Life table tests	P=0.534	P=0.136	P=0.692N	P=0.477
Logistic regression tests	P=0.499	P=0.157	P=0.679	P=0.448
Cochran-Armitage test	P=0.396N			
Fisher exact test		P=0.218	P=0.691N	P=0.691N
Mammary Gland: Fibroadenoma				
Overall rates	6/50 (12%)	9/50 (18%)	2/50 (4%)	1/50 (2%)
Adjusted rates	19.5%	40.5%	6.7%	7.1%
Terminal rates	2/24 (8%)	7/20 (35%)	0/24 (0%)	1/14 (7%)
First incidence (days)	683	689	703	729 (T)
Life table tests	P=0.055N	P=0.157	P=0.153N	P=0.213N
Logistic regression tests	P=0.057N	P=0.127	P=0.160N	P=0.224N
Cochran-Armitage test	P=0.012N			
Fisher exact test		P=0.288	P=0.134N	P=0.056N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rates	7/50 (14%)	9/50 (18%)	2/50 (4%)	1/50 (2%)
Adjusted rates	23.2%	40.5%	6.7%	7.1%
Terminal rates	3/24 (13%)	7/20 (35%)	0/24 (0%)	1/14 (7%)
First incidence (days)	683	689	703	729 (T)
Life table tests	P=0.033N	P=0.230	P=0.096N	P=0.152N
Logistic regression tests	P=0.034N	P=0.192	P=0.099N	P=0.161N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.393	P=0.080N	P=0.030N
Pancreas: Adenoma				
Overall rates	12/49 (24%)	1/49 (2%)	1/49 (2%)	0/50 (0%)
Adjusted rates	45.9%	4.5%	4.2%	0.0%
Terminal rates	10/24 (42%)	0/20 (0%)	1/24 (4%)	0/14 (0%)
First incidence (days)	705	724	729 (T)	–
Life table tests	P<0.001N	P=0.004N	P=0.001N	P=0.005N
Logistic regression tests	P<0.001N	P=0.003N	P<0.001N	P=0.004N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P<0.001N	P<0.001N	P<0.001N
Pancreatic Islets: Adenoma				
Overall rates	8/49 (16%)	2/49 (4%)	3/49 (6%)	6/50 (12%)
Adjusted rates	25.0%	7.3%	11.2%	32.5%
Terminal rates	3/24 (13%)	0/20 (0%)	2/24 (8%)	3/14 (21%)
First incidence (days)	594	604	701	514
Life table tests	P=0.316	P=0.105N	P=0.122N	P=0.375
Logistic regression tests	P=0.299	P=0.059N	P=0.122N	P=0.385
Cochran-Armitage test	P=0.464N			
Fisher exact test		P=0.046N	P=0.100N	P=0.371N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	9/49 (18%)	2/49 (4%)	3/49 (6%)	6/50 (12%)
Adjusted rates	28.6%	7.3%	11.2%	32.5%
Terminal rates	4/24 (17%)	0/20 (0%)	2/24 (8%)	3/14 (21%)
First incidence (days)	594	604	701	514
Life table tests	P=0.416	P=0.069N	P=0.077N	P=0.459
Logistic regression tests	P=0.396	P=0.037N	P=0.078N	P=0.466
Cochran-Armitage test	P=0.356N			
Fisher exact test		P=0.025N	P=0.060N	P=0.274N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	16/49 (33%)	22/50 (44%)	14/48 (29%)	10/50 (20%)
Adjusted rates	48.8%	60.8%	46.6%	48.8%
Terminal rates	9/24 (38%)	8/20 (40%)	9/24 (38%)	4/14 (29%)
First incidence (days)	594	435	633	635
Life table tests	P=0.453N	P=0.063	P=0.445N	P=0.461
Logistic regression tests	P=0.448N	P=0.169	P=0.521N	P=0.435
Cochran-Armitage test	P=0.032N			
Fisher exact test		P=0.170	P=0.440N	P=0.115N
Pituitary Gland (Pars Distalis): Carcinoma				
Overall rates	4/49 (8%)	1/50 (2%)	1/48 (2%)	0/50 (0%)
Adjusted rates	12.3%	5.0%	2.7%	0.0%
Terminal rates	1/24 (4%)	1/20 (5%)	0/24 (0%)	0/14 (0%)
First incidence (days)	617	729 (T)	654	–
Life table tests	P=0.070N	P=0.262N	P=0.199N	P=0.180N
Logistic regression tests	P=0.065N	P=0.211N	P=0.195N	P=0.151N
Cochran-Armitage test	P=0.033N			
Fisher exact test		P=0.175N	P=0.187N	P=0.056N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	20/49 (41%)	23/50 (46%)	15/48 (31%)	10/50 (20%)
Adjusted rates	56.3%	64.0%	48.1%	48.8%
Terminal rates	10/24 (42%)	9/20 (45%)	9/24 (38%)	4/14 (29%)
First incidence (days)	594	435	633	635
Life table tests	P=0.244N	P=0.147	P=0.249N	P=0.475N
Logistic regression tests	P=0.210N	P=0.357	P=0.291N	P=0.477N
Cochran-Armitage test	P=0.005N			
Fisher exact test		P=0.376	P=0.221N	P=0.021N
Preputial Gland: Adenoma				
Overall rates	2/50 (4%)	1/48 (2%)	5/50 (10%)	0/50 (0%)
Adjusted rates	8.3%	2.6%	20.8%	0.0%
Terminal rates	2/24 (8%)	0/19 (0%)	5/24 (21%)	0/14 (0%)
First incidence (days)	729 (T)	578	732 (T)	–
Life table tests	P=0.498N	P=0.573N	P=0.209	P=0.362N
Logistic regression tests	P=0.536N	P=0.532N	P=0.209	P=0.362N
Cochran-Armitage test	P=0.312N			
Fisher exact test		P=0.515N	P=0.218	P=0.247N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Preputial Gland: Carcinoma				
Overall rates	6/50 (12%)	2/48 (4%)	1/50 (2%)	1/50 (2%)
Adjusted rates	17.2%	5.1%	4.2%	6.3%
Terminal rates	1/24 (4%)	0/19 (0%)	1/24 (4%)	0/14 (0%)
First incidence (days)	507	577	733 (T)	702
Life table tests	P=0.095N	P=0.236N	P=0.072N	P=0.254N
Logistic regression tests	P=0.060N	P=0.129N	P=0.066N	P=0.184N
Cochran-Armitage test	P=0.030N			
Fisher exact test		P=0.148N	P=0.056N	P=0.056N
Preputial Gland: Adenoma or Carcinoma				
Overall rates	8/50 (16%)	3/48 (6%)	6/50 (12%)	1/50 (2%)
Adjusted rates	24.4%	7.5%	25.0%	6.3%
Terminal rates	3/24 (13%)	0/19 (0%)	6/24 (25%)	0/14 (0%)
First incidence (days)	507	577	732 (T)	702
Life table tests	P=0.120N	P=0.204N	P=0.406N	P=0.133N
Logistic regression tests	P=0.107N	P=0.101N	P=0.452N	P=0.100N
Cochran-Armitage test	P=0.026N			
Fisher exact test		P=0.113N	P=0.387N	P=0.015N
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rates	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rates	4.2%	0.0%	12.0%	0.0%
Terminal rates	1/24 (4%)	0/20 (0%)	2/24 (8%)	0/14 (0%)
First incidence (days)	729 (T)	–	719	–
Life table tests	P=0.642	P=0.536N	P=0.306	P=0.607N
Logistic regression tests	P=0.633	P=0.536N	P=0.297	P=0.607N
Cochran-Armitage test	P=0.503N			
Fisher exact test		P=0.500N	P=0.309	P=0.500N
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	4/50 (8%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rates	14.8%	4.0%	0.0%	5.6%
Terminal rates	3/24 (13%)	0/20 (0%)	0/24 (0%)	0/14 (0%)
First incidence (days)	683	687	–	697
Life table tests	P=0.179N	P=0.265N	P=0.065N	P=0.389N
Logistic regression tests	P=0.194N	P=0.248N	P=0.069N	P=0.416N
Cochran-Armitage test	P=0.101N			
Fisher exact test		P=0.181N	P=0.059N	P=0.181N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rates	2/50 (4%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rates	7.1%	2.2%	9.6%	0.0%
Terminal rates	1/24 (4%)	0/20 (0%)	1/24 (4%)	0/14 (0%)
First incidence (days)	702	529	684	–
Life table tests	P=0.396N	P=0.567N	P=0.489	P=0.386N
Logistic regression tests	P=0.381N	P=0.484N	P=0.462	P=0.388N
Cochran-Armitage test	P=0.243N			
Fisher exact test		P=0.500N	P=0.500	P=0.247N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	6/50 (12%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rates	21.3%	6.1%	9.6%	5.6%
Terminal rates	4/24 (17%)	0/20 (0%)	1/24 (4%)	0/14 (0%)
First incidence (days)	683	529	684	697
Life table tests	P=0.146N	P=0.225N	P=0.257N	P=0.211N
Logistic regression tests	P=0.152N	P=0.163N	P=0.280N	P=0.223N
Cochran-Armitage test	P=0.053N			
Fisher exact test		P=0.134N	P=0.243N	P=0.056N
Testes: Adenoma				
Overall rates	46/50 (92%)	45/50 (90%)	42/50 (84%)	24/50 (48%)
Adjusted rates	100.0%	100.0%	100.0%	95.9%
Terminal rates	24/24 (100%)	20/20 (100%)	24/24 (100%)	13/14 (93%)
First incidence (days)	507	520	486	488
Life table tests	P=0.272N	P=0.141	P=0.390N	P=0.452N
Logistic regression tests	P=0.479N	P=0.492	P=0.631N	P=0.555N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.500N	P=0.178N	P<0.001N
Thyroid Gland (C-cell): Adenoma				
Overall rates	12/50 (24%)	6/50 (12%)	7/49 (14%)	5/50 (10%)
Adjusted rates	40.9%	21.7%	25.9%	24.5%
Terminal rates	8/24 (33%)	2/20 (10%)	5/24 (21%)	1/14 (7%)
First incidence (days)	649	520	687	548
Life table tests	P=0.300N	P=0.226N	P=0.164N	P=0.391N
Logistic regression tests	P=0.338N	P=0.159N	P=0.192N	P=0.399N
Cochran-Armitage test	P=0.062N			
Fisher exact test		P=0.096N	P=0.166N	P=0.054N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	13/50 (26%)	7/50 (14%)	7/49 (14%)	5/50 (10%)
Adjusted rates	42.7%	24.4%	25.9%	24.5%
Terminal rates	8/24 (33%)	2/20 (10%)	5/24 (21%)	1/14 (7%)
First incidence (days)	649	520	687	548
Life table tests	P=0.222N	P=0.263N	P=0.117N	P=0.331N
Logistic regression tests	P=0.243N	P=0.170N	P=0.136N	P=0.327N
Cochran-Armitage test	P=0.034N			
Fisher exact test		P=0.105N	P=0.115N	P=0.033N
All Organs: Mononuclear Cell Leukemia				
Overall rates	23/50 (46%)	22/50 (44%)	15/50 (30%)	8/50 (16%)
Adjusted rates	72.0%	63.3%	43.0%	40.0%
Terminal rates	16/24 (67%)	9/20 (45%)	7/24 (29%)	3/14 (21%)
First incidence (days)	611	488	486	548
Life table tests	P=0.051N	P=0.341	P=0.108N	P=0.122N
Logistic regression tests	P=0.031N	P=0.560	P=0.113N	P=0.130N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.500N	P=0.074N	P=0.001N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
All Organs: Benign or Malignant Mesothelioma				
Overall rates	3/50 (6%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rates	8.4%	11.2%	4.0%	7.1%
Terminal rates	0/24 (0%)	0/20 (0%)	0/24 (0%)	1/14 (7%)
First incidence (days)	624	520	719	729 (T)
Life table tests	P=0.296N	P=0.385	P=0.320N	P=0.556N
Logistic regression tests	P=0.214N	P=0.547	P=0.326N	P=0.533N
Cochran-Armitage test	P=0.136N			
Fisher exact test		P=0.500	P=0.309N	P=0.309N
All Organs: Benign Neoplasms				
Overall rates	49/50 (98%)	49/50 (98%)	45/50 (90%)	26/50 (52%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	24/24 (100%)	20/20 (100%)	24/24 (100%)	14/14 (100%)
First incidence (days)	507	435	486	488
Life table tests	P=0.299N	P=0.115	P=0.407N	P=0.491N
Logistic regression tests	P=0.654	P=0.748N	–[f]	–
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.753N	P=0.102N	P<0.001N
All Organs: Malignant Neoplasms				
Overall rates	39/50 (78%)	33/50 (66%)	28/50 (56%)	11/50 (22%)
Adjusted rates	88.2%	76.8%	68.4%	54.2%
Terminal rates	19/24 (79%)	11/20 (55%)	12/24 (50%)	5/14 (36%)
First incidence (days)	507	437	486	548
Life table tests	P=0.007N	P=0.482	P=0.097N	P=0.014N
Logistic regression tests	P<0.001N	P=0.151N	P=0.037N	P=0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.133N	P=0.016N	P<0.001N
All Organs: Benign or Malignant Neoplasms				
Overall rates	49/50 (98%)	50/50 (100%)	45/50 (90%)	26/50 (52%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	24/24 (100%)	20/20 (100%)	24/24 (100%)	14/14 (100%)
First incidence (days)	507	435	486	488
Life table tests	P=0.288N	P=0.093	P=0.407N	P=0.491N
Logistic regression tests	–	–	–	–
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.500	P=0.102N	P<0.001N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone (including marrow), brain, epididymis, heart, kidney, large intestine, liver, lung, mammary gland, mandibular or mesenteric lymph node, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicles, skin, small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4
Historical Incidence of Adrenal Medulla Pheochromocytomas in Male F344/N Rats Administered Corn Oil by Gavage[a]

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence at Southern Research Institute			
Benzaldehyde	17/49	2/49	19/49
Dichlorvos	21/50	2/50	22/50
Furan	8/50	1/50	9/50
Furfural	11/50	2/50	11/50
γ-Butyrolactone	15/48	0/48	15/48
Pentachloroanisole	12/50	3/50	15/50
Total	84/297 (28.3%)	10/297 (3.4%)	91/297 (30.6%)
Standard deviation	9.5%	2.1%	9.8%
Range	16%-42%	0%-6%	18%-44%
Overall Historical Incidence			
Total	228/804 (28.4%)	33/804 (4.1%)	255/804[b] (31.7%)
Standard deviation	8.5%	3.9%	8.9%
Range	10%-42%	0%-14%	10%-44%

[a] Data as of 3 April 1991
[b] Includes two complex pheochromocytomas

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

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	23	21	14	5
Natural deaths	3	9	12	31
Survivors				
Terminal sacrifice	24	20	24	14
Animals examined microscopically	70	70	70	70
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Ulcer		1 (2%)		
Intestine large, cecum	(50)	(49)	(48)	(50)
Edema	1 (2%)		1 (2%)	1 (2%)
Parasite metazoan	2 (4%)		3 (6%)	
Ulcer	2 (4%)		1 (2%)	
Intestine large, colon	(50)	(50)	(49)	(49)
Parasite metazoan	5 (10%)		2 (4%)	5 (10%)
Intestine large, rectum	(50)	(50)	(49)	(47)
Edema				1 (2%)
Parasite metazoan	5 (10%)	6 (12%)	3 (6%)	3 (6%)
Lymphatic, dilatation				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis		4 (8%)	1 (2%)	2 (4%)
Basophilic focus	27 (54%)	27 (54%)	26 (52%)	8 (16%)
Clear cell focus	14 (28%)	7 (14%)	6 (12%)	4 (8%)
Congestion		2 (4%)	2 (4%)	13 (26%)
Degeneration, cystic	2 (4%)	5 (10%)	9 (18%)	6 (12%)
Eosinophilic focus	3 (6%)	9 (18%)	9 (18%)	1 (2%)
Granuloma	19 (38%)	10 (20%)	6 (12%)	8 (16%)
Hematopoietic cell proliferation	4 (8%)	2 (4%)	2 (4%)	
Hepatodiaphragmatic nodule		2 (4%)	2 (4%)	1 (2%)
Hyperplasia, focal	7 (14%)	5 (10%)		2 (4%)
Inflammation, chronic	6 (12%)	8 (16%)	9 (18%)	4 (8%)
Inflammation, chronic active			1 (2%)	
Mixed cell focus	1 (2%)	3 (6%)		1 (2%)
Bile duct, hyperplasia	45 (90%)	45 (90%)	44 (88%)	26 (52%)
Centrilobular, atrophy	2 (4%)		5 (10%)	
Centrilobular, necrosis		6 (12%)	6 (12%)	17 (34%)
Hepatocyte, pigmentation			1 (2%)	4 (8%)
Hepatocyte, vacuolization cytoplasmic	8 (16%)	2 (4%)	1 (2%)	2 (4%)
Kupffer cell, hyperplasia	3 (6%)	1 (2%)	4 (8%)	
Kupffer cell, pigmentation		1 (2%)		
Lobules, necrosis	2 (4%)	4 (8%)	1 (2%)	1 (2%)
Periportal, inflammation, chronic active				1 (2%)
Portal, necrosis				1 (2%)
Mesentery	(11)	(11)	(5)	(9)
Accessory spleen	1 (9%)	1 (9%)		
Fat, inflammation, pyogranulomatous	1 (9%)			
Fat, necrosis	6 (55%)	5 (45%)	4 (80%)	3 (33%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Alimentary System (continued)				
Pancreas	(49)	(49)	(49)	(50)
Atrophy	14 (29%)	17 (35%)	19 (39%)	9 (18%)
Cytoplasmic alteration		3 (6%)	2 (4%)	1 (2%)
Edema				1 (2%)
Fibrosis	1 (2%)			
Focal cellular change	1 (2%)		3 (6%)	
Hyperplasia, focal	19 (39%)	17 (35%)	8 (16%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)			
Inflammation, chronic	1 (2%)		1 (2%)	
Salivary glands	(50)	(50)	(48)	(50)
Atrophy		1 (2%)	1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Dysplasia			1 (2%)	
Edema	1 (2%)	2 (4%)	4 (8%)	
Erosion	2 (4%)		2 (4%)	
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic active			1 (2%)	
Mineralization		1 (2%)		
Ulcer	3 (6%)	4 (8%)	2 (4%)	
Mucosa, hyperplasia	6 (12%)	7 (14%)	5 (10%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Edema		1 (2%)	1 (2%)	
Erosion	3 (6%)	1 (2%)	2 (4%)	
Hemorrhage			1 (2%)	
Inflammation, chronic active		2 (4%)		
Mineralization	4 (8%)	3 (6%)	1 (2%)	1 (2%)
Ulcer	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Mucosa, hyperplasia	1 (2%)			
Tooth	(2)	(1)		
Developmental malformation		1 (100%)		
Cardiovascular System				
Blood vessel	(4)	(4)	(5)	(5)
Polyarteritis	4 (100%)	4 (100%)	4 (80%)	5 (100%)
Heart	(50)	(50)	(49)	(50)
Angiectasis				1 (2%)
Cardiomyopathy	33 (66%)	37 (74%)	36 (73%)	21 (42%)
Thrombus	1 (2%)		1 (2%)	
Epicardium, inflammation, chronic	1 (2%)			
Myocardium, inflammation, chronic	2 (4%)	3 (6%)	3 (6%)	7 (14%)
Endocrine System				
Adrenal gland, cortex	(49)	(50)	(50)	(50)
Accessory adrenal cortical nodule	14 (29%)	11 (22%)	8 (16%)	6 (12%)
Angiectasis	4 (8%)	2 (4%)	2 (4%)	4 (8%)
Clear cell focus	4 (8%)	5 (10%)	5 (10%)	3 (6%)
Congestion			2 (4%)	2 (4%)
Cyst	1 (2%)			
Hematopoietic cell proliferation	2 (4%)	2 (4%)	1 (2%)	
Hemorrhage				5 (10%)
Hyperplasia, diffuse			1 (2%)	
Hyperplasia, focal	7 (14%)	10 (20%)	7 (14%)	2 (4%)
Necrosis		2 (4%)	1 (2%)	
Vacuolization cytoplasmic, diffuse	3 (6%)	2 (4%)	1 (2%)	2 (4%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Endocrine System (continued)				
Adrenal gland, medulla	(50)	(50)	(50)	(48)
Angiectasis		1 (2%)		1 (2%)
Cyst		1 (2%)		
Hyperplasia	23 (46%)	26 (52%)	16 (32%)	9 (19%)
Infiltration cellular, lymphocyte		1 (2%)		
Islets, pancreatic	(49)	(49)	(49)	(50)
Cyst	1 (2%)		1 (2%)	
Hemorrhage	1 (2%)			
Hyperplasia	8 (16%)	7 (14%)	8 (16%)	3 (6%)
Pituitary gland	(49)	(50)	(48)	(50)
Pars distalis, angiectasis	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Pars distalis, cyst	5 (10%)	2 (4%)	4 (8%)	2 (4%)
Pars distalis, hemorrhage		1 (2%)		
Pars distalis, hyperplasia	9 (18%)	9 (18%)	5 (10%)	2 (4%)
Pars distalis, necrosis		1 (2%)		
Pars distalis, pigmentation	2 (4%)		1 (2%)	
Pars intermedia, angiectasis	1 (2%)	1 (2%)		1 (2%)
Pars intermedia, hyperplasia	2 (4%)			
Pars nervosa, cyst		1 (2%)		
Thyroid gland	(50)	(50)	(49)	(50)
Ultimobranchial cyst		3 (6%)		
C-cell, hyperplasia	9 (18%)	12 (24%)	5 (10%)	4 (8%)
Follicle, cyst	4 (8%)	6 (12%)	1 (2%)	2 (4%)
Follicular cell, hyperplasia			1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Edema	1 (2%)			
Inflammation, chronic	1 (2%)			
Preputial gland	(50)	(48)	(50)	(50)
Ectasia	4 (8%)	1 (2%)	1 (2%)	
Foreign body	1 (2%)		1 (2%)	
Inflammation, chronic	28 (56%)	23 (48%)	29 (58%)	15 (30%)
Inflammation, suppurative	11 (22%)	7 (15%)	7 (14%)	3 (6%)
Prostate	(50)	(50)	(50)	(50)
Cyst	2 (4%)	1 (2%)		
Edema	1 (2%)			
Fibrosis	2 (4%)		1 (2%)	
Inflammation, chronic	7 (14%)	2 (4%)	5 (10%)	4 (8%)
Inflammation, suppurative	25 (50%)	26 (52%)	20 (40%)	15 (30%)
Seminal vesicle	(50)	(50)	(49)	(50)
Edema	1 (2%)			
Inflammation, suppurative	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Mineralization	26 (52%)	21 (42%)	29 (58%)	14 (28%)
Interstitial cell, hyperplasia	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Seminiferous tubule, atrophy	5 (10%)	4 (8%)	7 (14%)	5 (10%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Hypercellularity	2 (4%)	3 (6%)	6 (12%)	
Hyperplasia, reticulum cell	1 (2%)	1 (2%)		
Hypocellularity	1 (2%)	1 (2%)	2 (4%)	
Myelofibrosis		2 (4%)		
Lymph node	(50)	(50)	(50)	(50)
Inguinal, hyperplasia, lymphoid		1 (2%)		
Inguinal, hyperplasia, plasma cell		1 (2%)	1 (2%)	
Inguinal, lymphatic, dilatation	1 (2%)			
Mediastinal, congestion				1 (2%)
Mediastinal, hemorrhage	8 (16%)	6 (12%)	10 (20%)	1 (2%)
Mediastinal, hyperplasia, lymphoid			1 (2%)	
Mediastinal, hyperplasia, plasma cell		5 (10%)	1 (2%)	1 (2%)
Mediastinal, pigmentation	4 (8%)	8 (16%)	2 (4%)	
Pancreatic, hemorrhage	1 (2%)			
Pancreatic, hyperplasia, lymphoid	2 (4%)			
Renal, hyperplasia, lymphoid	1 (2%)			
Renal, lymphatic, dilatation	1 (2%)			
Lymph node, mandibular	(50)	(49)	(49)	(49)
Congestion	1 (2%)		2 (4%)	5 (10%)
Hemorrhage			2 (4%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Hyperplasia, plasma cell	19 (38%)	18 (37%)	17 (35%)	5 (10%)
Hyperplasia, reticulum cell				1 (2%)
Infiltration cellular, polymorphonuclear			1 (2%)	
Lymphatic, dilatation	2 (4%)	6 (12%)	10 (20%)	2 (4%)
Lymph node, mesenteric	(50)	(50)	(49)	(48)
Congestion				1 (2%)
Erythrophagocytosis	1 (2%)	2 (4%)		
Hemorrhage	1 (2%)	1 (2%)	6 (12%)	2 (4%)
Hyperplasia, lymphoid			1 (2%)	
Hyperplasia, reticulum cell			1 (2%)	
Necrosis			1 (2%)	2 (4%)
Pigmentation			1 (2%)	
Lymphatic, dilatation		1 (2%)		1 (2%)
Spleen	(50)	(49)	(50)	(50)
Congestion	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Degeneration, fatty			1 (2%)	
Developmental malformation	1 (2%)			
Fibrosis	2 (4%)		3 (6%)	1 (2%)
Hematopoietic cell proliferation	9 (18%)	6 (12%)	7 (14%)	2 (4%)
Hemorrhage			1 (2%)	
Hyperplasia, mononuclear cell			1 (2%)	
Hyperplasia, re cell		2 (4%)	2 (4%)	
Necrosis	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Pigmentation, hemosiderin	5 (10%)	7 (14%)	8 (16%)	
Lymphoid follicle, atrophy		1 (2%)		
Red pulp, hyperplasia		1 (2%)		
Thymus	(46)	(47)	(47)	(47)
Congestion	1 (2%)		5 (11%)	13 (28%)
Cyst	3 (7%)	4 (9%)	1 (2%)	1 (2%)
Ectopic parathyroid gland				1 (2%)
Hemorrhage			5 (11%)	21 (45%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Integumentary System				
Mammary gland	(48)	(49)	(50)	(47)
Hyperplasia, cystic	17 (35%)	13 (27%)	11 (22%)	4 (9%)
Hyperplasia, lobular		2 (4%)	2 (4%)	
Skin	(50)	(49)	(50)	(50)
Acanthosis	2 (4%)		1 (2%)	1 (2%)
Angiectasis			1 (2%)	
Cyst epithelial inclusion	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Exudate	1 (2%)			1 (2%)
Fibrosis	1 (2%)			
Foreign body	1 (2%)			
Hyperkeratosis	1 (2%)		1 (2%)	
Hyperplasia, basal cell		1 (2%)		
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, granulomatous	1 (2%)			
Ulcer			1 (2%)	
Lip, hemorrhage			1 (2%)	
Scrotum, congestion			1 (2%)	13 (26%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Femur, osteopetrosis		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	6 (12%)	4 (8%)	3 (6%)	2 (4%)
Congestion		1 (2%)	4 (8%)	21 (42%)
Degeneration, focal			1 (2%)	
Hemorrhage	1 (2%)	2 (4%)	4 (8%)	
Hydrocephalus	1 (2%)	4 (8%)	1 (2%)	
Mineralization		1 (2%)	1 (2%)	
Necrosis	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Atelectasis	1 (2%)			
Congestion	2 (4%)	3 (6%)	6 (12%)	30 (60%)
Edema	3 (6%)	2 (4%)	1 (2%)	5 (10%)
Foreign body		3 (6%)		2 (4%)
Hemorrhage	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Infiltration cellular, histiocyte	33 (66%)	30 (60%)	28 (56%)	23 (46%)
Inflammation, chronic	7 (14%)	14 (28%)	10 (20%)	6 (12%)
Inflammation, subacute				1 (2%)
Inflammation, suppurative	1 (2%)	2 (4%)		1 (2%)
Leukocytosis		4 (8%)		
Metaplasia, osseous				1 (2%)
Alveolar epithelium, hyperplasia	6 (12%)	3 (6%)		1 (2%)
Mediastinum, inflammation, granulomatous	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Congestion				3 (6%)
Exudate	17 (34%)	17 (34%)	12 (24%)	9 (18%)
Foreign body	8 (16%)	6 (12%)	5 (10%)	2 (4%)
Fungus	14 (28%)	15 (30%)	11 (22%)	6 (12%)
Inflammation, chronic	2 (4%)	7 (14%)	11 (22%)	5 (10%)
Pigmentation		1 (2%)		
Mucosa, erosion				1 (2%)
Mucosa, hyperplasia	8 (16%)	7 (14%)	7 (14%)	3 (6%)
Mucosa, metaplasia, squamous	5 (10%)	8 (16%)	9 (18%)	5 (10%)
Nerve, hypertrophy	1 (2%)	1 (2%)		
Olfactory epithelium, pigmentation		29 (58%)	40 (80%)	25 (50%)
Trachea	(50)	(49)	(50)	(50)
Exudate				1 (2%)
Mucosa, hyperplasia		1 (2%)		
Special Senses System				
Eye	(2)	(7)	(2)	(2)
Cataract	1 (50%)	6 (86%)	1 (50%)	1 (50%)
Phthisis bulbi				1 (50%)
Cornea, hyperplasia		1 (14%)		
Retina, atrophy	2 (100%)	6 (86%)	1 (50%)	1 (50%)
Sclera, mineralization	1 (50%)	4 (57%)		1 (50%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Cyst	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Hydronephrosis			1 (2%)	
Infarct	1 (2%)		1 (2%)	
Inflammation, chronic	38 (76%)	35 (70%)	30 (60%)	20 (40%)
Inflammation, suppurative	10 (20%)	15 (30%)	20 (40%)	14 (28%)
Mineralization	20 (40%)	13 (26%)	15 (30%)	8 (16%)
Nephropathy	49 (98%)	49 (98%)	46 (92%)	27 (54%)
Artery, hypertrophy				1 (2%)
Renal tubule, pigmentation	1 (2%)	23 (46%)	22 (44%)	16 (32%)
Transitional epithelium, hyperplasia	2 (4%)	2 (4%)	1 (2%)	
Urethra	(2)			
Bulbourethral gland, ectasia	1 (50%)			
Urinary bladder	(50)	(50)	(50)	(50)
Edema		1 (2%)		1 (2%)
Mucosa, hyperplasia	1 (2%)			

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

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF PENTACHLOROANISOLE

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

	Vehicle Control	20 mg/kg	40 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
9-Month interim evaluation	10	10	10
15-Month interim evaluation	10	10	10
Early deaths			
Moribund	17	13	4
Natural deaths	4	2	2
Survivors			
Terminal sacrifice	29	35	44
Animals examined microscopically	70	70	70
Alimentary System			
Intestine large, colon	(49)	(1)	(49)
Intestine small, ileum	(50)	(1)	(50)
Liver	(50)	(50)	(50)
Hepatocellular adenoma			1 (2%)
Pancreas	(50)		(50)
Acinar cell, adenoma	2 (4%)		
Pharynx	(2)		(1)
Papilloma squamous	1 (50%)		
Stomach, forestomach	(50)	(1)	(50)
Sarcoma stromal, metastatic, uterus		1 (100%)	
Stomach, glandular	(50)	(1)	(50)
Cardiovascular System			
Heart	(50)		(50)
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma	1 (2%)		
Adrenal gland, medulla	(50)	(50)	(50)
Pheochromocytoma benign	3 (6%)	5 (10%)	9 (18%)
Pheochromocytoma benign, multiple		2 (4%)	
Pituitary gland	(49)	(50)	(50)
Pars distalis, adenoma	18 (37%)	21 (42%)	20 (40%)
Pars distalis, carcinoma	2 (4%)	2 (4%)	3 (6%)
Pars distalis, hamartoma			1 (2%)
Pars intermedia, adenoma	2 (4%)	2 (4%)	1 (2%)
Thyroid gland	(50)	(2)	(50)
C-cell, adenoma	7 (14%)		9 (18%)
C-cell, carcinoma	1 (2%)		
Follicular cell, adenoma	1 (2%)		
Follicular cell, carcinoma		1 (50%)	
General Body System			
None			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Genital System			
Clitoral gland	(50)	(8)	(50)
Adenoma	5 (10%)	4 (50%)	3 (6%)
Carcinoma	3 (6%)	1 (13%)	2 (4%)
Ovary	(50)	(5)	(50)
Granulosa cell tumor malignant		2 (40%)	
Uterus	(50)	(50)	(50)
Adenoma		1 (2%)	
Carcinoma *in situ*	1 (2%)		
Hemangioma			1 (2%)
Polyp stromal	13 (26%)	13 (26%)	7 (14%)
Sarcoma stromal	2 (4%)	1 (2%)	
Vagina	(2)	(1)	(3)
Carcinoma			1 (33%)
Leiomyoma	1 (50%)		
Polyp			1 (33%)
Sarcoma stromal, metastatic, uterus		1 (100%)	
Hematopoietic System			
Bone marrow	(50)		(50)
Lymph node	(50)	(11)	(50)
Renal, fibrosarcoma, metastatic, skin		1 (9%)	
Lymph node, mandibular	(50)	(3)	(50)
Lymph node, mesenteric	(49)	(3)	(50)
Spleen	(50)	(10)	(50)
Thymus	(47)		(48)
Thymoma benign			1 (2%)
Thymoma malignant	1 (2%)		
Integumentary System			
Mammary gland	(48)	(21)	(50)
Adenoma	3 (6%)		
Carcinoma			1 (2%)
Fibroadenoma	16 (33%)	10 (48%)	7 (14%)
Skin	(50)	(3)	(50)
Papilloma squamous	1 (2%)		
Squamous cell carcinoma			1 (2%)
Subcutaneous tissue, fibroma	1 (2%)	1 (33%)	
Subcutaneous tissue, fibrosarcoma		1 (33%)	
Musculoskeletal System			
Skeletal muscle		(1)	
Sarcoma stromal, metastatic, uterus		1 (100%)	
Nervous System			
Brain	(50)	(4)	(50)
Astrocytoma malignant	1 (2%)		
Carcinoma, metastatic, pituitary gland	1 (2%)		
Oligodendroglioma malignant	1 (2%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Respiratory System			
Lung	(50)	(7)	(50)
Alveolar/bronchiolar adenoma		1 (14%)	1 (2%)
Nose	(49)	(50)	(50)
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(50)
Urinary bladder	(50)	(1)	(49)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Leukemia mononuclear	11 (22%)	14 (28%)	9 (18%)
Lymphoma malignant lymphocytic			1 (2%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	45	41	41
Total primary neoplasms	98	82	80
Total animals with benign neoplasms	40	35	35
Total benign neoplasms	75	60	62
Total animals with malignant neoplasms	22	20	18
Total malignant neoplasms	23	22	18
Total animals with metastatic neoplasms	1	2	
Total metastatic neoplasms	1	4	

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control

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

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	58 4	58 5	59 3	59 4	59 5	60 3	60 4	60 5	61 3	61 4	61 5	62 5	63 3	63 4	63 5	64 1	64 2	64 3	64 4	64 5	65 3	65 4	65 5	66 4	66 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery						+		+			+			+	+					+					+	13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell, adenoma									X															X		2
Pharynx						+																		+		2
Papilloma squamous						X																				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue									+																	1
Tooth													+													2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																						X				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X		X	X					X	X		X							X		X	X		X	18
Pars distalis, carcinoma																										2
Pars intermedia, adenoma																		X							X	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X						X													7
C-cell, carcinoma																							X			1
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	2 1 3	3 5 3	4 4 4	4 7 7	5 2 2	5 2 6	5 7 9	5 7 9	5 8 9	5 9 0	5 9 6	6 1 6	6 2 0	6 4 0	6 6 9	6 8 3	6 8 4	6 8 7	7 0 5	7 0 5	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	6 5 1	6 6 1	6 0 2	6 0 1	6 2 1	6 6 2	5 9 1	6 1 1	6 2 2	5 7 1	5 8 1	6 5 2	6 2 3	6 3 1	6 2 4	5 8 2	5 1 2	5 9 2	5 8 3	6 6 3	6 3 2	5 7 2	5 7 3	5 7 4	5 7 5
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Carcinoma																			X	X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma *in situ*																									
Polyp stromal						X									X				X			X	X		
Sarcoma stromal										X			X												
Vagina													M												
Leiomyoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant		X																							
Integumentary System																									
Mammary gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X				X							
Fibroadenoma					X		X													X	X		X	X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibroma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	5 8 4	5 8 5	5 9 3	5 9 4	5 9 5	6 0 3	6 0 4	6 0 5	6 1 3	6 1 4	6 1 5	6 2 5	6 3 3	6 3 4	6 3 5	6 4 1	6 4 2	6 4 3	6 4 4	6 4 5	6 5 3	6 5 4	6 5 5	6 6 4	6 6 5	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X								X					X			X	5
Carcinoma																								X		3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma *in situ*											X															1
Polyp stromal	X	X	X				X										X		X	X	X					13
Sarcoma stromal																										2
Vagina				+																				+		2
Leiomyoma				X																						1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	47
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																									X	3
Fibroadenoma		X	X		X		X			X							X	X		X	X	X			16
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous				X																						1
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	2 1 3	3 5 3	4 4 4	4 7 7	5 2 2	5 2 6	5 7 9	5 7 9	5 8 9	5 9 0	5 9 6	6 1 6	6 2 0	6 4 0	6 6 9	6 8 3	6 8 4	6 8 7	7 0 5	7 0 5	7 1 8	7 2 9	7 2 9	7 2 9
Carcass ID Number	6 5 1	6 6 1	6 0 2	6 0 1	6 2 1	6 6 2	5 9 1	6 1 1	6 2 2	5 7 1	5 8 1	6 5 2	6 2 3	6 3 1	6 2 4	5 8 2	6 1 2	5 9 2	5 8 3	6 6 3	6 3 2	5 7 2	5 7 3	5 7 4	5 7 5
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant			X																						
Carcinoma, metastatic, pituitary gland															X										
Oligodendroglioma malignant												X													
Peripheral nerve																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra				+																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X										X						X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	5 8 4	5 8 5	5 9 3	5 9 4	5 9 5	6 0 3	6 0 4	6 0 5	6 1 3	6 1 4	6 1 5	6 2 5	6 3 3	6 3 4	6 3 5	6 4 1	6 4 2	6 4 3	6 4 4	6 4 5	6 5 3	6 5 4	6 5 5	6 6 4	6 6 5	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Carcinoma, metastatic, pituitary gland																										1
Oligodendroglioma malignant																										1
Peripheral nerve																								+		1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																				+						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X			X					X	X		X								X				11

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg

Number of Days on Study	3 3 5 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 3 4 4 8 1 2 4 6 7 8 8 9 0 1 2 3 3 3 3 3 3 3 3 3 3 0 5 1 9 1 5 7 7 3 7 9 5 2 8 4 2 6 6 6 6 6 6 6 6 6
Carcass ID Number	8 8 8 9 9 8 8 8 8 8 8 9 9 9 9 8 8 8 8 8 8 8 8 8 8 5 5 7 0 2 5 8 5 9 5 8 3 3 0 2 7 6 6 6 6 6 7 7 7 8 1 2 1 1 1 3 1 4 5 5 2 2 1 2 2 2 1 2 3 4 5 3 4 5 3
Alimentary System	
Intestine large	+
Intestine large, cecum	+
Intestine large, colon	+
Intestine large, rectum	+
Intestine small	+
Intestine small, duodenum	+
Intestine small, ileum	+
Intestine small, jejunum	+
Liver	+ +
Mesentery	+ +
Stomach	+
Stomach, forestomach	+
Sarcoma stromal, metastatic, uterus	X
Stomach, glandular	+
Cardiovascular System	
None	
Endocrine System	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Adrenal gland, medulla	+ +
Pheochromocytoma benign	X
Pheochromocytoma benign, multiple	X
Pituitary gland	+ +
Pars distalis, adenoma	X X X X X X X X X
Pars distalis, carcinoma	
Pars intermedia, adenoma	X
Thyroid gland	+
Follicular cell, carcinoma	
General Body System	
None	
Genital System	
Clitoral gland	+ +
Adenoma	X
Carcinoma	X
Ovary	+ + + +
Granulosa cell tumor malignant	X
Uterus	+ +
Adenoma	X
Polyp stromal	X X X X X X
Sarcoma stromal	X
Vagina	+
Sarcoma stromal, metastatic, uterus	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	
Carcass ID Number	8 8 4	8 8 5	8 9 1	8 9 2	8 9 3	8 9 4	9 0 3	9 0 4	9 0 5	9 1 1	9 1 2	9 1 3	9 1 4	9 1 5	9 2 3	9 2 4	9 2 5	9 3 3	9 3 4	9 3 5	9 4 1	9 4 2	9 4 3	9 4 4	9 4 5	Total Tissues/ Tumors
Alimentary System																										
Intestine large																										1
Intestine large, cecum																										1
Intestine large, colon																										1
Intestine large, rectum																										1
Intestine small																										1
Intestine small, duodenum																										1
Intestine small, ileum																										1
Intestine small, jejunum																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery								+																		3
Stomach																										1
Stomach, forestomach																										1
Sarcoma stromal, metastatic, uterus																										1
Stomach, glandular																										1
Cardiovascular System																										
None																										
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign										X			X						X					X	5
Pheochromocytoma benign, multiple	X																									2
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X		X	X			X	X	X				X							X	X	21
Pars distalis, carcinoma										X				X												2
Pars intermedia, adenoma																							X			2
Thyroid gland								+																		2
Follicular cell, carcinoma								X																		1
General Body System																										
None																										
Genital System																										
Clitoral gland			+		+	+															+		+		+	8
Adenoma						X																	X		X	4
Carcinoma																										1
Ovary		+					+																			5
Granulosa cell tumor malignant							X																			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Polyp stromal	X					X								X	X		X				X		X			13
Sarcoma stromal																										1
Vagina																										1
Sarcoma stromal, metastatic, uterus																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg
(continued)

Number of Days on Study	3 3 0	3 4 5	5 4 1	5 8 9	6 1 1	6 2 5	6 4 7	6 6 7	6 7 3	6 8 7	6 8 9	6 9 5	7 0 2	7 1 8	7 2 4	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	8 5 1	8 5 2	8 7 1	9 0 1	9 2 1	8 5 3	8 8 1	8 5 4	8 9 5	8 5 5	8 8 2	9 3 2	9 3 1	9 0 2	9 2 2	8 7 2	8 6 1	8 6 2	8 6 3	8 6 4	8 6 5	8 7 3	8 7 4	8 7 5	8 8 3
Hematopoietic System																									
Lymph node	+	+			+			+					+					+	+					+	
Renal, fibrosarcoma, metastatic, skin	X																								
Lymph node, mandibular					+																				
Lymph node, mesenteric								+										+							
Spleen		+				+		+		+	+	+	+											+	
Integumentary System																									
Mammary gland				+			+	+	+	+		+	+		+	+			+						
Fibroadenoma										X		X			X										
Skin	+																						+		
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma	X																								
Musculoskeletal System																									
Bone				+																		+			
Skeletal muscle					+																				
Sarcoma stromal, metastatic, uterus					X																				
Nervous System																									
Brain		+						+					+			+									
Respiratory System																									
Lung	+					+			+			+	+											+	+
Alveolar/bronchiolar adenoma									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X		X		X	X					X								X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	
Carcass ID Number	8 8 4	8 8 5	8 9 1	8 9 2	8 9 3	8 9 4	9 0 3	9 0 4	9 0 5	9 1 1	9 1 2	9 1 3	9 1 4	9 1 5	9 2 3	9 2 4	9 2 5	9 3 3	9 3 4	9 3 5	9 4 1	9 4 2	9 4 3	9 4 4	9 4 5	Total Tissues/ Tumors
Hematopoietic System																										
Lymph node							+	+		M														+		11
Renal, fibrosarcoma, metastatic, skin																										1
Lymph node, mandibular								+																+		3
Lymph node, mesenteric							+																			3
Spleen													+					+								10
Integumentary System																										
Mammary gland				+	+		+	+	+	+			+	+				+			+				+	21
Fibroadenoma				X	X		X	X	X	X				X												10
Skin	+																									3
Subcutaneous tissue, fibroma	X																									1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone														+	+			+			+					6
Skeletal muscle																										1
Sarcoma stromal, metastatic, uterus																										1
Nervous System																										
Brain																										4
Respiratory System																										
Lung																										7
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+														+						+				4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder													+													1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X				X	X							X			X	X	14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg

Number of Days on Study	5 1 7	5 7 0	6 2 8	7 1 2	7 1 5	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	7 7 1	7 4 1	7 1 2	7 1 1	7 3 1	7 7 3	7 1 2	7 1 3	7 1 4	7 1 5	7 2 1	7 2 2	7 2 3	7 2 4	7 2 5	7 3 2	7 3 3	7 3 4	7 3 5	7 4 2	7 4 3	7 4 4	7 4 5	7 5 1	7 5 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery									+			+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx											+														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																							+		
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign				X		X				X								X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X				X	X	X	X			X			X								X	
Pars distalis, carcinoma																				X			X		
Pars distalis, hamartoma																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma	X							X														X		X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 5 3	7 5 4	7 5 5	7 6 1	7 6 2	7 6 3	7 6 4	7 6 5	7 7 4	7 7 5	7 8 1	7 8 2	7 8 3	7 8 4	7 8 5	7 9 1	7 9 2	7 9 3	7 9 4	7 9 5	8 0 1	8 0 2	8 0 3	8 0 4	8 0 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma														X												1
Mesentery								+								+			+			+			+	7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Tooth																						+				1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X				X		X			X		X											9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X	X	X	X		X						X	X	X			X		X			20
Pars distalis, carcinoma																						X				3
Pars distalis, hamartoma																			X							1
Pars intermedia, adenoma														X												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X		X	X																	X			9

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	5 1 7	5 7 0	6 2 8	7 1 2	7 1 5	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	7 7 1	7 4 1	7 7 2	7 1 1	7 3 1	7 7 3	7 1 2	7 1 3	7 1 4	7 1 5	7 2 1	7 2 2	7 2 3	7 2 4	7 2 5	7 3 2	7 3 3	7 3 4	7 3 5	7 4 2	7 4 3	7 4 4	7 4 5	7 5 1	7 5 2
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Carcinoma				X		X																			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma												X													
Polyp stromal	X																	X		X					
Vagina		+																							
Carcinoma		X																							
Polyp		X																							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Thymoma benign																		X							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma								X					X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 5 3	7 5 4	7 5 5	7 6 1	7 6 2	7 6 3	7 6 4	7 6 5	7 7 4	7 7 5	7 8 1	7 8 2	7 8 3	7 8 4	7 8 5	7 9 1	7 9 2	7 9 3	7 9 4	7 9 5	8 0 1	8 0 2	8 0 3	8 0 4	8 0 5	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X								X								3
Carcinoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Polyp stromal			X													X		X		X						7
Vagina									+									+							M	3
Carcinoma																										1
Polyp																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma					X																					1
Fibroadenoma					X	X												X		X			X			7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	5 1 7	5 7 0	6 2 8	7 1 2	7 1 5	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	7 7 1	7 4 1	7 7 2	7 1 1	7 3 1	7 7 3	7 1 2	7 1 3	7 1 4	7 1 5	7 2 1	7 2 2	7 2 3	7 2 4	7 2 5	7 3 2	7 3 3	7 3 4	7 3 5	7 4 2	7 4 3	7 4 4	7 4 5	7 5 1	7 5 2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																										
Eye													+									+				
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X		X	X	X							X				
Lymphoma malignant lymphocytic	X																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 5 3	7 5 4	7 5 5	7 6 1	7 6 2	7 6 3	7 6 4	7 6 5	7 7 4	7 7 5	7 8 1	7 8 2	7 8 3	7 8 4	7 8 5	7 9 1	7 9 2	7 9 3	7 9 4	7 9 5	8 0 1	8 0 2	8 0 3	8 0 4	8 0 5	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear								+																		1
Eye		+			+														+				+	+	+	8
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X			X			X							X	9
Lymphoma malignant lymphocytic																										1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Pentachloroanisole

	Vehicle Control	20 mg/kg	40 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	3/50 (6%)	7/50 (14%)	9/50 (18%)
Adjusted rates[b]	10.0%	19.1%	19.5%
Terminal rates[c]	2/29 (7%)	6/35 (17%)	7/44 (16%)
First incidence (days)	718	673	712
Life table tests[d]	P=0.193	P=0.247	P=0.219
Logistic regression tests[d]	P=0.135	P=0.232	P=0.170
Cochran-Armitage test[d]	P=0.049		
Fisher exact test[d]		P=0.159	P=0.061
Clitoral Gland: Adenoma			
Overall rates	5/50 (10%)	4/8 (50%)[e]	3/50 (6%)
Adjusted rates	15.8%		6.8%
Terminal rates	4/29 (14%)		3/44 (7%)
First incidence (days)	579		729 (T)
Life table tests			P=0.177N
Logistic regression tests			P=0.276N
Fisher exact test			P=0.357N
Clitoral Gland: Carcinoma			
Overall rates	3/50 (6%)	1/8 (13%)[e]	2/50 (4%)
Adjusted rates	9.5%		4.3%
Terminal rates	1/29 (3%)		0/44 (0%)
First incidence (days)	705		712
Life table tests			P=0.320N
Logistic regression tests			P=0.414N
Fisher exact test			P=0.500N
Clitoral Gland: Adenoma or Carcinoma			
Overall rates	8/50 (16%)	5/8 (63%)[e]	5/50 (10%)
Adjusted rates	24.2%		10.8%
Terminal rates	5/29 (17%)		3/44 (7%)
First incidence (days)	579		712
Life table tests			P=0.094N
Logistic regression tests			P=0.177N
Fisher exact test			P=0.277N
Mammary Gland: Fibroadenoma			
Overall rates	16/50 (32%)	10/50 (20%)	7/50 (14%)
Adjusted rates	47.5%	26.1%	15.9%
Terminal rates	12/29 (41%)	7/35 (20%)	7/44 (16%)
First incidence (days)	522	687	729 (T)
Life table tests	P=0.001N	P=0.052N	P=0.002N
Logistic regression tests	P=0.005N	P=0.066N	P=0.008N
Cochran-Armitage test	P=0.020N		
Fisher exact test		P=0.127N	P=0.028N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Mammary Gland: Adenoma			
Overall rates	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rates	8.9%	0.0%	0.0%
Terminal rates	1/29 (3%)	0/35 (0%)	0/44 (0%)
First incidence (days)	640	–[f]	–
Life table tests	P=0.021N	P=0.092N	P=0.072N
Logistic regression tests	P=0.035N	P=0.116N	P=0.117N
Cochran-Armitage test	P=0.037N		
Fisher exact test		P=0.121N	P=0.121N
Mammary Gland: Adenoma or Fibroadenoma			
Overall rates	19/50 (38%)	10/50 (20%)	7/50 (14%)
Adjusted rates	53.4%	26.1%	15.9%
Terminal rates	13/29 (45%)	7/35 (20%)	7/44 (16%)
First incidence (days)	522	687	729 (T)
Life table tests	P<0.001N	P=0.013N	P<0.001N
Logistic regression tests	P<0.001N	P=0.017N	P=0.001N
Cochran-Armitage test	P=0.004N		
Fisher exact test		P=0.038N	P=0.006N
Mammary Gland: Adenoma or Carcinoma			
Overall rates	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rates	8.9%	0.0%	2.3%
Terminal rates	1/29 (3%)	0/35 (0%)	1/44 (2%)
First incidence (days)	640	–	729 (T)
Life table tests	P=0.109N	P=0.092N	P=0.192N
Logistic regression tests	P=0.163N	P=0.116N	P=0.287N
Cochran-Armitage test	P=0.174N		
Fisher exact test		P=0.121N	P=0.309N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	18/49 (37%)	21/50 (42%)	20/50 (40%)
Adjusted rates	53.5%	50.9%	43.3%
Terminal rates	13/28 (46%)	15/35 (43%)	18/44 (41%)
First incidence (days)	589	589	570
Life table tests	P=0.135N	P=0.496N	P=0.166N
Logistic regression tests	P=0.410N	P=0.559	P=0.468N
Cochran-Armitage test	P=0.410		
Fisher exact test		P=0.371	P=0.449
Pituitary Gland (Pars Distalis): Carcinoma			
Overall rates	2/49 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rates	5.4%	5.7%	6.8%
Terminal rates	0/28 (0%)	2/35 (6%)	3/44 (7%)
First incidence (days)	640	729 (T)	729 (T)
Life table tests	P=0.580	P=0.622N	P=0.663
Logistic regression tests	P=0.466	P=0.676N	P=0.534
Cochran-Armitage test	P=0.417		
Fisher exact test		P=0.684N	P=0.510

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rates	20/49 (41%)	23/50 (46%)	23/50 (46%)
Adjusted rates	56.0%	55.9%	49.9%
Terminal rates	13/28 (46%)	17/35 (49%)	21/44 (48%)
First incidence (days)	589	589	570
Life table tests	P=0.146N	P=0.468N	P=0.181N
Logistic regression tests	P=0.471N	P=0.564	P=0.543N
Cochran-Armitage test	P=0.338		
Fisher exact test		P=0.376	P=0.376
Thyroid Gland (C-cell): Adenoma			
Overall rates	7/50 (14%)	0/2 (0%)[e]	9/50 (18%)
Adjusted rates	19.7%		19.8%
Terminal rates	3/29 (10%)		8/44 (18%)
First incidence (days)	444		517
Life table tests			P=0.524N
Logistic regression tests			P=0.346
Fisher exact test			P=0.393
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	8/50 (16%)	0/2 (0%)[e]	9/50 (18%)
Adjusted rates	22.8%		19.8%
Terminal rates	4/29 (14%)		8/44 (18%)
First incidence (days)	444		517
Life table tests			P=0.399N
Logistic regression tests			P=0.471
Fisher exact test			P=0.500
Uterus: Stromal Polyp			
Overall rates	13/50 (26%)	13/50 (26%)	7/50 (14%)
Adjusted rates	39.7%	32.9%	15.4%
Terminal rates	10/29 (34%)	9/35 (26%)	6/44 (14%)
First incidence (days)	526	667	517
Life table tests	P=0.011N	P=0.381N	P=0.015N
Logistic regression tests	P=0.044N	P=0.453N	P=0.063N
Cochran-Armitage test	P=0.093N		
Fisher exact test		P=0.590N	P=0.105N
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rates	15/50 (30%)	14/50 (28%)	7/50 (14%)
Adjusted rates	42.7%	34.3%	15.4%
Terminal rates	10/29 (34%)	9/35 (26%)	6/44 (14%)
First incidence (days)	526	611	517
Life table tests	P=0.004N	P=0.296N	P=0.005N
Logistic regression tests	P=0.025N	P=0.413N	P=0.035N
Cochran-Armitage test	P=0.040N		
Fisher exact test		P=0.500N	P=0.045N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
All Organs: Mononuclear Cell Leukemia			
Overall rates	11/50 (22%)	14/50 (28%)	9/50 (18%)
Adjusted rates	32.8%	32.8%	20.5%
Terminal rates	8/29 (28%)	8/35 (23%)	9/44 (20%)
First incidence (days)	526	345	729 (T)
Life table tests	P=0.098N	P=0.513	P=0.115N
Logistic regression tests	P=0.347N	P=0.327	P=0.277N
Cochran-Armitage test	P=0.363N		
Fisher exact test		P=0.322	P=0.402N
All Organs: Benign Neoplasms			
Overall rates	40/50 (80%)	35/50 (70%)	35/50 (70%)
Adjusted rates	90.8%	79.5%	71.4%
Terminal rates	25/29 (86%)	26/35 (74%)	30/44 (68%)
First incidence (days)	444	589	517
Life table tests	P<0.001N	P=0.036N	P=0.001N
Logistic regression tests	P=0.037N	P=0.064N	P=0.077N
Cochran-Armitage test	P=0.154N		
Fisher exact test		P=0.178N	P=0.178N
All Organs: Malignant Neoplasms			
Overall rates	22/50 (44%)	20/50 (40%)	18/50 (36%)
Adjusted rates	52.2%	45.4%	37.4%
Terminal rates	10/29 (34%)	12/35 (34%)	14/44 (32%)
First incidence (days)	353	330	517
Life table tests	P=0.034N	P=0.231N	P=0.042N
Logistic regression tests	P=0.423N	P=0.514N	P=0.415N
Cochran-Armitage test	P=0.238N		
Fisher exact test		P=0.420N	P=0.270N
All Organs: Benign or Malignant Neoplasms			
Overall rates	45/50 (90%)	41/50 (82%)	41/50 (82%)
Adjusted rates	93.7%	83.7%	83.6%
Terminal rates	26/29 (90%)	27/35 (77%)	36/44 (82%)
First incidence (days)	353	330	517
Life table tests	P<0.001N	P=0.057N	P<0.001N
Logistic regression tests	P=0.133N	P=0.160N	P=0.113N
Cochran-Armitage test	P=0.165N		
Fisher exact test		P=0.194N	P=0.194N

(T) Terminal sacrifice

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone (including marrow), brain, clitoral gland, heart, kidney, large intestine, liver, lung, mammary gland, mandibular or mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, salivary gland, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, urinary bladder, and uterus; for other tissues, denominator is number of animals necropsied.

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

[c] Observed incidence at terminal kill

[d] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

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

[f] Not applicable; no neoplasms in animal group

TABLE B4
Historical Incidence of Adrenal Medulla Pheochromocytomas in Female F344/N Rats Administered Corn Oil by Gavage[a]

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence at Southern Research Institute			
Benzaldehyde	5/49	2/49	7/49
Dichlorvos	4/50	0/50	4/50
Furan	2/50	0/50	3/50
Furfural	2/47	1/47	3/47
γ-Butyrolactone	1/50	0/50	1/50
Pentachloroanisole	3/50	0/50	3/50
Total	17/296 (5.7%)	3/296 (1.0%)	21/296 (7.1%)
Standard deviation	2.9%	1.7%	4.0%
Range	2%-10%	0%-4%	2%-14%
Overall Historical Incidence			
Total	41/802 (5.1%)	5/802 (0.6%)	47/802[b] (5.9%)
Standard deviation	2.7%	1.2%	3.5%
Range	0%-10%	0%-4%	0%-14%

[a] Data as of 3 April 1991
[b] Includes one complex pheochromocytoma

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Pentachloroanisole[a]

	Vehicle Control	20 mg/kg	40 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
9-Month interim evaluation	10	10	10
15-Month interim evaluation	10	10	10
Early deaths			
Moribund	17	13	4
Natural deaths	4	2	2
Survivors			
Terminal sacrifice	29	35	44
Animals examined microscopically	70	70	70
Alimentary System			
Intestine large, cecum	(50)	(1)	(50)
Inflammation, chronic	1 (2%)		
Parasite metazoan	2 (4%)		
Intestine large, colon	(49)	(1)	(49)
Inflammation, chronic	1 (2%)		
Parasite metazoan	2 (4%)		2 (4%)
Intestine large, rectum	(50)	(1)	(49)
Edema			1 (2%)
Inflammation, chronic	2 (4%)		
Parasite metazoan	7 (14%)		9 (18%)
Intestine small, ileum	(50)	(1)	(50)
Inflammation, chronic			1 (2%)
Intestine small, jejunum	(50)	(1)	(50)
Inflammation, chronic			1 (2%)
Necrosis			1 (2%)
Liver	(50)	(50)	(50)
Angiectasis		4 (8%)	2 (4%)
Basophilic focus	42 (84%)	44 (88%)	45 (90%)
Clear cell focus	5 (10%)	3 (6%)	2 (4%)
Developmental malformation		1 (2%)	5 (10%)
Eosinophilic focus	1 (2%)		2 (4%)
Granuloma	29 (58%)	19 (38%)	24 (48%)
Hematopoietic cell proliferation	2 (4%)	4 (8%)	3 (6%)
Hepatodiaphragmatic nodule	3 (6%)	7 (14%)	5 (10%)
Hyperplasia, focal	4 (8%)	6 (12%)	5 (10%)
Inflammation, chronic	11 (22%)	10 (20%)	12 (24%)
Inflammation, chronic active	1 (2%)		
Mixed cell focus		4 (8%)	4 (8%)
Bile duct, hyperplasia	31 (62%)	27 (54%)	17 (34%)
Centrilobular, atrophy	1 (2%)	1 (2%)	
Centrilobular, necrosis	1 (2%)	1 (2%)	1 (2%)
Hepatocyte, pigmentation		18 (36%)	24 (48%)
Hepatocyte, vacuolization cytoplasmic	4 (8%)	3 (6%)	1 (2%)
Kupffer cell, pigmentation	3 (6%)	2 (4%)	1 (2%)
Lobules, necrosis	2 (4%)	3 (6%)	1 (2%)
Oval cell, hyperplasia	1 (2%)		1 (2%)
Portal, necrosis			1 (2%)
Mesentery	(13)	(3)	(7)
Cyst	1 (8%)		
Necrosis			1 (14%)
Fat, inflammation, chronic active	2 (15%)		
Fat, necrosis	10 (77%)	3 (100%)	6 (86%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Alimentary System (continued)			
Pancreas	(50)		(50)
Atrophy	11 (22%)		10 (20%)
Cytoplasmic alteration	2 (4%)		
Hyperplasia, focal	3 (6%)		
Inflammation, chronic			3 (6%)
Duct, hyperplasia	1 (2%)		
Salivary glands	(50)		(50)
Atrophy			3 (6%)
Duct, dilatation	1 (2%)		1 (2%)
Stomach, forestomach	(50)	(1)	(50)
Edema	3 (6%)		1 (2%)
Foreign body		1 (100%)	
Inflammation, chronic active	1 (2%)	1 (100%)	1 (2%)
Ulcer	2 (4%)		1 (2%)
Mucosa, hyperplasia	3 (6%)	1 (100%)	3 (6%)
Stomach, glandular	(50)	(1)	(50)
Erosion	2 (4%)		
Mineralization	3 (6%)		
Mucosa, hyperplasia			1 (2%)
Tooth	(2)		(1)
Developmental malformation			1 (100%)
Inflammation, suppurative	1 (50%)		
Cardiovascular System			
Heart	(50)		(50)
Cardiomyopathy	20 (40%)		31 (62%)
Myocardium, inflammation, chronic	4 (8%)		1 (2%)
Endocrine System			
Adrenal gland	(50)	(50)	(50)
Hypertrophy, focal		1 (2%)	
Adrenal gland, cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	9 (18%)	13 (26%)	13 (26%)
Angiectasis	24 (48%)	30 (60%)	27 (54%)
Clear cell focus	4 (8%)	4 (8%)	4 (8%)
Cyst			1 (2%)
Degeneration, fatty		1 (2%)	
Hematopoietic cell proliferation	2 (4%)		
Hyperplasia, focal	12 (24%)	13 (26%)	12 (24%)
Hypertrophy, focal	1 (2%)	3 (6%)	4 (8%)
Necrosis		1 (2%)	
Vacuolization cytoplasmic, diffuse			1 (2%)
Adrenal gland, medulla	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
Hyperplasia	10 (20%)	18 (36%)	25 (50%)
Islets, pancreatic	(50)		(50)
Hyperplasia	2 (4%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Endocrine System (continued)			
Pituitary gland	(49)	(50)	(50)
Pars distalis, angiectasis	4 (8%)	7 (14%)	8 (16%)
Pars distalis, cyst	20 (41%)	27 (54%)	20 (40%)
Pars distalis, hyperplasia	9 (18%)	8 (16%)	8 (16%)
Pars distalis, pigmentation	9 (18%)	10 (20%)	9 (18%)
Pars intermedia, angiectasis		1 (2%)	1 (2%)
Pars intermedia, cyst	1 (2%)	2 (4%)	1 (2%)
Pars intermedia, pigmentation		1 (2%)	
Pars nervosa, cyst	1 (2%)		
Thyroid gland	(50)	(2)	(50)
Ultimobranchial cyst	3 (6%)		1 (2%)
C-cell, hyperplasia	5 (10%)		13 (26%)
Follicle, cyst			1 (2%)
Follicular cell, hyperplasia			1 (2%)
General Body System			
None			
Genital System			
Clitoral gland	(50)	(8)	(50)
Ectasia	4 (8%)	2 (25%)	2 (4%)
Hyperplasia			1 (2%)
Inflammation, chronic	3 (6%)	1 (13%)	5 (10%)
Inflammation, suppurative	3 (6%)		4 (8%)
Ovary	(50)	(5)	(50)
Cyst	1 (2%)	1 (20%)	6 (12%)
Uterus	(50)	(50)	(50)
Abscess	2 (4%)	1 (2%)	2 (4%)
Angiectasis		1 (2%)	
Cyst	1 (2%)		2 (4%)
Hemorrhage		3 (6%)	1 (2%)
Hydrometra	7 (14%)	2 (4%)	6 (12%)
Hyperplasia, cystic	13 (26%)	13 (26%)	20 (40%)
Inflammation, suppurative			2 (4%)
Necrosis		1 (2%)	
Myometrium, hyperplasia			1 (2%)
Hematopoietic System			
Bone marrow	(50)		(50)
Hypercellularity	1 (2%)		2 (4%)
Hyperplasia, reticulum cell	3 (6%)		3 (6%)
Lymph node	(50)	(11)	(50)
Bronchial, hemorrhage			1 (2%)
Bronchial, pigmentation			1 (2%)
Inguinal, hyperplasia, plasma cell	1 (2%)	1 (9%)	
Lumbar, hyperplasia, plasma cell		1 (9%)	
Lumbar, lymphatic, dilatation		1 (9%)	
Mediastinal, hemorrhage	7 (14%)		2 (4%)
Mediastinal, hyperplasia, lymphoid			1 (2%)
Mediastinal, hyperplasia, plasma cell		1 (9%)	2 (4%)
Mediastinal, pigmentation	10 (20%)	1 (9%)	7 (14%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Hematopoietic System (continued)			
Lymph node (continued)			
Pancreatic, hemorrhage		1 (9%)	
Pancreatic, hyperplasia, plasma cell	1 (2%)		
Pancreatic, infiltration cellular, histiocyte			1 (2%)
Pancreatic, lymphatic, dilatation	1 (2%)		
Renal, hemorrhage			1 (2%)
Renal, pigmentation		1 (9%)	1 (2%)
Lymph node, mandibular	(50)	(3)	(50)
Hemorrhage		1 (33%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (33%)	2 (4%)
Hyperplasia, plasma cell	14 (28%)	1 (33%)	20 (40%)
Infiltration cellular, mast cell	1 (2%)		
Pigmentation			1 (2%)
Lymphatic, dilatation	1 (2%)	1 (33%)	5 (10%)
Lymph node, mesenteric	(49)	(3)	(50)
Hemorrhage	2 (4%)	1 (33%)	1 (2%)
Hyperplasia, lymphoid			3 (6%)
Lymphatic, dilatation			1 (2%)
Spleen	(50)	(10)	(50)
Congestion			2 (4%)
Developmental malformation		1 (10%)	
Fibrosis			1 (2%)
Hematopoietic cell proliferation	15 (30%)	4 (40%)	6 (12%)
Hyperplasia, RE cell	1 (2%)		
Necrosis	1 (2%)	1 (10%)	
Pigmentation, hemosiderin	5 (10%)	2 (20%)	7 (14%)
Lymphoid follicle, hyperplasia			2 (4%)
Thymus	(47)		(48)
Cyst	3 (6%)		2 (4%)
Integumentary System			
Mammary gland	(48)	(21)	(50)
Hyperplasia, cystic	38 (79%)	15 (71%)	33 (66%)
Hyperplasia, lobular	4 (8%)	2 (10%)	2 (4%)
Skin	(50)	(3)	(50)
Hemorrhage		1 (33%)	
Inflammation, chronic			1 (2%)
Inflammation, granulomatous	1 (2%)		
Musculoskeletal System			
Bone	(50)	(6)	(50)
Calvarium, osteopetrosis	5 (10%)	6 (100%)	
Femur, osteopetrosis	6 (12%)		1 (2%)
Nervous System			
Brain	(50)	(4)	(50)
Compression	6 (12%)	3 (75%)	4 (8%)
Degeneration, focal	1 (2%)		
Hemorrhage	1 (2%)		1 (2%)
Hydrocephalus	4 (8%)	1 (25%)	4 (8%)
Necrosis			1 (2%)
Pigmentation	1 (2%)		
Meninges, fibrosis	1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Respiratory System			
Lung	(50)	(7)	(50)
Congestion	2 (4%)	1 (14%)	1 (2%)
Edema	2 (4%)		
Hemorrhage	1 (2%)		
Infiltration cellular, histiocyte	24 (48%)	4 (57%)	31 (62%)
Inflammation, chronic	12 (24%)	1 (14%)	18 (36%)
Inflammation, suppurative		1 (14%)	1 (2%)
Pigmentation, cholesterol	1 (2%)		
Thrombus			1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	2 (29%)	1 (2%)
Smooth muscle, hyperplasia	1 (2%)		
Nose	(49)	(50)	(50)
Developmental malformation			1 (2%)
Exudate	3 (6%)	8 (16%)	7 (14%)
Foreign body	1 (2%)	3 (6%)	1 (2%)
Fungus	1 (2%)	5 (10%)	1 (2%)
Inflammation, chronic	5 (10%)	13 (26%)	11 (22%)
Glands, hyperplasia	1 (2%)		
Glands, necrosis	1 (2%)		
Mucosa, hyperplasia		5 (10%)	2 (4%)
Mucosa, metaplasia, squamous		4 (8%)	
Olfactory epithelium, pigmentation		46 (92%)	50 (100%)
Trachea	(50)		(50)
Inflammation, chronic			1 (2%)
Special Senses System			
Eye	(1)	(4)	(8)
Cataract	1 (100%)	3 (75%)	8 (100%)
Phthisis bulbi		1 (25%)	
Cornea, inflammation, chronic active			1 (13%)
Cornea, mineralization			1 (13%)
Retina, atrophy	1 (100%)	3 (75%)	8 (100%)
Sclera, mineralization			2 (25%)
Urinary System			
Kidney	(50)	(50)	(50)
Cyst	1 (2%)	1 (2%)	1 (2%)
Hydronephrosis	1 (2%)		1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic	7 (14%)	11 (22%)	10 (20%)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)
Mineralization	21 (42%)	24 (48%)	15 (30%)
Nephropathy	41 (82%)	48 (96%)	42 (84%)
Renal tubule, atrophy			1 (2%)
Renal tubule, degeneration	1 (2%)		
Renal tubule, dilatation	1 (2%)	1 (2%)	1 (2%)
Renal tubule, pigmentation		43 (86%)	45 (90%)
Transitional epithelium, hyperplasia	4 (8%)		2 (4%)
Urethra	(1)		
Inflammation, chronic	1 (100%)		
Necrosis	1 (100%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Urinary System (continued)			
Urinary bladder	(50)	(1)	(49)
Hemorrhage			1 (2%)
Inflammation, chronic	1 (2%)		
Inflammation, subacute			2 (4%)
Mucosa, hyperplasia	1 (2%)		

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

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF PENTACHLOROANISOLE

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

	Vehicle Control	20 mg/kg	40 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
9-Month interim evaluation	10	10	10
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths	1	1	
Moribund	17	20	22
Natural deaths	2	2	
Survivors			
Died last week of study			1
Terminal sacrifice	30	27	27
Animals examined microscopically	70	70	70
Alimentary System			
Intestine small, ileum	(50)	(22)	(49)
Intestine small, jejunum	(50)	(23)	(49)
Adenocarcinoma			1 (2%)
Liver	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)	5 (10%)	3 (6%)
Hemangiosarcoma, multiple		3 (6%)	7 (14%)
Hepatocellular carcinoma	7 (14%)	14 (28%)	9 (18%)
Hepatocellular carcinoma, multiple	2 (4%)	2 (4%)	3 (6%)
Hepatocellular adenoma	18 (36%)	18 (36%)	13 (26%)
Hepatocellular adenoma, multiple	2 (4%)	6 (12%)	1 (2%)
Histiocytic sarcoma			1 (2%)
Mesentery	(2)	(9)	(4)
Fibrous histiocytoma		1 (11%)	
Squamous cell carcinoma, metastatic, stomach			1 (25%)
Pancreas	(50)	(23)	(50)
Fibrous histiocytoma		1 (4%)	
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Salivary glands	(50)	(23)	(50)
Stomach, forestomach	(50)	(50)	(50)
Fibrous histiocytoma		1 (2%)	
Papilloma squamous		1 (2%)	
Squamous cell carcinoma			1 (2%)
Stomach, glandular	(50)	(48)	(49)
Squamous cell carcinoma			1 (2%)
Cardiovascular System			
None			
Endocrine System			
Adrenal gland	(50)	(50)	(49)
Capsule, spindle cell, adenoma	4 (8%)		2 (4%)
Adrenal gland, cortex	(50)	(50)	(49)
Adenoma	1 (2%)		
Capsule, fibrous histiocytoma		1 (2%)	
Adrenal gland, medulla	(50)	(50)	(48)
Pheochromocytoma benign		4 (8%)	7 (15%)
Islets, pancreatic	(50)	(23)	(49)
Adenoma		1 (4%)	
Fibrous histiocytoma		1 (4%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Endocrine System (continued)			
Thyroid gland	(50)	(49)	(50)
C-cell, carcinoma	1 (2%)		
Follicular cell, adenoma		1 (2%)	
Follicular cell, carcinoma	1 (2%)		
General Body System			
Tissue NOS			(1)
Mediastinum, fibrosarcoma			1 (100%)
Genital System			
Epididymis	(50)	(24)	(50)
Fibrous histiocytoma		1 (4%)	
Prostate	(50)	(23)	(50)
Fibrous histiocytoma		1 (4%)	
Hepatocellular carcinoma, metastatic, liver		1 (4%)	
Seminal vesicle	(50)	(24)	(50)
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Testes	(50)	(23)	(50)
Interstitial cell, adenoma			1 (2%)
Hematopoietic System			
Bone marrow	(50)	(23)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)
Lymph node	(50)	(50)	(50)
Mediastinal, fibrous histiocytoma		1 (2%)	
Mediastinal, squamous cell carcinoma, metastatic, stomach			1 (2%)
Lymph node, mandibular	(48)	(49)	(49)
Lymph node, mesenteric	(50)	(49)	(50)
Fibrous histiocytoma		1 (2%)	
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Spleen	(50)	(50)	(50)
Hemangiosarcoma	3 (6%)	1 (2%)	5 (10%)
Thymus	(49)	(22)	(50)
Thymoma benign	1 (2%)		
Integumentary System			
Skin	(50)	(29)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma		1 (3%)	
Keratoacanthoma	1 (2%)		
Subcutaneous tissue, hemangioma		2 (7%)	
Musculoskeletal System			
Bone	(50)	(24)	(50)
Osteosarcoma		2 (8%)	
Skeletal muscle			(2)
Fibrosarcoma			1 (50%)
Hemangiosarcoma			1 (50%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Nervous System			
None			
Respiratory System			
Lung	(50)	(32)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	7 (22%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		
Alveolar/bronchiolar carcinoma	4 (8%)	4 (13%)	5 (10%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)	1 (3%)	
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (3%)	2 (4%)
Hepatocellular carcinoma, metastatic, multiple, liver		2 (6%)	2 (4%)
Histiocytic sarcoma			1 (2%)
Special Senses System			
Ear			(1)
Fibrosarcoma			1 (100%)
Harderian gland	(2)	(6)	(4)
Adenoma	2 (100%)	6 (100%)	4 (100%)
Urinary System			
Kidney	(50)	(25)	(50)
Hepatocellular carcinoma, metastatic, liver		1 (4%)	
Histiocytic sarcoma			1 (2%)
Renal tubule, carcinoma			1 (2%)
Urinary bladder	(50)	(24)	(50)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)
Lymphoma malignant histiocytic	2 (4%)	1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	2 (4%)	4 (8%)	8 (16%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	38	47	46
Total primary neoplasms	64	94	82
Total animals with benign neoplasms	29	36	25
Total benign neoplasms	37	46	32
Total animals with malignant neoplasms	21	30	35
Total malignant neoplasms	27	48	50
Total animals with metastatic neoplasms	2	4	5
Total metastatic neoplasms	2	5	9

[a] Number of animals examined microscopically at site and number of animal with lesion
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control

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

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 0 8 1	0 0 9 1	0 1 3 1	0 1 4 1	0 1 5 1	0 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 2 1 1	0 2 2 1	0 2 3 1	0 2 4 1	0 2 7 1	0 2 8 1	0 3 3 1	0 3 4 1	0 3 5 1	0 3 6 1	0 3 8 1	0 3 9 1	0 4 0 1	0 4 1 1	0 4 4 1	0 4 5 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatocellular carcinoma		X																	X							7
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma							X	X			X	X	X				X	X					X			18
Hepatocellular adenoma, multiple		X																								2
Mesentery													+													2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+		+	+	+	+	+	+		36
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, spindle cell, adenoma									X				X													4
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, carcinoma																										1
Follicular cell, carcinoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control
(continued)

Number of Days on Study	0 0 9	4 2 4	4 9 1	5 2 9	5 8 9	5 9 9	6 1 7	6 1 7	6 7 5	6 9 1	6 9 1	6 9 1	6 9 1	6 9 1	7 0 1	7 0 1	7 0 1	7 0 5	7 0 8	7 1 0	7 1 2	7 1 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 8 1	0 2 1	0 4 7 1	0 4 2 1	0 4 3 1	0 1 6 1	0 2 9 1	0 3 2 1	0 3 7 1	0 0 3 1	0 1 1 1	0 2 6 1	0 3 1 1	0 3 0 1	0 3 6 1	0 4 6 1	0 5 0 1	0 4 9 1	0 2 5 1	0 1 1 1	0 1 2 1	0 1 0 1	0 0 1 1	0 0 4 1	0 0 5 1	0 0 6 1	0 0 7 1
General Body System																											
None																											
Genital System																											
Coagulating gland							+																+		+		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																											
Preputial gland			+	+	+		+	+			+			+	+	+	+			+				+			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X	X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																											
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									X		
Keratoacanthoma																											
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 0 8 1	0 0 9 1	0 1 3 1	0 1 4 1	0 1 5 1	0 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 2 1 1	0 2 2 1	0 2 3 1	0 2 4 1	0 2 7 1	0 2 8 1	0 3 3 1	0 3 4 1	0 3 5 1	0 3 6 1	0 3 8 1	0 3 9 1	0 4 0 1	0 4 1 1	0 4 4 1	0 4 5 1	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Coagulating gland									+				+		+						+		+	+		9
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																								+		1
Preputial gland				+		+	+					+						+		+		+	+	+	+	22
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Thymoma benign													X													1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Keratoacanthoma																	X									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control
(continued)

Number of Days on Study	0	4	4	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	0	2	9	2	8	9	1	1	7	9	9	9	9	0	0	0	0	1	1	1	2	2	2	2	2
	9	4	1	9	9	9	7	7	5	1	1	1	1	1	1	5	8	0	2	7	9	9	9	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	4	4	4	1	2	3	3	0	1	2	3	3	4	5	4	2	1	1	0	0	0	0	0
	8	2	7	2	3	6	9	2	7	3	1	6	1	0	6	0	9	5	2	0	1	4	5	6	7
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																						X			
Alveolar/bronchiolar carcinoma, multiple												X													
Hepatocellular carcinoma, metastatic, liver															X		X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																+									
Adenoma																X									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic			X												X										
Lymphoma malignant mixed																									X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 0 8 1	0 0 9 1	0 1 3 1	0 1 4 1	0 1 5 1	0 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 2 1 1	0 2 2 1	0 2 3 1	0 2 4 1	0 2 7 1	0 2 8 1	0 3 3 1	0 3 4 1	0 3 5 1	0 3 6 1	0 3 8 1	0 3 9 1	0 4 0 1	0 4 1 1	0 4 4 1	0 4 5 1	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X	X		X										X		X						6
Alveolar/bronchiolar adenoma, multiple			X																							1
Alveolar/bronchiolar carcinoma																X	X	X								4
Alveolar/bronchiolar carcinoma, multiple			X																							2
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland	+																									2
Adenoma	X																									2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed											X															2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg

Number of Days on Study	5 9 2	6 5 1	6 7 6	6 8 2	6 9 0	6 9 1	6 9 1	6 9 6	7 0 1	7 0 1	7 0 2	7 0 2	7 0 2	7 0 4	7 0 4	7 0 5	7 0 1	7 1 1	7 1 5	7 1 6	7 1 6	7 1 7	7 1 7	7 1 7	7 1 9	7 2 9	7 3 1
Carcass ID Number	1 6 4 1	1 7 3 1	1 6 3 1	1 7 4 1	1 7 2 1	1 5 2 1	1 5 8 1	1 6 1 1	1 5 5 1	1 8 2 1	1 6 0 1	1 8 1 1	1 8 4 1	1 4 2 1	1 7 7 1	1 6 5 1	1 8 7 1	1 5 7 1	1 6 8 1	1 7 6 1	1 5 9 1	1 6 9 1	1 8 6 1	1 4 1 1	1 4 3 1
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Gallbladder	+	+	+	+	A	M	M	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, cecum	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, ileum	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X		X						X			X												
Hemangiosarcoma, multiple								X														X		X			
Hepatocellular carcinoma				X	X				X	X	X		X			X	X		X						X		
Hepatocellular carcinoma, multiple			X																				X				
Hepatocellular adenoma		X	X			X														X				X	X	X	
Hepatocellular adenoma, multiple													X					X			X	X					
Mesentery				+						+		+					+	+						+			
Fibrous histiocytoma												X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Fibrous histiocytoma												X															
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Fibrous histiocytoma												X															
Papilloma squamous																											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Tooth		+						+	+			+		+	+			+	+	+				+			
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, fibrous histiocytoma												X															
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign							X							X									X		X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Adenoma														X													
Fibrous histiocytoma												X															
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Follicular cell, adenoma																					X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 4 4 1	1 4 5 1	1 4 6 1	1 4 7 1	1 4 8 1	1 4 9 1	1 5 0 1	1 5 1 1	1 5 3 1	1 5 4 1	1 5 6 1	1 6 2 1	1 6 6 1	1 6 7 1	1 7 0 1	1 7 1 1	1 7 5 1	1 7 8 1	1 7 9 1	1 8 0 1	1 8 3 1	1 8 5 1	1 8 8 1	1 8 9 1	1 9 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus																										23
Gallbladder																										18
Intestine large																										23
Intestine large, cecum																										21
Intestine large, colon																										23
Intestine large, rectum																										23
Intestine small																+				+						25
Intestine small, duodenum																										22
Intestine small, ileum																+										22
Intestine small, jejunum																				+						23
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						5
Hemangiosarcoma, multiple																										3
Hepatocellular carcinoma			X							X								X						X		14
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma	X	X			X			X		X			X				X		X	X	X	X				18
Hepatocellular adenoma, multiple											X														X	6
Mesentery												+				+					+					9
Fibrous histiocytoma																										1
Pancreas																										23
Fibrous histiocytoma																										1
Salivary glands																										23
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Papilloma squamous																									X	1
Stomach, glandular	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Tooth																										10
Cardiovascular System																										
Heart																										23
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, fibrous histiocytoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										4
Islets, pancreatic																										23
Adenoma																										1
Fibrous histiocytoma																										1
Parathyroid gland																										22
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Follicular cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	5 9 2	6 5 1	6 7 6	6 8 2	6 9 0	6 9 1	6 9 1	6 9 6	7 0 1	7 0 1	7 0 2	7 0 2	7 0 2	7 0 4	7 0 4	7 0 5	7 1 1	7 1 5	7 1 6	7 1 6	7 1 7	7 1 7	7 1 7	7 2 9	7 3 1
Carcass ID Number	1 6 4 1	1 7 3 1	1 6 3 1	1 7 4 1	1 7 2 1	1 5 2 1	1 5 8 1	1 6 1 1	1 5 5 1	1 8 2 1	1 6 0 1	1 8 1 1	1 8 4 1	1 4 2 1	1 4 2 1	1 7 7 1	1 6 5 1	1 8 7 1	1 5 7 1	1 6 8 1	1 7 6 1	1 5 9 1	1 6 9 1	1 8 6 1	1 4 1 1	1 4 3 1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Fibrous histiocytoma												X													
Preputial gland	+	+	+				+	+	+	+	+	+	+			+	+	+	+	+	+	+	+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Fibrous histiocytoma												X													
Hepatocellular carcinoma, metastatic, liver			X																						
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, fibrous histiocytoma												X													
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hemangiosarcoma						X																			
Subcutaneous tissue, hemangioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Osteosarcoma																		X							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	731	732	733	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	44411	45511	46611	47111	48111	49111	50111	51111	53111	54111	56111	62111	66111	67111	70111	71111	75111	78111	79111	80111	83111	85111	88111	89111	90111	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis																							+			24
Fibrous histiocytoma																										1
Preputial gland			+		+		+		+	+		+	+			+	+	+		+	+	+	+			32
Prostate																										23
Fibrous histiocytoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Seminal vesicle																										24
Testes																										23
Hematopoietic System																										
Bone marrow																										23
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, fibrous histiocytoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus																										22
Integumentary System																										
Mammary gland																										
Skin						+			+						+		+	+					+			29
Hemangiosarcoma																										1
Subcutaneous tissue, hemangioma									X														X			2
Musculoskeletal System																										
Bone				+																						24
Osteosarcoma				X																						2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 9 5 7 8 9 9 9 9 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 2 3 2 1 6 2 0 1 1 6 1 1 2 2 2 4 4 5 1 5 6 6 7 7 7 9 1
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 6 7 6 7 7 5 5 6 5 8 6 8 8 4 7 6 8 5 6 7 5 6 8 4 4 4 3 3 4 2 2 8 1 5 2 0 1 4 2 7 5 7 7 8 6 9 9 6 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X X X X X
Alveolar/bronchiolar carcinoma	
Alveolar/bronchiolar carcinoma, multiple	X
Hepatocellular carcinoma, metastatic, liver	X
Hepatocellular carcinoma, metastatic, multiple, liver	X X
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	
Harderian gland	+ +
Adenoma	X X
Urinary System	
Kidney	+ +
Hepatocellular carcinoma, metastatic, liver	X
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant histiocytic	X
Lymphoma malignant lymphocytic	X
Lymphoma malignant mixed	X X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	731	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	14441	14451	14461	14471	14481	14491	15501	15511	15531	15541	15561	16021	16061	16071	17001	17011	17051	17081	17091	18001	18031	18051	18081	18091	19001	Total Tissues/ Tumors
Nervous System																										
Brain																										23
Respiratory System																										
Lung			+		+			+				+			+		+			+				+	32
Alveolar/bronchiolar adenoma			X												X											7
Alveolar/bronchiolar carcinoma								X				X								X				X		4
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, multiple, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea																										23
Special Senses System																										
Eye															+											1
Harderian gland							+				+				+		+									6
Adenoma							X				X				X		X									6
Urinary System																										
Kidney						+																				25
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder																										24
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed															X					X						4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg (continued)

Number of Days on Study	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 7 1	0 7 4 1	0 7 6 1	0 7 7 1	0 8 2 1	0 8 4 1	0 8 5 1	0 8 6 1	0 8 8 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 7 1	0 9 8 1	1 0 2 1	1 0 5 1	1 0 7 1	1 0 8 1	1 1 3 1	1 1 3 1	1 1 4 1	1 1 5 1	1 1 6 1	1 1 7 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma				X																						1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X											X											3
Hemangiosarcoma, multiple																			X		X				X	7
Hepatocellular carcinoma														X												9
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma		X	X		X		X		X				X	X	X											13
Hepatocellular adenoma, multiple																			X							1
Histiocytic sarcoma																										1
Mesentery								+			+															4
Squamous cell carcinoma, metastatic, stomach																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Tooth		+				+	+		+	+	+	+	+				+		+					+	+	24
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, spindle cell, adenoma											X															2
Adrenal gland, cortex	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign	X		X						X															X		7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg (continued)

Number of Days on Study	4 6 7	5 4 8	5 5 0	5 9 6	5 9 6	5 9 6	5 9 9	6 1 0	6 1 1	6 1 2	6 7 7	6 9 1	6 9 1	6 9 8	7 0 1	7 0 1	7 0 2	7 0 5	7 0 5	7 0 5	7 1 5	7 1 5	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 0 3 1	0 7 9 1	0 7 8 1	0 8 9 1	1 0 6 1	1 2 0 1	1 1 0 1	0 8 3 1	0 9 0 1	0 9 5 1	1 0 4 1	0 7 5 1	0 8 1 1	1 1 8 1	1 1 2 1	1 1 9 1	1 0 0 1	0 9 9 1	0 0 0 1	1 1 9 1	0 8 0 1	0 9 6 1	0 7 1 1	0 7 2 1	0 7 3 1
General Body System																									
Tissue NOS																									
Mediastinum, fibrosarcoma																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+				+		+	+		+		+	+		+	+	+	+	+	+	+			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach				X																					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, squamous cell carcinoma, metastatic, stomach				X																					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X								X		X					
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+															
Fibrosarcoma																									
Hemangiosarcoma										X															

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg (continued)

Number of Days on Study	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 7 1	0 7 4 1	0 7 6 1	0 7 7 1	0 8 2 1	0 8 4 1	0 8 5 1	0 8 6 1	0 8 8 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 7 1	0 9 8 1	0 9 9 1	1 0 2 1	1 0 5 1	1 0 7 1	1 0 8 1	1 1 1 1	1 1 3 1	1 1 4 1	1 1 5 1	1 1 6 1	1 1 7 1	Total Tissues/ Tumors
General Body System																											
Tissue NOS																			+								1
Mediastinum, fibrosarcoma																			X								1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland					+	+	+	+				+			+		+			+	+	+			+	+	26
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach																											1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma						X																					1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma															X												1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, squamous cell carcinoma, metastatic, stomach																											1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X				X	5
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																			+								2
Fibrosarcoma																			X								1
Hemangiosarcoma																											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg (continued)

Number of Days on Study	4 6 7	5 4 8	5 5 0	5 9 6	5 9 6	5 9 6	5 9 9	6 1 0	6 1 1	6 1 2	6 7 7	6 9 1	6 9 1	6 9 8	7 0 1	7 0 1	7 0 2	7 0 5	7 0 5	7 0 5	7 1 5	7 1 5	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 0 3 1	0 7 9 1	0 7 8 1	0 8 9 1	1 0 6 1	1 2 0 1	1 1 0 1	0 8 3 1	0 9 0 1	0 9 5 1	1 0 4 1	0 7 5 1	0 8 1 1	1 1 8 1	1 1 2 1	1 1 9 1	1 0 0 1	0 9 9 1	1 0 1 1	1 0 9 1	1 0 0 1	0 8 1 1	0 9 6 1	0 7 1 1	0 7 2 1	0 7 3 1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Alveolar/bronchiolar carcinoma																								X	
Hepatocellular carcinoma, metastatic, liver						X								X											
Hepatocellular carcinoma, metastatic, multiple, liver												X							X						
Histiocytic sarcoma									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Fibrosarcoma																									
Harderian gland															+										
Adenoma															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Renal tubule, carcinoma																					X				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymphoma malignant mixed	X	X					X						X						X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg (continued)

Number of Days on Study	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 8 7 1	0 7 4 1	0 7 6 1	0 7 7 1	0 8 2 1	0 8 4 1	0 8 5 1	0 8 6 1	0 8 8 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 7 1	0 9 8 1	0 9 9 1	1 0 2 1	1 0 5 1	1 0 7 1	1 0 8 1	1 1 1 1	1 1 3 1	1 1 4 1	1 1 5 1	1 1 6 1	1 1 7 1	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X	X									X														4
Alveolar/bronchiolar carcinoma			X			X											X	X								5
Hepatocellular carcinoma, metastatic, liver																										2
Hepatocellular carcinoma, metastatic, multiple, liver																										2
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																		+								1
Fibrosarcoma																		X								1
Harderian gland														+						+		+				4
Adenoma														X						X		X				4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant mixed				X																X			X			8

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Pentachloroanisole

	Vehicle Control	20 mg/kg	40 mg/kg
Adrenal Gland: Adenoma			
Overall rates[a]	4/41 (10%)	0/28 (0%)	2/10 (20%)
Adjusted rates[b]	13.5%	0.0%	27.6%
Terminal rates[c]	2/23 (9%)	0/14 (0%)	1/4 (25%)
First incidence (days)	589	–[e]	715
Life table tests[d]	P=0.484N	P=0.094N	P=0.655
Logistic regression tests[d]	P=0.529	P=0.119N	P=0.307
Cochran-Armitage test[d]	P=0.535		
Fisher exact test[d]		P=0.117N	P=0.334
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates	0/50 (0%)	4/50 (8%)	7/48 (15%)
Adjusted rates	0.0%	11.4%	23.3%
Terminal rates	0/30 (0%)	1/27 (4%)	5/27 (19%)
First incidence (days)	–	691	691
Life table tests	P=0.005	P=0.067	P=0.007
Logistic regression tests	P=0.004	P=0.069	P=0.007
Cochran-Armitage test	P=0.005		
Fisher exact test		P=0.059	P=0.005
Harderian Gland: Adenoma			
Overall rates	2/50 (4%)	6/50 (12%)	4/50 (8%)
Adjusted rates	6.1%	19.4%	13.2%
Terminal rates	1/30 (3%)	4/27 (15%)	3/28 (11%)
First incidence (days)	705	701	701
Life table tests	P=0.264	P=0.126	P=0.312
Logistic regression tests	P=0.264	P=0.160	P=0.318
Cochran-Armitage test	P=0.290		
Fisher exact test		P=0.134	P=0.339
Liver: Hepatocellular Adenoma			
Overall rates	20/50 (40%)	24/50 (48%)	14/50 (28%)
Adjusted rates	51.5%	65.6%	44.2%
Terminal rates	12/30 (40%)	15/27 (56%)	11/28 (39%)
First incidence (days)	424	651	596
Life table tests	P=0.207N	P=0.244	P=0.213N
Logistic regression tests	P=0.126N	P=0.356	P=0.142N
Cochran-Armitage test	P=0.129N		
Fisher exact test		P=0.273	P=0.146N
Liver: Hepatocellular Carcinoma			
Overall rates	9/50 (18%)	16/50 (32%)	12/50 (24%)
Adjusted rates	23.1%	38.8%	29.2%
Terminal rates	2/30 (7%)	5/27 (19%)	2/28 (7%)
First incidence (days)	599	676	596
Life table tests	P=0.262	P=0.125	P=0.294
Logistic regression tests	P=0.282	P=0.093	P=0.312
Cochran-Armitage test	P=0.281		
Fisher exact test		P=0.083	P=0.312

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	26/50 (52%)	34/50 (68%)	24/50 (48%)
Adjusted rates	60.1%	78.4%	58.8%
Terminal rates	13/30 (43%)	18/27 (67%)	12/28 (43%)
First incidence (days)	424	651	596
Life table tests	P=0.508N	P=0.122	P=0.523N
Logistic regression tests	P=0.360N	P=0.115	P=0.403N
Cochran-Armitage test	P=0.381N		
Fisher exact test		P=0.076	P=0.421N
Liver: Hemangiosarcoma			
Overall rates	2/50 (4%)	8/50 (16%)	10/50 (20%)
Adjusted rates	5.7%	20.0%	29.9%
Terminal rates	0/30 (0%)	1/27 (4%)	6/28 (21%)
First incidence (days)	701	682	612
Life table tests	P=0.014	P=0.069	P=0.015
Logistic regression tests	P=0.013	P=0.051	P=0.015
Cochran-Armitage test	P=0.014		
Fisher exact test		P=0.046	P=0.014
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	7/50 (14%)	7/32 (22%)	4/50 (8%)
Adjusted rates	22.0%	40.2%	13.4%
Terminal rates	6/30 (20%)	3/9 (33%)	3/28 (11%)
First incidence (days)	691	682	705
Life table tests	P=0.282N	P=0.125	P=0.300N
Logistic regression tests	P=0.257N	P=0.231	P=0.287N
Cochran-Armitage test	P=0.233N		
Fisher exact test		P=0.264	P=0.262N
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	6/50 (12%)	5/32 (16%)	5/50 (10%)
Adjusted rates	18.7%	45.7%	17.9%
Terminal rates	5/30 (17%)	4/9 (44%)	5/28 (18%)
First incidence (days)	691	691	729 (T)
Life table tests	P=0.494N	P=0.149	P=0.548N
Logistic regression tests	P=0.483N	P=0.324	P=0.541N
Cochran-Armitage test	P=0.439N		
Fisher exact test		P=0.438	P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	11/50 (22%)	12/32 (38%)	8/50 (16%)
Adjusted rates	33.4%	80.5%	27.3%
Terminal rates	9/30 (30%)	7/9 (78%)	7/28 (25%)
First incidence (days)	691	682	705
Life table tests	P=0.348N	P=0.013	P=0.361N
Logistic regression tests	P=0.318N	P=0.066	P=0.344N
Cochran-Armitage test	P=0.278N		
Fisher exact test		P=0.102	P=0.306N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
All Organs: Hemangiosarcoma			
Overall rates	4/50 (8%)	8/50 (16%)	10/50 (20%)
Adjusted rates	11.6%	20.0%	29.9%
Terminal rates	1/30 (3%)	1/27 (4%)	6/28 (21%)
First incidence (days)	701	682	612
Life table tests	P=0.056	P=0.215	P=0.068
Logistic regression tests	P=0.058	P=0.196	P=0.071
Cochran-Armitage test	P=0.060		
Fisher exact test		P=0.178	P=0.074
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	5/50 (10%)	10/50 (20%)	10/50 (20%)
Adjusted rates	14.7%	26.2%	29.9%
Terminal rates	2/30 (7%)	3/27 (11%)	6/28 (21%)
First incidence (days)	701	682	612
Life table tests	P=0.103	P=0.155	P=0.116
Logistic regression tests	P=0.109	P=0.159	P=0.124
Cochran-Armitage test	P=0.114		
Fisher exact test		P=0.131	P=0.131
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)			
Overall rates	4/50 (8%)	6/50 (12%)	8/50 (16%)
Adjusted rates	11.1%	16.8%	20.9%
Terminal rates	2/30 (7%)	2/27 (7%)	3/28 (11%)
First incidence (days)	491	592	467
Life table tests	P=0.137	P=0.374	P=0.175
Logistic regression tests	P=0.114	P=0.325	P=0.149
Cochran-Armitage test	P=0.141		
Fisher exact test		P=0.370	P=0.178
All Organs: Benign Neoplasms			
Overall rates	29/50 (58%)	36/50 (72%)	25/50 (50%)
Adjusted rates	70.2%	85.2%	70.9%
Terminal rates	18/30 (60%)	21/27 (78%)	18/28 (64%)
First incidence (days)	424	651	596
Life table tests	P=0.388N	P=0.124	P=0.402N
Logistic regression tests	P=0.236N	P=0.185	P=0.272N
Cochran-Armitage test	P=0.237N		
Fisher exact test		P=0.104	P=0.274N
All Organs: Malignant Neoplasms			
Overall rates	21/50 (42%)	30/50 (60%)	35/50 (70%)
Adjusted rates	50.3%	64.2%	74.2%
Terminal rates	10/30 (33%)	11/27 (41%)	16/28 (57%)
First incidence (days)	491	592	467
Life table tests	P=0.013	P=0.112	P=0.015
Logistic regression tests	P=0.003	P=0.067	P=0.005
Cochran-Armitage test	P=0.003		
Fisher exact test		P=0.055	P=0.004

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
All Organs: Benign or Malignant Neoplasms			
Overall rates	38/50 (76%)	47/50 (94%)	46/50 (92%)
Adjusted rates	80.8%	94.0%	95.8%
Terminal rates	21/30 (70%)	24/27 (89%)	26/28 (93%)
First incidence (days)	424	592	467
Life table tests	P=0.071	P=0.102	P=0.085
Logistic regression tests	P=0.018	P=0.023	P=0.035
Cochran-Armitage test	P=0.012		
Fisher exact test		P=0.011	P=0.027

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone (including marrow), brain, epididymis, gallbladder, heart, kidney, large intestine, liver, lung, mammary gland, mandibular or mesenteric lymph node, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicles, skin, small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Adrenal Medulla Pheochromocytomas in Male B6C3F$_1$ Mice Administered Corn Oil by Gavage[a]

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence at Southern Research Institute			
Benzaldehyde	2/49	0/49	2/49
Dichlorvos	2/48	0/48	2/48
Furan	1/49	0/49	1/49
Furfural	2/50	1/50	3/50
γ-Butyrolactone	1/48	1/48	2/48
p-Nitroaniline	1/50	0/50	1/50
Pentachloroanisole	0/50	0/50	0/50
Total	9/344 (2.6%)	2/344 (0.6%)	11/344 (3.2%)
Standard deviation	1.5%	1.0%	2.0%
Range	0%-4%	0%-2%	0%-6%
Overall Historical Incidence			
Total	17/682 (2.5%)	2/682 (0.3%)	19/682 (2.8%)
Standard deviation	1.6%	0.7%	1.9%
Range	0%-4%	0%-2%	0%-6%

[a] Data as of 3 April 1991

TABLE C4b
Historical Incidence of Malignant Lymphomas in Male B6C3F$_1$ Mice Administered Corn Oil by Gavage[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzaldehyde	1/50
Dichlorvos	7/50
Furan	5/50
Furfural	5/50
γ-Butyrolactone	4/50
p-Nitroaniline	4/50
Pentachloroanisole	4/50
Total	30/350 (8.6%)[b]
Standard deviation	3.6%
Range	2%-14%
Overall Historical Incidence	
Total	69/700 (9.9%)
Standard deviation	3.9%
Range	2%-18%

[a] Data as of 3 April 1991
[b] Includes data for histiocytic, lymphocytic, mixed, NOS, and undifferentiated cell type lymphomas

TABLE C4c
Historical Incidence of Osteosarcomas in Male B6C3F$_1$ Mice Administered Corn Oil by Gavage[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzaldehyde	0/50
Dichlorvos	0/50
Furan	0/50
Furfural	0/50
γ-Butyrolactone	0/50
p-Nitroaniline	0/50
Pentachloroanisole	0/50
Overall Historical Incidence	
Total	1/700 (0.1%)
Standard deviation	0.5%
Range	0%-2%

[a] Data as of 3 April 1991

TABLE C4d
Historical Incidence of Liver Hemangiomas and Hemangiosarcomas in Male B6C3F$_1$ Mice Administered Corn Oil by Gavage[a]

Study	Incidence in Controls	
	Hemangioma	Hemangiosarcoma
Historical Incidence at Southern Research Institute		
Benzaldehyde	1/50	0/50
Dichlorvos	0/50	1/50
Furan	0/50	2/50
Furfural	1/50	2/50
γ-Butyrolactone	0/50	2/50
p-Nitroaniline	0/50	0/50
Pentachloroanisole	0/50	2/50
Total	2/350 (0.6%)	9/350 (2.6%)
Standard deviation	1.0%	1.9%
Range	0%-2%	0%-4%
Overall Historical Incidence		
Total	3/699 (0.4%)	15/699 (2.1%)
Standard deviation	0.9%	2.1%
Range	0%-2%	0%-6%

[a] Data as of 3 April 1991

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Pentachloroanisole[a]

	Vehicle Control	20 mg/kg	40 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
9-Month interim evaluation	10	10	10
15-Month interim evaluation	10	10	10
Early deaths			
Accidental deaths	1	1	
Moribund	17	20	22
Natural deaths	2	2	
Survivors			
Terminal sacrifice	30	27	27
Died last week of study			1
Animals examined microscopically	70	70	70
Alimentary System			
Intestine large, colon	(50)	(23)	(50)
Inflammation, suppurative			1 (2%)
Intestine large, rectum	(50)	(23)	(50)
Inflammation, suppurative			1 (2%)
Intestine small, ileum	(50)	(22)	(49)
Hyperplasia		1 (5%)	
Liver	(50)	(50)	(50)
Angiectasis	1 (2%)	3 (6%)	
Basophilic focus	5 (10%)	1 (2%)	1 (2%)
Basophilic focus, multiple		1 (2%)	
Clear cell focus	2 (4%)	1 (2%)	2 (4%)
Clear cell focus, multiple		3 (6%)	3 (6%)
Cytologic alterations		50 (100%)	50 (100%)
Eosinophilic focus	8 (16%)	1 (2%)	
Eosinophilic focus, multiple	2 (4%)		
Fibrosis	1 (2%)		
Hematopoietic cell proliferation	1 (2%)		2 (4%)
Inflammation, subacute		49 (98%)	49 (98%)
Mixed cell focus	7 (14%)	4 (8%)	5 (10%)
Mixed cell focus, multiple	2 (4%)	11 (22%)	22 (44%)
Necrosis	2 (4%)		1 (2%)
Biliary tract, dilatation		1 (2%)	2 (4%)
Biliary tract, fibrosis			1 (2%)
Biliary tract, hyperplasia		47 (94%)	48 (96%)
Kupffer cell, pigmentation	1 (2%)	50 (100%)	50 (100%)
Mesentery	(2)	(9)	(4)
Hemorrhage		2 (22%)	
Fat, necrosis	2 (100%)	5 (56%)	2 (50%)
Pancreas	(50)	(23)	(50)
Acinar cell, atrophy	5 (10%)	4 (17%)	3 (6%)
Duct, dilatation			3 (6%)
Stomach, forestomach	(50)	(50)	(50)
Hyperplasia	19 (38%)	23 (46%)	24 (48%)
Stomach, glandular	(50)	(48)	(49)
Hyperplasia	1 (2%)		
Tooth	(36)	(10)	(24)
Dysplasia	35 (97%)	10 (100%)	23 (96%)
Foreign body	1 (3%)		
Inflammation, chronic			1 (4%)
Inflammation, subacute	1 (3%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Cardiovascular System			
Heart	(50)	(23)	(50)
Inflammation, subacute			1 (2%)
Endocrine System			
Adrenal gland	(50)	(50)	(49)
Capsule, spindle cell, hyperplasia	4 (8%)	2 (4%)	3 (6%)
Adrenal gland, cortex	(50)	(50)	(49)
Accessory adrenal cortical nodule	1 (2%)		1 (2%)
Hypertrophy, focal	9 (18%)	4 (8%)	7 (14%)
Adrenal gland, medulla	(50)	(50)	(48)
Hyperplasia		13 (26%)	29 (60%)
Hypertrophy		3 (6%)	36 (75%)
Parathyroid gland	(49)	(22)	(50)
Cyst	2 (4%)		
Pituitary gland	(44)	(50)	(47)
Pars distalis, cyst	3 (7%)	1 (2%)	4 (9%)
Pars distalis, hyperplasia	1 (2%)	1 (2%)	
Thyroid gland	(50)	(49)	(50)
Follicular cell, hyperplasia	1 (2%)		
General Body System			
None			
Genital System			
Epididymis	(50)	(24)	(50)
Granuloma sperm			1 (2%)
Preputial gland	(22)	(32)	(26)
Inflammation, subacute	3 (14%)	5 (16%)	2 (8%)
Duct, cyst	20 (91%)	26 (81%)	26 (100%)
Seminal vesicle	(50)	(24)	(50)
Inflammation, subacute		1 (4%)	
Testes	(50)	(23)	(50)
Atrophy	1 (2%)		
Hematopoietic System			
Bone marrow	(50)	(23)	(50)
Myeloid cell, hypercellularity			2 (4%)
Lymph node	(50)	(50)	(50)
Inguinal, hyperplasia, lymphoid		1 (2%)	
Mediastinal, hyperplasia, lymphoid			1 (2%)
Lymph node, mesenteric	(50)	(49)	(50)
Angiectasis			1 (2%)
Congestion			1 (2%)
Hematopoietic cell proliferation	1 (2%)		
Hyperplasia, lymphoid	1 (2%)	2 (4%)	1 (2%)
Thrombus		1 (2%)	
Spleen	(50)	(50)	(50)
Hematopoietic cell proliferation	7 (14%)	8 (16%)	10 (20%)
Hemorrhage	1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Integumentary System			
Skin	(50)	(29)	(50)
Inflammation, suppurative		1 (3%)	
Musculoskeletal System			
Bone	(50)	(24)	(50)
Hypertrophy			1 (2%)
Nervous System			
Brain	(50)	(23)	(50)
Hemorrhage			1 (2%)
Necrosis			1 (2%)
Respiratory System			
Lung	(50)	(32)	(50)
Foreign body		1 (3%)	
Hemorrhage		1 (3%)	1 (2%)
Infiltration cellular, histiocyte	7 (14%)	3 (9%)	5 (10%)
Thrombus			1 (2%)
Alveolar epithelium, hyperplasia	7 (14%)	4 (13%)	2 (4%)
Nose	(50)	(50)	(50)
Exudate, serous	1 (2%)		
Foreign body	2 (4%)	14 (28%)	10 (20%)
Inflammation, suppurative	5 (10%)	12 (24%)	10 (20%)
Mucosa, atrophy	1 (2%)		
Special Senses System			
None			
Urinary System			
Kidney	(50)	(25)	(50)
Inflammation, subacute		1 (4%)	
Nephropathy	21 (42%)	12 (48%)	17 (34%)
Cortex, cyst	4 (8%)	3 (12%)	4 (8%)
Renal tubule, hyperplasia	1 (2%)		1 (2%)

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

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF PENTACHLOROANISOLE

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

	Vehicle Control	20 mg/kg	40 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
9-Month interim evaluation	10	10	10
15-Month interim evaluation	10	10	7
Early deaths			
Accidental deaths	1	1	
Moribund	17	18	29
Natural deaths	8	6	8
Survivors			
Terminal sacrifice	24	25	16
Animals examined microscopically	70	70	70
Alimentary System			
Intestine large, cecum	(43)	(21)	(49)
Intestine small, duodenum	(48)	(21)	(49)
Polyp adenomatous			1 (2%)
Intestine small, jejunum	(48)	(23)	(49)
Adenocarcinoma			1 (2%)
Sarcoma	1 (2%)		
Liver	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
Hepatoblastoma			1 (2%)
Hepatocellular carcinoma	4 (8%)	2 (4%)	2 (4%)
Hepatocellular adenoma	8 (16%)	6 (12%)	10 (20%)
Hepatocellular adenoma, multiple		2 (4%)	2 (4%)
Hepatocholangiocarcinoma			1 (2%)
Histiocytic sarcoma	1 (2%)		
Sarcoma		1 (2%)	
Mesentery	(25)	(18)	(24)
Cholangiocarcinoma, metastatic, liver			1 (4%)
Fibrosarcoma			1 (4%)
Hemangiosarcoma	1 (4%)		2 (8%)
Sarcoma	1 (4%)	2 (11%)	
Pancreas	(50)	(28)	(50)
Cholangiocarcinoma, metastatic, liver			1 (2%)
Fibrosarcoma			1 (2%)
Sarcoma	1 (2%)		
Salivary glands	(50)	(25)	(49)
Hemangiosarcoma	1 (2%)		
Stomach, forestomach	(50)	(45)	(50)
Papilloma squamous		2 (4%)	
Sarcoma	1 (2%)		
Stomach, glandular	(50)	(44)	(50)
Carcinoid tumor malignant	1 (2%)		
Tooth		(1)	
Sarcoma		1 (100%)	
Cardiovascular System			
Heart	(50)	(25)	(50)
Cholangiocarcinoma, metastatic, liver			1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(49)
Adrenal gland, medulla	(50)	(49)	(48)
Pheochromocytoma benign		1 (2%)	
Islets, pancreatic	(50)	(25)	(50)
Pituitary gland	(47)	(49)	(50)
Pars distalis, adenoma	7 (15%)	5 (10%)	3 (6%)
Pars intermedia, adenoma		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)		
Follicular cell, carcinoma			1 (2%)
General Body System			
None			
Genital System			
Ovary	(45)	(36)	(50)
Cystadenoma, papillary	1 (2%)		2 (4%)
Hemangioma			1 (2%)
Luteoma		1 (3%)	
Sarcoma		1 (3%)	
Teratoma malignant	1 (2%)		
Teratoma NOS		1 (3%)	
Uterus	(46)	(43)	(50)
Adenoma		1 (2%)	
Fibrous histiocytoma		1 (2%)	
Hemangioma	1 (2%)		
Hemangiosarcoma			1 (2%)
Histiocytic sarcoma	1 (2%)		
Leiomyoma		1 (2%)	
Leiomyosarcoma		1 (2%)	
Sarcoma		2 (5%)	1 (2%)
Sarcoma stromal		1 (2%)	
Hematopoietic System			
Bone marrow	(50)	(25)	(50)
Hemangiosarcoma	2 (4%)		1 (2%)
Lymph node	(50)	(50)	(50)
Bronchial, cholangiocarcinoma, metastatic, liver			1 (2%)
Iliac, sarcoma		1 (2%)	
Mediastinal, cholangiocarcinoma, metastatic, liver			1 (2%)
Renal, neoplasm NOS, metastatic, ovary	1 (2%)		
Lymph node, mandibular	(49)	(47)	(49)
Mast cell tumor benign	1 (2%)		
Lymph node, mesenteric	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		
Spleen	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)	3 (6%)	
Thymus	(48)	(24)	(47)
Fibrosarcoma			1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Integumentary System			
Mammary gland	(49)	(23)	(50)
Adenocarcinoma	1 (2%)	1 (4%)	
Skin	(50)	(26)	(50)
Subcutaneous tissue, fibrosarcoma			1 (2%)
Subcutaneous tissue, hemangiosarcoma	2 (4%)	1 (4%)	
Musculoskeletal System			
Skeletal muscle		(1)	(3)
Fibrosarcoma		1 (100%)	1 (33%)
Rhabdomyosarcoma			1 (33%)
Nervous System			
Brain	(50)	(26)	(50)
Meningioma benign			1 (2%)
Respiratory System			
Lung	(50)	(27)	(50)
Adenocarcinoma, metastatic, harderian gland		2 (7%)	
Alveolar/bronchiolar adenoma	2 (4%)	1 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma		1 (4%)	1 (2%)
Cholangiocarcinoma, metastatic, liver			1 (2%)
Fibrosarcoma			1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		1 (2%)
Mediastinum, fibrosarcoma			1 (2%)
Special Senses System			
Ear	(2)	(1)	(1)
Fibrosarcoma		1 (100%)	
Harderian gland	(6)	(2)	(4)
Adenocarcinoma		2 (100%)	
Adenoma	3 (50%)		4 (100%)
Urinary System			
Kidney	(50)	(25)	(50)
Cholangiocarcinoma, metastatic, liver			1 (2%)
Urinary bladder	(49)	(26)	(47)
Hemangioma		1 (4%)	
Histiocytic sarcoma	1 (2%)		
Sarcoma		1 (4%)	
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	8 (16%)
Lymphoma malignant mixed	4 (8%)	7 (14%)	4 (8%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Neoplasm Summary			
Total animals with primary neoplasms[c]	32	31	30
Total primary neoplasms	52	56	58
Total animals with benign neoplasms	21	19	18
Total benign neoplasms	24	22	25
Total animals with malignant neoplasms	19	20	23
Total malignant neoplasms	28	33	33
Total animals with metastatic neoplasms	2	2	1
Total metastatic neoplasms	2	2	8
Total animals with neoplasms uncertain-benign or malignant		1	
Total uncertain neoplasms		1	

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control

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

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 0 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 2 2 1	2 1 5 1	2 1 8 1	2 2 4 1	2 2 5 1	2 2 6 1	2 2 9 1	2 3 0 1	2 3 5 1	2 3 7 1	2 3 9 1	2 4 1 1	2 4 2 1	2 4 3 1	2 4 5 1	2 4 6 1	2 4 7 1	2 4 8 1	2 5 0 1	2 5 1 1	2 5 2 1	2 5 4 1	2 5 8 1	2 5 9 1	2 6 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X						X																		4
Hepatocellular adenoma			X			X				X	X						X									8
Histiocytic sarcoma																										1
Mesentery			+		+			+		+			+				+	+			+	+		+	+	25
Hemangiosarcoma																		X								1
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma															X											1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor malignant										X																1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Pars distalis, adenoma		X			X					X												X				7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma						X																				1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	0 7 2	0 8 1	4 0 0	4 1 0	4 1 1	4 2 8	4 7 4	4 7 7	4 7 7	5 0 5	5 1 7	5 6 0	5 7 6	5 8 3	6 0 5	6 1 1	6 2 4	6 3 3	6 3 9	6 7 4	6 7 4	6 7 5	6 8 7	7 0 2	7 0 4
Carcass ID Number	2 3 6 1	2 4 9 1	2 5 7 1	2 3 2 1	2 1 4 1	2 1 6 1	2 3 1 1	2 1 7 1	2 4 0 1	2 5 5 1	2 1 9 1	2 3 8 1	2 5 6 1	2 1 3 1	2 2 0 1	2 2 8 1	2 4 4 1	2 1 1 1	2 2 7 1	2 3 3 1	2 3 4 1	2 5 3 1	2 2 1 1	2 1 2 1	2 2 3 1
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Cystadenoma, papillary																									
Teratoma malignant		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																				X					
Histiocytic sarcoma								X																	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal, neoplasm NOS, metastatic, ovary		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor benign														X											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 0 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 2 1	2 1 5	2 1 8	2 2 4	2 2 5	2 2 6	2 2 9	2 3 0	2 3 5	2 3 7	2 3 9	2 4 1	2 4 2	2 4 3	2 4 4	2 4 5	2 4 6	2 4 7	2 4 8	2 5 0	2 5 1	2 5 2	2 5 4	2 5 5	2 5 8	2 5 9	2 6 0	Total Tissues/ Tumors
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																												
None																												
Genital System																												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	+			45
Cystadenoma, papillary									X																			1
Teratoma malignant																												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	+			46
Hemangioma																												1
Histiocytic sarcoma																												1
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Hemangiosarcoma																X		X										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Renal, neoplasm NOS, metastatic, ovary																												1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Mast cell tumor benign																												1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Hemangiosarcoma															X													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Hemangiosarcoma	X															X												2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			48
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Adenocarcinoma										X																		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Subcutaneous tissue, hemangiosarcoma	X																											2
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	0	0	4	4	4	4	4	4	4	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7
	7	8	0	1	1	2	7	7	7	0	1	6	7	8	0	1	2	3	3	7	7	7	8	0	0
	2	1	0	0	1	8	4	7	7	5	7	0	6	3	5	1	4	3	9	4	4	5	7	2	4
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
	3	4	5	3	1	1	3	1	4	5	1	3	5	1	2	2	4	1	2	3	3	5	2	1	2
	6	9	7	2	4	6	1	7	0	5	9	8	6	3	0	8	4	1	7	3	4	3	1	2	3
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Hepatocellular carcinoma, metastatic, liver																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland													+												
Adenoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymphoma malignant histiocytic																								X	
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																				X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: Vehicle Control (continued)

Number of Days on Study	7 0 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 2 1	2 1 5	2 1 8	2 2 4	2 2 5	2 2 6	2 2 9	2 3 0	2 3 5	2 3 7	2 3 9	2 4 1	2 4 2	2 4 3	2 4 5	2 4 6	2 4 7	2 4 8	2 5 0	2 5 1	2 5 2	2 5 4	2 5 8	2 5 9	2 6 0	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		2
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear											+								+							2
Harderian gland				+			+				+								+		+					6
Adenoma				X															X							3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic											X													X		2
Lymphoma malignant mixed													X	X											X	4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg

Number of Days on Study	0 1 1	3 1 8	3 3 3	3 6 5	4 1 5	4 2 8	4 3 4	4 3 8	4 4 4	4 7 2	4 9 9	5 2 6	5 3 1	5 4 9	5 4 9	5 6 4	5 8 3	5 8 3	5 9 8	5 9 8	6 4 7	6 5 2	6 6 1	6 8 7	7 0 4
Carcass ID Number	3 6 0 1	3 5 9 1	3 6 6 1	3 7 8 1	3 5 7 1	3 6 2 1	3 9 4 1	3 9 7 1	3 7 1 1	3 5 5 1	3 7 0 1	3 5 2 1	3 5 4 1	3 9 0 1	3 9 5 1	3 9 2 1	3 6 1 1	3 8 9 1	3 5 1 1	3 6 7 1	3 7 4 1	3 6 4 1	3 7 7 1	3 7 9 1	3 9 6 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+	A	+	+	+
Intestine small, ileum	M	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									X
Hepatocellular adenoma								X																	
Hepatocellular adenoma, multiple																									
Sarcoma																		X							
Mesentery		+	+	+	+		+	+				+	+					+	+						
Sarcoma																		X	X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																			+						
Sarcoma																			X						
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	729	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	3751	3531	3561	3581	3631	3651	3681	3691	3721	3731	3761	3801	3811	3821	3831	3841	3851	3861	3871	3881	3911	3931	3981	3991	4001	Total Tissues/ Tumors
Alimentary System																										
Esophagus																										25
Gallbladder																										23
Intestine large																										24
Intestine large, cecum																										21
Intestine large, colon																										24
Intestine large, rectum																										24
Intestine small																										23
Intestine small, duodenum																										21
Intestine small, ileum																										21
Intestine small, jejunum																										23
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																									X	2
Hepatocellular adenoma				X						X	X				X		X									6
Hepatocellular adenoma, multiple														X		X										2
Sarcoma																										1
Mesentery									+		+				+	+	+				+	+			+	18
Sarcoma																										2
Pancreas												+				+			+							28
Salivary glands																										25
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+		+		+		+	+	+	+	+	+	+		+		+	+	+	+	+	+	+	45
Papilloma squamous					X																		X			2
Stomach, glandular		+	+		+		+		+	+	+	+	+	+	+		+		+	+	+	+	+	+	+	44
Tooth																										1
Sarcoma																										1
Cardiovascular System																										
Heart																										25
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic																										25
Parathyroid gland																										25
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X				X		X					X								X						5
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg
(continued)

Number of Days on Study	0 1 1	3 1 8	3 3 3	3 6 5	4 1 5	4 2 8	4 3 4	4 3 8	4 4 4	4 7 2	4 9 9	5 2 6	5 3 1	5 4 9	5 4 9	5 6 4	5 8 3	5 8 3	5 9 8	5 9 8	6 4 7	6 5 2	6 6 1	6 8 7	7 0 4
Carcass ID Number	3 6 0 1	3 5 9 1	3 6 6 1	3 7 8 1	3 5 7 1	3 6 2 1	3 9 4 1	3 9 7 1	3 7 1 1	3 5 5 1	3 7 0 1	3 5 2 1	3 5 4 1	3 9 0 1	3 9 5 1	3 9 2 1	3 6 1 1	3 8 9 1	3 5 1 1	3 6 7 1	3 7 4 1	3 6 4 1	3 7 4 1	3 7 9 1	3 9 6 1
General Body System																									
None																									
Genital System																									
Clitoral gland																									+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																									
Sarcoma																		X							
Teratoma NOS									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibrous histiocytoma																									
Leiomyoma																									
Leiomyosarcoma																									
Sarcoma																		X	X						
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, sarcoma																		X							
Lymph node, mandibular	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma															X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 7 5 1	3 5 3 1	3 5 6 1	3 5 8 1	3 6 3 1	3 6 5 1	3 6 8 1	3 6 9 1	3 7 2 1	3 7 3 1	3 7 6 1	3 8 0 1	3 8 1 1	3 8 2 1	3 8 3 1	3 8 4 1	3 8 5 1	3 8 6 1	3 8 7 1	3 8 8 1	3 9 1 1	3 9 3 1	3 9 8 1	3 9 9 1	4 0 0 1	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland																										1
Ovary				+	+	+	+			+		+		+	+			+				+		+		36
Luteoma																		X								1
Sarcoma																										1
Teratoma NOS																										1
Uterus	+	+	+	+			+	+	+	+	+	+	+				+	+		+	+		+	+	+	43
Adenoma									X																	1
Fibrous histiocytoma																				X						1
Leiomyoma												X														1
Leiomyosarcoma											X															1
Sarcoma																										2
Sarcoma stromal																					X					1
Hematopoietic System																										
Bone marrow																										25
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Iliac, sarcoma																										1
Lymph node, mandibular	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X							X																3
Thymus																							+			24
Integumentary System																										
Mammary gland									+																	23
Adenocarcinoma									X																	1
Skin																					+					26
Subcutaneous tissue, hemangiosarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg
(continued)

Number of Days on Study	0 1 1	3 1 8	3 3 3	3 6 5	4 1 5	4 2 8	4 3 4	4 3 8	4 4 4	4 7 2	4 9 9	5 2 6	5 3 1	5 4 9	5 4 9	5 6 4	5 8 3	5 8 3	5 9 8	5 9 8	6 4 7	6 5 2	6 6 1	6 8 7	7 0 4
Carcass ID Number	3 6 0 1	3 5 9 1	3 6 6 1	3 7 8 1	3 5 7 1	3 6 2 1	3 9 4 1	3 9 7 1	3 7 1 1	3 5 5 1	3 7 0 1	3 5 2 1	3 5 4 1	3 9 0 1	3 9 5 1	3 9 2 1	3 6 1 1	3 8 9 1	3 5 1 1	3 6 7 1	3 7 4 1	3 6 4 1	3 7 7 1	3 7 9 1	3 9 6 1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Fibrosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																			X					X	
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Fibrosarcoma																									
Harderian gland																			+					+	
Adenocarcinoma																			X					X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Sarcoma																			X						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																					X				
Lymphoma malignant lymphocytic															X										
Lymphoma malignant mixed										X								X				X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 20 mg/kg (continued)

Number of Days on Study	729	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	3751	3531	3561	3581	3631	3651	3681	3691	3721	3731	3761	3801	3811	3821	3831	3841	3851	3861	3871	3881	3911	3931	3981	3991	4001	Total Tissues/ Tumors
Musculoskeletal System																										
Bone																										25
Skeletal muscle				+																						1
Fibrosarcoma				X																						1
Nervous System																										
Brain	+																									26
Spinal cord																										1
Respiratory System																										
Lung											+									+						27
Adenocarcinoma, metastatic, harderian gland																										2
Alveolar/bronchiolar adenoma																				X						1
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea																										25
Special Senses System																										
Ear																								+		1
Fibrosarcoma																								X		1
Harderian gland																										2
Adenocarcinoma																										2
Urinary System																										
Kidney																										25
Urinary bladder																					+					26
Hemangioma																					X					1
Sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed										X							X			X			X			7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg (continued)

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

Carcass ID Number	Total Tissues/ Tumors
Alimentary System	
Esophagus	50
Gallbladder	49
Intestine large	50
Intestine large, cecum	49
Intestine large, colon	49
Intestine large, rectum	50
Intestine small	49
Intestine small, duodenum	49
Polyp adenomatous	1
Intestine small, ileum	49
Intestine small, jejunum	49
Adenocarcinoma	1
Liver	50
Hemangiosarcoma	1
Hepatoblastoma	1
Hepatocellular carcinoma	2
Hepatocellular adenoma	10
Hepatocellular adenoma, multiple	2
Hepatocholangiocarcinoma	1
Mesentery	24
Cholangiocarcinoma, metastatic, liver	1
Fibrosarcoma	1
Hemangiosarcoma	2
Pancreas	50
Cholangiocarcinoma, metastatic, liver	1
Fibrosarcoma	1
Salivary glands	49
Stomach	50
Stomach, forestomach	50
Stomach, glandular	50
Cardiovascular System	
Heart	50
Cholangiocarcinoma, metastatic, liver	1
Endocrine System	
Adrenal gland	49
Adrenal gland, cortex	49
Adrenal gland, medulla	48
Islets, pancreatic	50
Parathyroid gland	48
Pituitary gland	50
Pars distalis, adenoma	3
Thyroid gland	50
Follicular cell, carcinoma	1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	2 9 1	3 2 3	3 6 5	3 7 5	3 7 6	3 8 1	3 8 6	3 8 9	3 8 9	4 1 4	4 7 0	4 7 2	4 9 9	4 9 9	5 1 9	5 2 7	5 5 1	5 6 3	5 7 1	5 7 6	5 8 3	5 9 7	6 1 2	6 3 2	6 5 3
Carcass ID Number	3 0 8 1	2 9 6 1	2 8 5 1	3 2 9 1	3 2 5 1	3 2 3 1	2 9 4 1	3 0 1 1	3 2 1 1	3 1 9 1	3 1 8 1	2 8 7 1	3 0 5 1	3 2 7 1	2 8 9 1	3 0 4 1	3 2 8 1	3 1 1 1	3 2 0 1	3 3 0 1	3 0 1 1	3 1 9 1	2 8 2 1	3 2 4 1	2 9 9 1
General Body System																									
None																									
Genital System																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																									
Hemangioma																			X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Sarcoma																							X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, cholangiocarcinoma, metastatic, liver																			X						
Mediastinal, cholangiocarcinoma, metastatic, liver																			X						
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								X	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								+	
Fibrosarcoma																								X	
Rhabdomyosarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

| Number of Days on Study | 6 6 6 6 7 7 7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg
(continued)

Number of Days on Study	2 9 1	3 2 3	3 6 5	3 7 5	3 7 6	3 8 1	3 8 6	3 8 9	3 8 9	4 1 4	4 7 0	4 7 2	4 9 9	4 9 9	5 1 9	5 2 7	5 5 1	5 6 3	5 7 1	5 7 6	5 8 3	5 9 7	6 1 2	6 3 2	6 5 3
Carcass ID Number	3 0 8 1	2 9 6 1	2 8 5 1	3 2 9 1	3 2 5 1	3 2 3 1	2 9 4 1	3 0 1 1	3 2 1 1	3 1 9 1	3 1 8 1	2 8 7 1	3 0 5 1	3 2 7 1	2 8 9 1	3 0 4 1	2 1 8 1	3 1 1 1	3 2 0 1	3 0 0 1	3 1 5 1	2 9 2 1	2 8 2 1	3 2 4 1	2 9 9 1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma benign																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Cholangiocarcinoma, metastatic, liver																				X					
Fibrosarcoma																								X	
Hepatocellular carcinoma, metastatic, liver																				X					
Mediastinum, fibrosarcoma																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																		+							
Eye																									
Harderian gland														+											
Adenoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver																				X					
Urinary bladder	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																					X				X
Lymphoma malignant mixed																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Pentachloroanisole: 40 mg/kg (continued)

| Number of Days on Study | 6 6 6 6 7 7 7

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Pentachloroanisole

	Vehicle Control	20 mg/kg	40 mg/kg
Harderian Gland: Adenoma			
Overall rates[a]	3/50 (6%)	0/50 (0%)	4/50 (8%)
Adjusted rates[b]	10.7%	0.0%	20.9%
Terminal rates[c]	2/24 (8%)	0/25 (0%)	3/16 (19%)
First incidence (days)	576	–[e]	499
Life table tests[d]	P=0.276	P=0.124N	P=0.325
Logistic regression tests[d]	P=0.355	P=0.126N	P=0.432
Cochran-Armitage test[d]	P=0.406		
Fisher exact test[d]		P=0.121N	P=0.500
Harderian Gland: Adenoma or Adenocarcinoma			
Overall rates	3/50 (6%)	2/50 (4%)	4/50 (8%)
Adjusted rates	10.7%	6.7%	20.9%
Terminal rates	2/24 (8%)	0/25 (0%)	3/16 (19%)
First incidence (days)	576	598	499
Life table tests	P=0.279	P=0.516N	P=0.325
Logistic regression tests	P=0.366	P=0.512N	P=0.432
Cochran-Armitage test	P=0.417		
Fisher exact test		P=0.500N	P=0.500
Liver: Hepatocellular Adenoma			
Overall rates	8/50 (16%)	8/50 (16%)	12/50 (24%)
Adjusted rates	28.2%	29.7%	53.4%
Terminal rates	5/24 (21%)	7/25 (28%)	7/16 (44%)
First incidence (days)	477	438	381
Life table tests	P=0.046	P=0.591N	P=0.065
Logistic regression tests	P=0.097	P=0.569	P=0.124
Cochran-Armitage test	P=0.185		
Fisher exact test		P=0.607N	P=0.227
Liver: Hepatocellular Carcinoma			
Overall rates	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rates	13.5%	7.7%	12.5%
Terminal rates	2/24 (8%)	1/25 (4%)	2/16 (13%)
First incidence (days)	410	704	729 (T)
Life table tests	P=0.378N	P=0.335N	P=0.498N
Logistic regression tests	P=0.303N	P=0.349N	P=0.387N
Cochran-Armitage test	P=0.252N		
Fisher exact test		P=0.339N	P=0.339N
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma			
Overall rates	11/50 (22%)	10/50 (20%)	14/50 (28%)
Adjusted rates	37.1%	36.1%	63.8%
Terminal rates	7/24 (29%)	8/25 (32%)	9/16 (56%)
First incidence (days)	410	438	381
Life table tests	P=0.067	P=0.479N	P=0.082
Logistic regression tests	P=0.151	P=0.544N	P=0.187
Cochran-Armitage test	P=0.277		
Fisher exact test		P=0.500N	P=0.322

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Liver: Hepatoblastoma or Hepatocellular Carcinoma			
Overall rates	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted rates	13.5%	7.7%	16.7%
Terminal rates	2/24 (8%)	1/25 (4%)	2/16 (13%)
First incidence (days)	410	704	702
Life table tests	P=0.569N	P=0.335N	P=0.636
Logistic regression tests	P=0.487N	P=0.349N	P=0.567N
Cochran-Armitage test	P=0.417N		
Fisher exact test		P=0.339N	P=0.500N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	7/47 (15%)	5/49 (10%)	3/50 (6%)
Adjusted rates	26.5%	20.0%	18.8%
Terminal rates	4/22 (18%)	5/25 (20%)	3/16 (19%)
First incidence (days)	674	729 (T)	729 (T)
Life table tests	P=0.224N	P=0.324N	P=0.300N
Logistic regression tests	P=0.178N	P=0.358N	P=0.232N
Cochran-Armitage test	P=0.101N		
Fisher exact test		P=0.350N	P=0.134N
All Organs: Hemangiosarcoma			
Overall rates	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted rates	17.8%	10.5%	18.8%
Terminal rates	3/24 (13%)	2/25 (8%)	3/16 (19%)
First incidence (days)	410	549	729 (T)
Life table tests	P=0.451N	P=0.349N	P=0.569N
Logistic regression tests	P=0.348N	P=0.370N	P=0.443N
Cochran-Armitage test	P=0.283N		
Fisher exact test		P=0.357N	P=0.357N
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	6/50 (12%)	4/50 (8%)	4/50 (8%)
Adjusted rates	20.4%	14.4%	21.4%
Terminal rates	3/24 (13%)	3/25 (12%)	3/16 (19%)
First incidence (days)	410	549	576
Life table tests	P=0.496N	P=0.370N	P=0.591N
Logistic regression tests	P=0.374N	P=0.389N	P=0.447N
Cochran-Armitage test	P=0.303N		
Fisher exact test		P=0.370N	P=0.370N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)			
Overall rates	7/50 (14%)	9/50 (18%)	12/50 (24%)
Adjusted rates	26.2%	27.8%	52.3%
Terminal rates	5/24 (21%)	4/25 (16%)	6/16 (38%)
First incidence (days)	674	472	583
Life table tests	P=0.033	P=0.391	P=0.036
Logistic regression tests	P=0.057	P=0.360	P=0.049
Cochran-Armitage test	P=0.124		
Fisher exact test		P=0.393	P=0.154

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
All Organs: Benign Neoplasms			
Overall rates	21/50 (42%)	19/50 (38%)	18/50 (36%)
Adjusted rates	62.7%	67.1%	72.2%
Terminal rates	12/24 (50%)	16/25 (64%)	10/16 (63%)
First incidence (days)	477	438	381
Life table tests	P=0.304	P=0.407N	P=0.344
Logistic regression tests	P=0.544N	P=0.511N	P=0.568N
Cochran-Armitage test	P=0.304N		
Fisher exact test		P=0.419N	P=0.341N
All Organs: Malignant Neoplasms			
Overall rates	19/50 (38%)	20/50 (40%)	23/50 (46%)
Adjusted rates	57.8%	58.3%	81.3%
Terminal rates	11/24 (46%)	11/25 (44%)	11/16 (69%)
First incidence (days)	81	472	571
Life table tests	P=0.038	P=0.498	P=0.040
Logistic regression tests	P=0.099	P=0.453	P=0.117
Cochran-Armitage test	P=0.239		
Fisher exact test		P=0.500	P=0.272
All Organs: Benign or Malignant Neoplasms			
Overall rates	32/50 (64%)	31/50 (62%)	30/50 (60%)
Adjusted rates	86.0%	83.5%	93.6%
Terminal rates	19/24 (79%)	19/25 (76%)	14/16 (88%)
First incidence (days)	81	438	381
Life table tests	P=0.128	P=0.498N	P=0.132
Logistic regression tests	P=0.426	P=0.587N	P=0.467
Cochran-Armitage test	P=0.379N		
Fisher exact test		P=0.500N	P=0.418N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone (including marrow), brain, clitoral gland, gallbladder, heart, kidney, large intestine, liver, lung, mammary gland, mandibular or mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, salivary gland, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, urinary bladder, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Malignant Lymphomas in Female B6C3F$_1$ Mice Administered Corn Oil by Gavage[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzaldehyde	13/50
Dichlorvos	16/50
Furan	20/50
Furfural	9/50
γ-Butyrolactone	11/50
p-Nitroaniline	9/50
Pentachloroanisole	7/50
Total	85/350 (24.3%)
Standard deviation	9.1%
Range	14%-40%
Overall Historical Incidence	
Total	155/698 (22.2%)[b]
Standard deviation	8.3%
Range	4%-40%

[a] Data as of 3 April 1991
[b] Includes data for histiocytic, lymphocytic, mixed, NOS, and undifferentiated cell type lymphomas

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Pentachloroanisole[a]

	Vehicle Control	20 mg/kg	40 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
9-Month interim evaluation	10	10	10
15-Month interim evaluation	10	10	7
Early deaths			
Accidental deaths	1	1	
Moribund	17	18	29
Natural deaths	8	6	8
Survivors			
Terminal sacrifice	24	25	16
Animals examined microscopically	70	70	70
Alimentary System			
Gallbladder	(46)	(23)	(49)
Dilatation	1 (2%)		
Liver	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
Basophilic focus	2 (4%)	1 (2%)	
Cytologic alterations	1 (2%)	34 (68%)	39 (78%)
Eosinophilic focus	5 (10%)	1 (2%)	1 (2%)
Eosinophilic focus, multiple			3 (6%)
Hematopoietic cell proliferation	9 (18%)	6 (12%)	9 (18%)
Inflammation, subacute	1 (2%)	28 (56%)	32 (64%)
Mixed cell focus		2 (4%)	2 (4%)
Mixed cell focus, multiple			5 (10%)
Necrosis	1 (2%)	2 (4%)	2 (4%)
Vacuolization cytoplasmic		1 (2%)	
Biliary tract, dilatation			1 (2%)
Biliary tract, hyperplasia	1 (2%)	16 (32%)	30 (60%)
Kupffer cell, pigmentation		37 (74%)	48 (96%)
Mesentery	(25)	(18)	(24)
Hemorrhage		1 (6%)	
Inflammation, suppurative	8 (32%)	7 (39%)	8 (33%)
Fat, necrosis	14 (56%)	8 (44%)	8 (33%)
Pancreas	(50)	(28)	(50)
Acinar cell, atrophy	4 (8%)	3 (11%)	2 (4%)
Duct, dilatation	1 (2%)	1 (4%)	2 (4%)
Salivary glands	(50)	(25)	(49)
Atrophy	1 (2%)		
Foreign body	1 (2%)		
Stomach, forestomach	(50)	(45)	(50)
Cyst epithelial inclusion	1 (2%)		
Foreign body	1 (2%)		
Hyperplasia	12 (24%)	7 (16%)	6 (12%)
Cardiovascular System			
Heart	(50)	(25)	(50)
Inflammation, subacute	1 (2%)		
Mineralization	1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Endocrine System			
Adrenal gland	(50)	(50)	(49)
Capsule, spindle cell, hyperplasia		1 (2%)	
Adrenal gland, cortex	(50)	(50)	(49)
Accessory adrenal cortical nodule	2 (4%)	1 (2%)	
Hypertrophy, focal			1 (2%)
Necrosis	1 (2%)		
Parathyroid gland	(47)	(25)	(48)
Cyst		1 (4%)	
Pituitary gland	(47)	(49)	(50)
Pars distalis, cyst			1 (2%)
Pars distalis, hyperplasia	12 (26%)	8 (16%)	4 (8%)
Thyroid gland	(50)	(50)	(50)
Inflammation, subacute	1 (2%)		
Follicular cell, hyperplasia	5 (10%)	1 (2%)	1 (2%)
General Body System			
None			
Genital System			
Clitoral gland		(1)	(1)
Duct, cyst		1 (100%)	1 (100%)
Ovary	(45)	(36)	(50)
Abscess	12 (27%)	14 (39%)	18 (36%)
Cyst	3 (7%)	8 (22%)	5 (10%)
Hemorrhage		3 (8%)	
Uterus	(46)	(43)	(50)
Dilatation	9 (20%)		4 (8%)
Hyperplasia, cystic	42 (91%)	36 (84%)	46 (92%)
Inflammation, suppurative	5 (11%)	6 (14%)	10 (20%)
Mucosa, cyst	2 (4%)		1 (2%)
Hematopoietic System			
Bone marrow	(50)	(25)	(50)
Myeloid cell, hypercellularity	17 (34%)	11 (44%)	21 (42%)
Lymph node	(50)	(50)	(50)
Iliac, hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)
Iliac, inflammation, suppurative	1 (2%)		
Mediastinal, hyperplasia, lymphoid			1 (2%)
Mediastinal, inflammation, suppurative	2 (4%)		1 (2%)
Renal, hyperplasia, lymphoid	1 (2%)	1 (2%)	4 (8%)
Renal, inflammation, suppurative			1 (2%)
Lymph node, mandibular	(49)	(47)	(49)
Hyperplasia, lymphoid	1 (2%)		
Lymph node, mesenteric	(50)	(49)	(50)
Angiectasis		1 (2%)	1 (2%)
Hematopoietic cell proliferation			2 (4%)
Spleen	(50)	(50)	(50)
Hematopoietic cell proliferation	21 (42%)	18 (36%)	28 (56%)
Hyperplasia, lymphoid	1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Integumentary System			
Mammary gland	(49)	(23)	(50)
Hyperplasia	1 (2%)		
Skin	(50)	(26)	(50)
Inflammation		1 (4%)	
Musculoskeletal System			
Bone	(50)	(25)	(50)
Hypertrophy	1 (2%)		
Nervous System			
Brain	(50)	(26)	(50)
Hemorrhage	1 (2%)		
Inflammation, subacute	1 (2%)		
Respiratory System			
Lung	(50)	(27)	(50)
Abscess	1 (2%)		
Foreign body	1 (2%)		
Infiltration cellular, histiocyte	1 (2%)	2 (7%)	1 (2%)
Inflammation, suppurative		1 (4%)	
Alveolar epithelium, hyperplasia	1 (2%)	2 (7%)	
Mediastinum, inflammation, suppurative	5 (10%)	5 (19%)	3 (6%)
Nose	(50)	(50)	(50)
Foreign body	7 (14%)	15 (30%)	19 (38%)
Fungus			1 (2%)
Inflammation, suppurative	5 (10%)	13 (26%)	21 (42%)
Special Senses System			
Harderian gland	(6)	(2)	(4)
Hyperplasia	2 (33%)		
Urinary System			
Kidney	(50)	(25)	(50)
Amyloid deposition	2 (4%)		
Hydronephrosis	1 (2%)	2 (8%)	
Nephropathy	12 (24%)	3 (12%)	8 (16%)
Cortex, cyst	1 (2%)		
Glomerulus, inflammation		2 (8%)	
Transitional epithelium, hyperplasia		1 (4%)	

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

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Pentachloroanisole was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strain (TA100, TA1535, TA1537, and TA98) 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 prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of pentachloroanisole. High dose was limited to 10,000 μg/plate. All positive assays were repeated under the conditions which elicited the positive response.

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 which was not dose-related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A negative response was obtained when no increase in revertant colonies was observed following chemical treatment.

MOUSE LYMPHOMA CELL MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1987). Pentachloroanisole was supplied as a coded aliquot by Radian Corporation (Austin, TX). The highest dose of pentachloroanisole was determined by solubility or toxicity and did not exceed 0.05 mg/mL. Mouse lymphoma L5178Y cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM *l*-glutamine, 110 μg/mL sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (TFT) resistant cells, subcultures were exposed once to medium containing THMG (thymidine, hypoxanthine, methotrexate, glycine) for 1 day, to THG for 1 day, and to normal medium for 3 to 5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the livers of Aroclor 1254-induced male rats.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6 x 10^6 cells in 10 mL of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with pentachloroanisole continued for 4 hours, at which time the medium plus pentachloroanisole was removed and the cells were resuspended in 20 mL of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3 x 10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of TFT-resistant cells ($TK^{-/-}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 10 to 12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for pentachloroanisole to be considered capable of inducing TFT-resistance; a single significant response led to a "questionable" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr *et al.* (1985). This assay was initially performed

without S9; because a clearly positive response was not obtained, the experiment was repeated with induced S9.

Chinese Hamster Ovary Cell Cytogenetics Protocols

Testing was performed as reported by Galloway *et al.* (1985, 1987) and is presented briefly below. Pentachloroanisole was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). 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 three doses of pentachloroanisole; the high dose was limited by toxicity or solubility, but did not exceed 700 μg/mL.

In the SCE test without S9, CHO cells were incubated for 26 hours with pentachloroanisole in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing pentachloroanisole 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 pentachloroanisole, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no pentachloroanisole and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining was the same as for cells treated without S9. For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells.

In the Abs test without S9, cells were incubated in McCoy's 5A medium with pentachloroanisole for 20 hours; Colcemid was added and incubation continued. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with pentachloroanisole and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 18 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. For the SCE test, 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; 100 first-division metaphase cells were scored at each dose level for the Abs test. 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).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. 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. A single increased dose was considered weak evidence of a positive reponse; two increased doses were sufficient to evaluate the trial as positive. Chromosomal aberration data are presented as percentage of cells with aberrations. Both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.05$) difference for one dose point was considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive (Galloway *et al.*, 1987).

RESULTS

Pentachloroanisole (10 to 10,000 μg/plate) was tested for induction of gene mutations in four strains of *Salmonella typhimurium* (TA100, TA1535, TA1537, and TA98) using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1; Mortelmans *et al.*, 1986). No clear evidence of mutagenic activity was observed in strain TA100 or TA1535 with or without S9, but positive responses were obtained with the strains TA1537 and TA98 in the absence of S9; no increases in mutagenic colonies occurred in these strains with S9. Precipitation occurred at 1,000 μg/plate and higher concentrations. In the mouse lymphoma assay, pentachloroanisole induced trifluorothymidine resistance in L5178Y cells over a concentration range of 18.75 to 500 μg/mL in the presence of Aroclor 1254-induced male F344 rat liver S9; without S9, the responses were weak, not dose related, and inconsistent (Table E2; McGregor *et al.*, 1987). Precipitation occurred in this assay also, at about the 125 μg/mL dose level, and this may have been a factor in the lack of a clear dose-response relationship for all but one of the positive trials. In cytogenetic tests with Chinese hamster ovary (CHO) cells, pentachloroanisole induced sister chromatid exchanges (SCEs) (Table E3), but not chromosomal aberrations (Abs) (Table E4), with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9. A delayed harvest protocol was required in the SCE test to offset pentachloroanisole-induced cell cycle delay and allow detection of the positive responses. Delayed harvest was also used for the Abs test to offset the cell cycle delay induced by pentachloroanisole. Precipitation occurred in the SCE and Abs tests for all pentachloroanisole concentrations of 35 μg/mL and higher.

TABLE E1
Mutagenicity of Pentachloroanisole in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9	+10% hamster S9	+10% rat S9
TA100				
	0	109 ± 4.4	136 ± 6.9	111 ± 5.8
	10		126 ± 0.6	141 ± 4.5
	33		131 ± 8.4	143 ± 2.6
	100	84 ± 5.7	114 ± 11.1	117 ± 14.7
	333	97 ± 0.7	83 ± 5.5	79 ± 1.2
	1,000	94 ± 4.1[c]	22 ± 5.5[c]	69 ± 11.6[c]
	3,333	84 ± 5.3[c]		
	6,666			
	10,000	89 ± 3.5[c]		
Trial summary		Negative	Negative	Equivocal
Positive control[d]		219 ± 21.8	2,130 ± 37.6	761 ± 81.5
TA1535				
	0	13 ± 2.6	7 ± 1.3	6 ± 0.6
	10		7 ± 0.6	6 ± 0.6
	33		7 ± 1.5	9 ± 0.9
	100	10 ± 1.2	8 ± 0.6	7 ± 1.2
	333	10 ± 1.5	8 ± 0.9	4 ± 0.9
	1,000	7 ± 2.0[c]	3 ± 0.6[c]	5 ± 0.6[c]
	3,333	7 ± 1.5[c]		
	10,000	9 ± 2.1[c]		
Trial summary		Negative	Negative	Negative
Positive control		129 ± 5.6	464 ± 43.3	187 ± 12.4

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% rat S9 Trial 1
TA1537					
	0	7 ± 0.6	4 ± 1.2	8 ± 1.5	7 ± 1.9
	10			8 ± 0.6	6 ± 1.2
	33			3 ± 1.3	6 ± 2.0
	100	6 ± 2.0		5 ± 1.5	3 ± 0.3
	333	6 ± 1.5	5 ± 1.2	2 ± 0.3	1 ± 0.3
	1,000	7 ± 2.3[c]	5 ± 1.5[c]	1 ± 0.0[c]	1 ± 0.0[c]
	3,333	15 ± 0.3[c]	12 ± 1.2[c]		
	6,666		19 ± 1.2[c]		
	10,000	24 ± 1.9[c]	34 ± 3.2[c]		
Trial summary		Positive	Positive	Negative	Negative
Positive control		124 ± 15.8	254 ± 7.0	265 ± 4.6	236 ± 7.1

TABLE E1
Mutagenicity of Pentachloroanisole in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% rat S9 Trial 1
TA98					
	0	14 ± 1.2	12 ± 2.3	23 ± 3.2	20 ± 0.3
	10			18 ± 1.9	18 ± 1.2
	33			15 ± 2.0	22 ± 1.8
	100	11 ± 2.8		12 ± 1.2	19 ± 1.9
	333	11 ± 1.5	11 ± 3.0	9 ± 1.0	16 ± 0.7
	1,000	9 ± 0.7[c]	15 ± 1.7[c]	4 ± 0.9[c]	19 ± 0.6[c]
	3,333	23 ± 5.2[c]	20 ± 2.7[c]		
	6,666		33 ± 5.5[c]		
	10,000	39 ± 7.1[c]	45 ± 4.1[c]		
Trial summary		Positive	Positive	Negative	Negative
Positive control		510 ± 12.1	397 ± 21.4	1,731 ± 43.6	364 ± 43.6

[a] Study performed at SRI, International. The protocol and these data are presented in Mortelmans *et al.* (1986).
[b] Revertants are presented as mean ± the standard error from three plates.
[c] Precipitate on plate
[d] 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE E2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Pentachloroanisole[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Dimethylsulfoxide						
		68	108	56	28	
		60	92	48	27	27
Ethyl methanesulfonate						
		57	66	261	154	
	250	65	78	264	136	145[d]
Pentachloroanisole						
	31.25	81	106	68	28	
	62.5	80	90	53	22	
		69	92	68	33	28
	125	86	76	107	42	
		44	27	78	59	50[d]
	250	102	34	215	70	
		118	28	112	32	51[d]
	500	97	32	130	45	
		100	48	120	40	42
Trial 2						
Dimethylsulfoxide						
		54	115	107	66	
		64	88	99	52	
		64	98	94	49	
		63	98	80	42	52
Ethyl methanesulfonate						
		56	93	413	247	
	250	65	79	466	241	244[d]
Pentachloroanisole						
	31.25	99	127	146	49	
		60	124	66	36	43
	62.5	72	109	102	47	
		55	97	94	57	52
	125[e]	69	74	128	62	
		61	91	116	63	63
	250	87	34	161	62	
		51	25	123	81	71
	500	51	18	125	82	
		52	23	134	85	83[d]

TABLE E2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Pentachloroanisole
(continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 1						
Dimethylsulfoxide						
		63	100	143	76	
		79	109	175	74	
		68	97	133	66	
		51	94	108	71	71
Methylcholanthrene						
		26	21	680	855	
	2.5	39	23	739	626	741[d]
Pentachloroanisole						
	31.25	69	79	247	119	
		52	36	523	333	226[d]
	62.5	84	59	320	126	
		64	54	188	99	113[d]
	125	67	105	262	130	
		66	43	149	75	102
	250	70	12	337	160	
		63	11	220	116	138[d]
	500	68	14	332	164	
		70	10	191	91	127[d]
Trial 2						
Dimethylsulfoxide						
		52	77	122	79	
		80	132	105	44	
		92	92	177	64	62
Methylcholanthrene						
		23	11	961	1,408	
	2.5	51	27	956	627	1,017[d]
Pentachloroanisole						
	18.75	56	54	264	158	
		89	78	302	113	135[d]
	37.5	58	53	273	158	
		105	82	364	115	137[d]
	75[e]	56	39	287	171	
		109	60	376	115	143[d]
	150	88	58	436	166	
		86	47	340	133	149[d]
	300	98	17	714	243	
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Pentachloroanisole (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9 (continued)						
Trial 3						
Dimethylsulfoxide						
		72	95	50	23	
		87	105	57	22	
		77	112	45	19	
		64	88	74	39	26
Methylcholanthrene						
		44	25	508	383	
	2.5	43	24	467	359	371[d]
Pentachloroanisole						
	50	64	42	141	73	
		59	44	144	81	77[d]
	75	66	29	136	69	
		64	34	81	42	55[d]
	100	57	27	81	47	
		55	28	101	61	54[d]
	125	66	21	114	57	
		96	18	171	60	58[d]
	150	54	16	92	57	
		52	20	88	57	57[d]
Trial 4						
Dimethylsulfoxide						
		77	104	195	85	
		83	127	158	63	
		57	81	134	78	
		65	89	169	87	78
Methylcholanthrene						
		43	27	700	545	
	2.5	46	30	598	436	491[d]
Pentachloroanisole						
	15	64	79	150	78	
		79	92	159	67	72
	25	84	65	218	87	
		76	72	188	82	84
	50	52	40	196	124	
		51	32	255	166	145[d]
	75	37	6	387	350	
		36	7	324	299	324[d]
	100	Lethal				
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Pentachloroanisole
(continued)

[a] Study performed at Inveresk Research International. The experimental protocol and these data are presented in McGregor *et al.* (1987). The highest dose of pentachloroanisole was determined by solubility and toxicity. All dosed were tested in triplicate; the average of the three tests is presented in the table. Cells (6 x 10^5/mL) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3 x 10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
[b] Mean ± standard error from three replicate plates of approximately 10^6 cells each.
[c] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF 10^6 cells treated); MF=mutant fraction.
[d] Significant positive response ($P<0.05$)
[e] Precipitation at this and higher doses

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Pentachloroanisole[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Summary: Positive								
Dimethylsulfoxide		50	1,049	694	0.66	13.9	26.3	
Mitomycin-C	0.001	39	809	692	0.85	17.7	26.3	29.29
	0.010	5	106	236	2.22	47.2	26.3	236.53
Pentachloroanisole	75	36	744	475	0.63	13.2	26.3	-3.50
	100	50	1,043	882	0.84	17.6	34.3[c]	27.82°
	125	50	1,043	840	0.80	16.8	34.3[c]	21.73°
								P<0.001[d]
+S9								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide		50	1,044	574	0.54	11.5	25.8	
Cyclophosphamide	0.35	50	1,046	790	0.75	15.8	25.8	37.37
	2.00	5	104	187	1.79	37.4	25.8	227.04
Pentachloroanisole	117	50	1,044	606	0.58	12.1	25.8	5.57
	350	50	1,052	642	0.61	12.8	25.8	11.00
	700	50	1,042	950	0.91	19.0	34.0[c]	65.82°
								P<0.001
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,049	634	0.60	12.7	26.3	
Cyclophosphamide	0.35	50	1,046	855	0.81	17.1	26.3	35.24
	2.00	5	105	193	1.83	38.6	26.3	204.13
Pentachloroanisole	595	50	1,040	757	0.72	15.1	26.3	20.43°
	648	50	1,040	968	0.93	19.4	34.3[c]	54.00°
	700	50	1,042	878	0.84	17.6	34.3[c]	39.42°
								P<0.001

° Positive (≥20% increase over solvent control)

[a] Study performed at Litton Bionetics, Inc. SCE=sister chromatid exchange; BrdU=bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1985, 1987). Precipitate was observed at all dose levels.

[b] SCE's/chromosome of culture exposed to pentachloroanisole relative to those of culture exposed to solvent.

[c] Because pentachloroanisole induced a delay in the cell division cycle, harvest times were extended to maximize the proportion of second division cells available for analysis.

[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Pentachloroanisole[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs
Trial 1 – Harvest time: 22.5 hours[b] Summary: Negative					**Trial 1** – Harvest time: 22.5 hours[b] Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	2	0.02	2.0		100	0	0.00	0.0
Mitomycin-C					Cyclophosphamide				
0.04	50	14	0.28	24.0	12.5	50	15	0.30	22.0
Pentachloroanisole					Pentachloroanisole				
101	100	1	0.01	1.0	595	100	5	0.05	4.0
126	100	1	0.01	1.0	648	100	3	0.03	3.0
151	100	0	0.00	0.0	700	100	4	0.04	3.0
				P=0.909[c]					P=0.126

[a] Study performed at Litton Bionetics, Inc. Abs=aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985, 1987). Precipitate was noted at most dose levels.

[b] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphases at harvest.

[c] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

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

TABLE F1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Studies of Pentachloroanisole 228

TABLE F2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 9-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole 229

TABLE F3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole 230

TABLE F4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Studies of Pentachloroanisole 231

TABLE F5 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole 232

TABLE F6 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole 233

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	40 mg/kg	80 mg/kg	120 mg/kg
Male				
n	10	10	3	
Necropsy body weight	356 ± 6	326 ± 5**	318 ± 6**	
Brain				
Absolute	2.03 ± 0.03	1.94 ± 0.03*	1.86 ± 0.02**	
Relative	5.70 ± 0.09	5.95 ± 0.08	5.84 ± 0.04	
Heart				
Absolute	0.91 ± 0.03	0.90 ± 0.05	0.93 ± 0.03	
Relative	2.57 ± 0.07	2.74 ± 0.13	2.92 ± 0.05	
R. Kidney				
Absolute	1.07 ± 0.04	1.15 ± 0.03	1.16 ± 0.02	
Relative	3.01 ± 0.08	3.51 ± 0.07**	3.66 ± 0.04**	
Liver				
Absolute	12.30 ± 0.36	12.98 ± 0.38	13.15 ± 0.25	
Relative	34.53 ± 0.68	39.74 ± 0.85**	41.36 ± 0.31**	
Lungs				
Absolute	1.33 ± 0.06	1.34 ± 0.04	1.43 ± 0.10	
Relative	3.72 ± 0.15	4.11 ± 0.13	4.51 ± 0.35*	
R. Testis				
Absolute	1.49 ± 0.04	1.41 ± 0.03	1.44 ± 0.02	
Relative	4.17 ± 0.09	4.31 ± 0.08	4.53 ± 0.06*	
Thymus				
Absolute	0.37 ± 0.02	0.30 ± 0.03	0.27 ± 0.05	
Relative	1.03 ± 0.05	0.92 ± 0.09	0.85 ± 0.15	
Female				
n	10	10	10	2
Necropsy body weight	202 ± 4	195 ± 3	192 ± 3	189 ± 12
Brain				
Absolute	1.83 ± 0.02	1.80 ± 0.02	1.77 ± 0.03	1.76 ± 0.06
Relative	9.08 ± 0.12	9.25 ± 0.12	9.21 ± 0.19	9.33 ± 0.27
Heart				
Absolute	0.60 ± 0.01	0.60 ± 0.01	0.61 ± 0.01	0.61 ± 0.10
Relative	2.96 ± 0.07	3.08 ± 0.06	3.20 ± 0.05*	3.18 ± 0.30
R. Kidney				
Absolute	0.64 ± 0.02	0.70 ± 0.02	0.72 ± 0.02*	0.82 ± 0.14**
Relative	3.20 ± 0.06	3.58 ± 0.09**	3.75 ± 0.09**	4.31 ± 0.47**
Liver				
Absolute	6.76 ± 0.18	7.31 ± 0.14	7.94 ± 0.17**	9.08 ± 1.87**
Relative	33.54 ± 0.74	37.59 ± 0.60**	41.34 ± 0.70**	47.61 ± 6.87**
Lungs				
Absolute	0.91 ± 0.02	1.00 ± 0.04	0.94 ± 0.04	1.02 ± 0.16
Relative	4.52 ± 0.09	5.14 ± 0.16*	4.93 ± 0.23*	5.36 ± 0.51
Thymus				
Absolute	0.25 ± 0.01	0.24 ± 0.01	0.27 ± 0.03	0.25 ± 0.03
Relative	1.26 ± 0.06	1.22 ± 0.04	1.38 ± 0.15	1.32 ± 0.08

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data calculated for 120 mg/kg males and 140 mg/kg and 180 mg/kg rats due to 100% mortality.

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 9-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
n	10	10	10	10
Necropsy body weight	463 ± 12	447 ± 8	431 ± 7°	396 ± 5°°
Brain				
Absolute	2.09 ± 0.02	2.09 ± 0.02	2.06 ± 0.01	2.06 ± 0.02
Relative	4.52 ± 0.08	4.68 ± 0.06	4.79 ± 0.07°	5.22 ± 0.07°°
R. Kidney				
Absolute	1.22 ± 0.04	1.27 ± 0.03	1.25 ± 0.03	1.27 ± 0.02
Relative	2.62 ± 0.06	2.84 ± 0.05°	2.92 ± 0.08°°	3.22 ± 0.05°°
Liver				
Absolute	13.51 ± 0.42	13.37 ± 0.26	13.09 ± 0.29[b]	13.82 ± 0.19
Relative	29.13 ± 0.33	29.95 ± 0.34	30.46 ± 0.48°[b]	34.95 ± 0.50°°
Thymus				
Absolute	0.29 ± 0.02	0.27 ± 0.03	0.32 ± 0.05	0.24 ± 0.03
Relative	0.62 ± 0.04	0.62 ± 0.07	0.75 ± 0.10	0.61 ± 0.07
Female				
n	10		10	10
Necropsy body weight	245 ± 5		236 ± 4	227 ± 5°
Brain				
Absolute	1.89 ± 0.02		1.92 ± 0.02	1.87 ± 0.01
Relative	7.73 ± 0.11		8.16 ± 0.12°	8.27 ± 0.18°
R. Kidney				
Absolute	0.71 ± 0.02		0.77 ± 0.02	0.75 ± 0.02
Relative	2.91 ± 0.05		3.25 ± 0.08°°	3.33 ± 0.08°°
Liver				
Absolute	6.71 ± 0.27		7.36 ± 0.12	6.93 ± 0.26
Relative	27.31 ± 0.77		31.25 ± 0.53°°	30.49 ± 0.74°°
Thymus				
Absolute	0.24 ± 0.03		0.20 ± 0.02	0.18 ± 0.02
Relative	0.96 ± 0.10		0.84 ± 0.09	0.78 ± 0.08

° Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
°° P≤0.01
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data calculated for 10 mg/kg females due to 100% mortality.
[b] n=9

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
n	10	9	9	5
Necropsy body weight	508 ± 8	479 ± 23	472 ± 9	425 ± 10**
Brain				
Absolute	2.09 ± 0.03	2.09 ± 0.02	2.04 ± 0.04	2.04 ± 0.07
Relative	4.12 ± 0.09	4.46 ± 0.26	4.33 ± 0.13	4.80 ± 0.13*
R. Kidney				
Absolute	1.35 ± 0.03	1.44 ± 0.06	1.40 ± 0.03	1.41 ± 0.07
Relative	2.66 ± 0.05	3.10 ± 0.24	2.96 ± 0.05	3.32 ± 0.10**
Liver				
Absolute	13.90 ± 0.39	14.74 ± 0.30	14.76 ± 0.45[b]	14.68 ± 0.69
Relative	27.32 ± 0.48	31.75 ± 2.60	30.93 ± 0.63[b]	34.53 ± 1.38**
Thymus				
Absolute	0.30 ± 0.03	0.36 ± 0.05	0.27 ± 0.04	0.23 ± 0.02
Relative	0.59 ± 0.06	0.76 ± 0.10	0.58 ± 0.09	0.54 ± 0.04
Female				
n	9		10	10
Necropsy body weight	291 ± 8		285 ± 7	268 ± 5*
Brain				
Absolute	1.89 ± 0.02		1.86 ± 0.03	1.93 ± 0.01
Relative	6.54 ± 0.17		6.56 ± 0.18	7.22 ± 0.13**
R. Kidney				
Absolute	0.76 ± 0.02		0.85 ± 0.02**	0.86 ± 0.02**
Relative	2.63 ± 0.05		3.00 ± 0.05**	3.20 ± 0.07**
Liver				
Absolute	6.82 ± 0.29		7.70 ± 0.27	7.92 ± 0.35*
Relative	23.40 ± 0.63		27.10 ± 1.13*	29.58 ± 1.18**
Thymus				
Absolute	0.22 ± 0.02		0.19 ± 0.02	0.24 ± 0.03
Relative	0.76 ± 0.06		0.66 ± 0.07	0.88 ± 0.11

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data calculated for 10 mg/kg females due to 100% mortality.
[b] n=8

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	40 mg/kg	80 mg/kg	120 mg/kg	140 mg/kg	180 mg/kg
Male						
n	10	10	10	1[b]		
Necropsy body weight	35.1 ± 0.8	34.5 ± 0.8	34.6 ± 0.4	32.0		
Brain						
Absolute	0.46 ± 0.02	0.44 ± 0.01	0.45 ± 0.01	0.45		
Relative	13.05 ± 0.63	12.73 ± 0.21	12.90 ± 0.19	14.06		
Heart						
Absolute	0.18 ± 0.01	0.17 ± 0.01	0.17 ± 0.00	0.15		
Relative	5.00 ± 0.23	4.78 ± 0.10	5.04 ± 0.12	4.69		
R. Kidney						
Absolute	0.31 ± 0.01	0.33 ± 0.01	0.33 ± 0.01	0.31		
Relative	8.78 ± 0.26	9.51 ± 0.22°	9.51 ± 0.22°	9.69		
Liver						
Absolute	2.04 ± 0.08	2.10 ± 0.07	2.33 ± 0.06°°	2.32		
Relative	58.12 ± 1.93	60.88 ± 1.15	67.38 ± 1.61°°	72.50		
Lungs						
Absolute	0.23 ± 0.01	0.20 ± 0.01	0.20 ± 0.01	0.17		
Relative	6.44 ± 0.44	5.82 ± 0.31	5.89 ± 0.20	5.31		
R. Testis						
Absolute	0.11 ± 0.00	0.11 ± 0.00	0.11 ± 0.00	0.10		
Relative	3.22 ± 0.10	3.16 ± 0.08	3.15 ± 0.09	3.13		
Thymus						
Absolute	0.05 ± 0.01[c]	0.04 ± 0.00	0.05 ± 0.00	0.05		
Relative	1.43 ± 0.23[c]	1.17 ± 0.12	1.35 ± 0.11	1.56		
Female						
n	10	10	10	10	10	4
Necropsy body weight	25.4 ± 0.3	26.1 ± 0.3	26.1 ± 0.2	26.2 ± 0.3	26.7 ± 0.3°	26.0 ± 0.4
Brain						
Absolute	0.46 ± 0.00	0.46 ± 0.02	0.46 ± 0.01	0.47 ± 0.01	0.49 ± 0.02	0.45 ± 0.02
Relative	18.30 ± 0.33	17.52 ± 0.61	17.75 ± 0.27	17.96 ± 0.36	18.24 ± 0.56	17.32 ± 0.71
Heart						
Absolute	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.00	0.15 ± 0.01	0.12 ± 0.00
Relative	5.09 ± 0.25	5.07 ± 0.34	4.79 ± 0.18	5.11 ± 0.12	5.50 ± 0.25	4.62 ± 0.14
R. Kidney						
Absolute	0.19 ± 0.01	0.20 ± 0.01	0.21 ± 0.00°°	0.21 ± 0.00°°	0.22 ± 0.01°°	0.21 ± 0.00°°
Relative	7.28 ± 0.24	7.59 ± 0.19	8.01 ± 0.14°	8.06 ± 0.13°°	8.35 ± 0.26°°	7.89 ± 0.09°
Liver						
Absolute	1.25 ± 0.04	1.53 ± 0.03°°	1.61 ± 0.02°°	1.70 ± 0.02°°	1.88 ± 0.06°°	1.64 ± 0.08°°
Relative	49.21 ± 1.08	58.51 ± 0.71°°	61.78 ± 0.91°°	65.05 ± 0.92°°	70.48 ± 1.90°°	62.78 ± 2.26°°
Lungs						
Absolute	0.18 ± 0.01	0.19 ± 0.01	0.19 ± 0.01	0.20 ± 0.01	0.22 ± 0.02	0.18 ± 0.01
Relative	7.23 ± 0.42	7.34 ± 0.32	7.11 ± 0.43	7.74 ± 0.41	8.34 ± 0.58	6.92 ± 0.26
Thymus						
Absolute	0.05 ± 0.01	0.05 ± 0.00	0.05 ± 0.00	0.05 ± 0.00	0.05 ± 0.01	0.06 ± 0.00
Relative	2.00 ± 0.21	1.99 ± 0.13	1.92 ± 0.15	1.98 ± 0.12	1.98 ± 0.21	2.21 ± 0.10

° Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
°° P≤0.01
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No data calculated for 140 mg/kg and 180 mg/kg males due to 100% mortality.
[b] No standard error calculated due to high mortality in this group
[c] n=9

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	20 mg/kg	40 mg/kg
Male			
n	10	10	10
Necropsy body weight	43.9 ± 1.0	45.0 ± 1.2	40.3 ± 1.0*
Brain			
Absolute	0.47 ± 0.00	0.46 ± 0.00	0.46 ± 0.00
Relative	10.6 ± 0.3	10.4 ± 0.3	11.5 ± 0.3*
R. Kidney			
Absolute	0.34 ± 0.01	0.36 ± 0.01	0.34 ± 0.01
Relative	7.80 ± 0.15	8.07 ± 0.25	8.44 ± 0.22*
Liver			
Absolute	1.65 ± 0.06	1.90 ± 0.10	1.81 ± 0.10
Relative	37.43 ± 0.88	42.01 ± 1.60*	44.73 ± 1.91**
R. Testis			
Absolute	0.13 ± 0.00	0.12 ± 0.00	0.13 ± 0.00
Relative	2.84 ± 0.08	2.69 ± 0.09	3.27 ± 0.13**
Thymus			
Absolute	0.05 ± 0.00	0.05 ± 0.01	0.04 ± 0.00
Relative	1.04 ± 0.10	1.18 ± 0.13	0.86 ± 0.09
Female			
n	10	9	10
Necropsy body weight	37.0 ± 2.0	35.2 ± 2.1	35.7 ± 1.5
Brain			
Absolute	0.48 ± 0.01	0.47 ± 0.01	0.48 ± 0.01
Relative	13.4 ± 0.8	13.9 ± 1.0	13.6 ± 0.5
R. Kidney			
Absolute	0.21 ± 0.01	0.22 ± 0.01	0.23 ± 0.01
Relative	5.78 ± 0.26	6.40 ± 0.22	6.39 ± 0.16
Liver			
Absolute	1.23 ± 0.06	1.32 ± 0.05	1.50 ± 0.03**
Relative	33.59 ± 1.41	38.15 ± 1.45*	42.59 ± 1.34**
Thymus			
Absolute	0.05 ± 0.00	0.04 ± 0.00	0.05 ± 0.00
Relative	1.30 ± 0.05	1.20 ± 0.08	1.32 ± 0.11

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

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	20 mg/kg	40 mg/kg
Male			
n	10	10	10
Necropsy body weight	48.7 ± 0.9	50.6 ± 0.8	47.7 ± 2.3
Brain			
Absolute	0.47 ± 0.01	0.48 ± 0.01	0.49 ± 0.01*
Relative	9.66 ± 0.16	9.46 ± 0.23	10.44 ± 0.37
R. Kidney			
Absolute	0.41 ± 0.01	0.45 ± 0.02	0.42 ± 0.02
Relative	8.43 ± 0.16	8.79 ± 0.40	8.84 ± 0.33
Liver			
Absolute	2.51 ± 0.26	3.13 ± 0.15	3.17 ± 0.26
Relative	52.56 ± 6.60	61.75 ± 2.16	65.59 ± 2.27*
Thymus			
Absolute	0.07 ± 0.01	0.07 ± 0.01	0.05 ± 0.00
Relative	1.32 ± 0.15	1.37 ± 0.17	1.07 ± 0.09
Female			
n	10	10	7
Necropsy body weight	47.6 ± 1.8	46.4 ± 2.3	48.7 ± 3.3
Brain			
Absolute	0.49 ± 0.01	0.47 ± 0.01	0.46 ± 0.01*
Relative	10.4 ± 0.4	10.3 ± 0.5	9.7 ± 0.6
R. Kidney			
Absolute	0.25 ± 0.01	0.25 ± 0.01[b]	0.27 ± 0.01
Relative	5.38 ± 0.21	5.68 ± 0.15[b]	5.56 ± 0.21
Liver			
Absolute	1.59 ± 0.05	1.85 ± 0.10*[b]	2.01 ± 0.12**
Relative	33.53 ± 1.22	39.52 ± 1.29**[b]	41.49 ± 0.91**
Thymus			
Absolute	0.05 ± 0.01	0.04 ± 0.01	0.06 ± 0.01
Relative	1.01 ± 0.11	0.93 ± 0.09	1.11 ± 0.17

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY

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TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Studies of Pentachloroanisole[a]

Analysis	Vehicle Control	40 mg/kg	80 mg/kg	120 mg/kg
Male				
n	10	10	3	
Hematology				
Hematocrit (%)	38.2 ± 0.3	39.1 ± 0.3	40.2 ± 0.7*	
Hemoglobin (g/dL)	15.3 ± 0.1	15.9 ± 0.1**	16.4 ± 0.3**	
Erythrocytes (10^6/μL)	8.27 ± 0.04	8.24 ± 0.05	8.29 ± 0.06	
Mean cell volume (fL)	46.4 ± 0.2	47.4 ± 0.2**	48.7 ± 0.3**	
Mean cell hemoglobin (pg)	18.5 ± 0.1	19.3 ± 0.1**	19.7 ± 0.2**	
Mean cell hemoglobin concentration (g/dL)	40.0 ± 0.1	40.7 ± 0.1**	40.7 ± 0.2*	
Leukocytes (10^3/μL)	4.23 ± 0.33	4.66 ± 0.26	3.67 ± 0.48	
n	10	10	3	
Clinical chemistry				
Alkaline phosphatase (IU/L)	194 ± 7	144 ± 4**	133 ± 2**	
Alanine aminotransferase (IU/L)	37 ± 2	34 ± 2	51 ± 16	
Aspartate aminotransferase (IU/L)	77 ± 5	53 ± 2**	73 ± 13	
Sorbitol dehydrogenase (IU/L)	10 ± 1[b]	11 ± 1	17 ± 6	
Cholinesterase (IU/L)	628.1 ± 16.7	564.7 ± 12.2**	532.0 ± 6.4**	
Female				
n	10	10	8	1[c]
Hematology				
Hematocrit (%)	37.1 ± 0.3	37.4 ± 0.3	37.2 ± 0.3	36.7
Hemoglobin (g/dL)	15.2 ± 0.1	15.0 ± 0.1*	14.8 ± 0.1**	14.7
Erythrocytes (10^6/μL)	7.57 ± 0.06	7.42 ± 0.05*	7.46 ± 0.05	7.28
Mean cell volume (fL)	49.1 ± 0.2	50.3 ± 0.2**	49.8 ± 0.2**	50.0
Mean cell hemoglobin (pg)	20.0 ± 0.1	20.2 ± 0.1	19.9 ± 0.1	20.2
Mean cell hemoglobin concentration (g/dL)	40.9 ± 0.2	40.1 ± 0.2**	39.9 ± 0.2**	40.1
Leukocytes (10^3/μL)	3.95 ± 0.15	5.27 ± 0.18**	4.39 ± 0.15	3.80
n	10	10	10	2
Clinical chemistry				
Alkaline phosphatase (IU/L)	147 ± 5	150 ± 6	226 ± 11**	181 ± 0*
Alanine aminotransferase (IU/L)	33 ± 1	31 ± 1	33 ± 1	33 ± 6
Aspartate aminotransferase (IU/L)	75 ± 3	60 ± 3**	62 ± 4**	53 ± 8*
Cholinesterase (IU/L)	2,658 ± 165	2,177 ± 112*	1,259 ± 53**	1,058 ± 2**
Sorbitol dehydrogenase (IU/L)	10 ± 1[d]	2 ± 0**[e]	3 ± 0[e]	14 ± 1[f]

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. No data calculated for 120 mg/kg, 140 mg/kg, and 180 mg/kg males or for 140 mg/kg and 180 mg/kg females due to 100% mortality
[b] n=7
[c] No standard error calculated due to high mortality in this group
[d] n=4
[e] n=8
[f] n=2

TABLE G2
Hematology and Clinical Chemistry Data for Rats at the 9-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
n	9	7	9	9
Hematology				
Hematocrit (%)	45.9 ± 0.6	45.7 ± 0.2	45.5 ± 0.3	45.8 ± 0.3
Hemoglobin (g/dL)	12.4 ± 1.4	14.6 ± 0.4	14.6 ± 0.3	15.0 ± 0.2
Erythrocytes ($10^6/\mu L$)	6.74 ± 0.09	6.83 ± 0.03	6.80 ± 0.04	6.82 ± 0.04
Mean cell volume (fL)	68.1 ± 0.2	66.9 ± 0.3**	67.1 ± 0.3*	67.1 ± 0.1**
Mean cell hemoglobin (pg)	18.3 ± 2.0	21.3 ± 0.5	21.5 ± 0.3	22.0 ± 0.2
Mean cell hemoglobin concentration (g/dL)	27.0 ± 3.0	31.9 ± 0.7	32.1 ± 0.6	32.8 ± 0.2
Platelets ($10^3/\mu L$)	4.7 ± 0.1	4.9 ± 0.1	4.7 ± 0.1	4.4 ± 0.1
Reticulocytes (%)	1.6 ± 0.1	1.5 ± 0.1	1.9 ± 0.2	1.2 ± 0.1
Leukocytes ($10^3/\mu L$)	7.68 ± 0.67	7.71 ± 0.86	7.13 ± 0.65	7.04 ± 0.43
Segmented neutrophils (%)	28.33 ± 2.94	29.86 ± 3.23	25.44 ± 2.06	25.89 ± 2.75
Lymphocytes (%)	67.33 ± 2.92	65.71 ± 3.16	69.78 ± 2.39	68.67 ± 2.95
Monocytes (%)	0.33 ± 0.17	0.43 ± 0.30	0.33 ± 0.24	0.56 ± 0.24
Eosinophils (%)	0.89 ± 0.26	1.14 ± 0.40	0.78 ± 0.32	0.67 ± 0.33
Nucleated erythrocytes (/100 leukocytes)	1.50 ± 0.50[b]	2.00[c]	1.00 ± 0.00[b]	1.00 ± 0.00[d]
n	10	10	10	10
Clinical chemistry				
Urea nitrogen (mg/dL)	14.1 ± 0.7	14.5 ± 0.8	14.6 ± 0.6	18.5 ± 0.9**
Methemoglobin (g/dL)	0.27 ± 0.06[e]	0.62 ± 0.22[f]	0.35 ± 0.06[e]	0.53 ± 0.14[e]
Alanine aminotransferase (IU/L)	46 ± 1	49 ± 2	50 ± 2	63 ± 8**
Aspartate aminotransferase (IU/L)	71 ± 5	74 ± 7	69 ± 3	86 ± 7
Sorbitol dehydrogenase (IU/L)	7 ± 0	6 ± 1	8 ± 0	7 ± 1

TABLE G2
Hematology and Clinical Chemistry Data for Rats at the 9-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Female			
n	6	7	9
Hematology			
Hematocrit (%)	39.3 ± 1.8	40.3 ± 1.3	41.8 ± 0.7
Hemoglobin (g/dL)	12.9 ± 0.9	13.2 ± 0.6	14.4 ± 0.2
Erythrocytes ($10^6/\mu L$)	5.44 ± 0.25	5.57 ± 0.17	5.88 ± 0.11*
Mean cell volume (fL)	72.3 ± 0.2	72.4 ± 0.2	71.1 ± 0.2**
Mean cell hemoglobin (pg)	23.6 ± 0.8	23.7 ± 0.8	24.4 ± 0.2
Mean cell hemoglobin concentration (g/dL)	32.7 ± 1.1	32.7 ± 1.1	34.3 ± 0.2
Platelets ($10^3/\mu L$)	3.9 ± 0.5	4.4 ± 0.3	4.8 ± 0.1*
Reticulocytes (%)	1.7 ± 0.2	1.9 ± 0.2	1.7 ± 0.2
Leukocytes ($10^3/\mu L$)	4.32 ± 0.32	4.14 ± 0.32	5.37 ± 0.30
Segmented neutrophils (%)	18.00 ± 3.18	22.71 ± 4.14	20.22 ± 3.23
Lymphocytes (%)	75.83 ± 3.43	70.57 ± 4.92	74.56 ± 2.93
Monocytes (%)	0.67 ± 0.49	0.29 ± 0.18	0.78 ± 0.32
Eosinophils (%)	1.83 ± 0.70	0.57 ± 0.30	1.22 ± 0.32
Nucleated erythrocytes (/100 leukocytes)	1.50 ± 0.50[b]	1.33 ± 0.33[d]	2.00 ± 0.71[g]
n	10	10	10
Clinical chemistry			
Urea nitrogen (mg/dL)	14.5 ± 0.5	16.6 ± 0.7*	16.8 ± 0.8*
Methemoglobin (g/dL)	0.35 ± 0.06[h]	0.42 ± 0.06[f]	0.32 ± 0.06[e]
Alanine aminotransferase (IU/L)	36 ± 2	29 ± 1*	30 ± 1*
Aspartate aminotransferase (IU/L)	65 ± 4	65 ± 5	55 ± 4
Sorbitol dehydrogenase (IU/L)	6 ± 1	4 ± 0	7 ± 0

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. No measurements taken for 10 mg/kg females.
[b] n=2
[c] No standard error calculated due to high mortality
[d] n=3
[e] n=9
[f] n=7
[g] n=4
[h] n=6

TABLE G3
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
n	10	9	9	5
Hematology				
Hematocrit (%)	41.9 ± 0.4	42.4 ± 0.7	43.4 ± 1.0	43.9 ± 1.2
Hemoglobin (g/dL)	14.9 ± 0.2	15.2 ± 0.2	15.7 ± 0.3°	15.7 ± 0.4
Erythrocytes (10^6/μL)	8.88 ± 0.09	9.21 ± 0.11°	9.57 ± 0.24°°	9.45 ± 0.16°°
Mean cell volume (fL)	47.2 ± 0.2	46.0 ± 0.7	46.2 ± 0.6	46.4 ± 0.6
Mean cell hemoglobin (pg)	16.8 ± 0.1	16.5 ± 0.2	16.7 ± 0.2	16.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)	35.5 ± 0.2	35.9 ± 0.3	36.2 ± 0.2	35.8 ± 0.3
Platelets (10^3/μL)	5.6 ± 0.1	5.1 ± 0.2°	4.8 ± 0.2°°	4.4 ± 0.2°°
Reticulocytes (%)	2.1 ± 0.2	2.0 ± 0.2	1.5 ± 0.1°	1.7 ± 0.2
Leukocytes (10^3/μL)	2.84 ± 0.11	3.30 ± 0.37	3.08 ± 0.21	3.28 ± 0.22
Segmented neutrophils (%)	39.00 ± 2.05	38.56 ± 3.16	37.22 ± 2.69	32.00 ± 2.83
Lymphocytes (%)	57.60 ± 2.21	57.56 ± 2.98	60.67 ± 2.59	64.80 ± 2.40
Atypical lymphocytes (%)	2.00 ± 0.45	2.78 ± 0.49	1.67 ± 0.44	2.00 ± 0.71
Monocytes (%)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (%)	1.40 ± 0.34	1.11 ± 0.35	0.44 ± 0.18	1.20 ± 0.20
Nucleated erythrocytes (/100 leukocytes)	0.30 ± 0.21	0.44 ± 0.24	0.22 ± 0.15	–[b]
n	10	9	9	5
Clinical chemistry				
Urea nitrogen (mg/dL)	13.5 ± 0.8	10.9 ± 0.8	14.6 ± 1.2	17.3 ± 0.5°
Alanine aminotransferase (IU/L)	50 ± 4	52 ± 3	63 ± 3°	86 ± 15°
Aspartate aminotransferase (IU/L)	63 ± 5	70 ± 4	71 ± 4	82 ± 10
Sorbitol dehydrogenase (IU/L)	13 ± 3	12 ± 1	14 ± 2	18 ± 4

TABLE G3
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Female			
n	9	10	10
Hematology			
Hematocrit (%)	41.9 ± 0.5	41.8 ± 0.4	40.9 ± 0.3
Hemoglobin (g/dL)	15.2 ± 0.1	14.9 ± 0.1	14.7 ± 0.1*
Erythrocytes (10^6/μL)	8.22 ± 0.07	8.16 ± 0.10	8.12 ± 0.07
Mean cell volume (fL)	51.0 ± 0.5	51.2 ± 0.4	50.4 ± 0.4
Mean cell hemoglobin (pg)	18.5 ± 0.1	18.2 ± 0.1	18.1 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	36.2 ± 0.2	35.7 ± 0.2	36.0 ± 0.3
Platelets (10^3/μL)	4.6 ± 0.3	4.7 ± 0.1	4.3 ± 0.2
Reticulocytes (%)	2.4 ± 0.1	1.9 ± 0.2*	1.6 ± 0.1**
Leukocytes (10^3/μL)	2.24 ± 0.17	2.14 ± 0.12	2.32 ± 0.14
Segmented neutrophils (%)	34.78 ± 3.13	34.70 ± 3.16	30.80 ± 2.35
Lymphocytes (%)	62.44 ± 2.82	62.60 ± 3.33	67.50 ± 2.40
Atypical lymphocytes (%)	1.78 ± 0.57	1.90 ± 0.38	1.10 ± 0.28
Monocytes (%)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (%)	0.89 ± 0.35	0.70 ± 0.30	0.60 ± 0.22
Nucleated erythrocytes (/100 leukocytes)	0.22 ± 0.15	0.90 ± 0.41	2.00 ± 0.75*
n	9	10	10
Clinical chemistry			
Urea nitrogen (mg/dL)	11.7 ± 0.6	13.3 ± 0.8	15.7 ± 1.0**
Alanine aminotransferase (IU/L)	44 ± 6	36 ± 3	42 ± 3
Aspartate aminotransferase (IU/L)	69 ± 8	62 ± 3	67 ± 4
Sorbitol dehydrogenase (IU/L)	10 ± 1	9 ± 1	12 ± 1

[a] Mean ± standard error. No measurements taken for 10 mg/kg females.
[b] No data calculated

TABLE G4
Hematology and Clinical Chemistry Data for Mice in the 13-Week Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	40 mg/kg	80 mg/kg	120 mg/kg
Male				
n	10	10	9	1[b]
Hematology				
Hematocrit (%)	36.6 ± 0.5	39.3 ± 0.7°°	41.6 ± 0.6°°	40.0
Hemoglobin (g/dL)	13.8 ± 0.2	14.6 ± 0.3°	15.3 ± 0.2°°	15.1
Erythrocytes ($10^6/\mu L$)	8.46 ± 0.13	8.88 ± 0.17°	9.40 ± 0.10°°	9.42
Mean cell volume (fL)	43.2 ± 0.3	44.3 ± 0.4	44.3 ± 0.3	42.0
Mean cell hemoglobin (pg)	16.3 ± 0.1	16.4 ± 0.2	16.3 ± 0.1	16.0
Mean cell hemoglobin concentration (g/dL)	37.6 ± 0.1	37.0 ± 0.2°	36.8 ± 0.1°°	37.8
Leukocytes ($10^3/\mu L$)	4.80 ± 0.38	3.73 ± 0.49	4.79 ± 0.88	4.80
n	9	10	6	1[b]
Clinical chemistry				
Alkaline phosphatase (IU/L)	25 ± 1	–[c]	32 ± 2[d]	–[c]
Alanine aminotransferase (IU/L)	17 ± 3	17 ± 4	23 ± 9	7
Aspartate aminotransferase (IU/L)	105 ± 12	169 ± 49	111 ± 7	71

TABLE G4
Hematology and Clinical Chemistry Data for Mice in the 13-Week Gavage Studies of Pentachloroanisole (continued)

	Vehicle Control	40 mg/kg	80 mg/kg	120 mg/kg	140 mg/kg	180 mg/kg
Female						
n	7	10	8	9	7	1[b]
Hematology						
Hematocrit (%)	37.4 ± 0.5	41.9 ± 0.4**	42.5 ± 0.4**	42.3 ± 0.5**	43.1 ± 0.6**	41.1
Hemoglobin (g/dL)	14.1 ± 0.2	14.8 ± 0.2*	15.1 ± 0.2**	15.2 ± 0.2**	15.3 ± 0.4**	15.4
Erythrocytes ($10^6/\mu L$)	8.55 ± 0.13	9.24 ± 0.07**	9.27 ± 0.11**	9.29 ± 0.11**	9.42 ± 0.15**	9.32
Mean cell volume (fL)	43.7 ± 0.3	45.6 ± 0.2**	45.9 ± 0.2**	45.6 ± 0.2**	45.9 ± 0.1**	44.0
Mean cell hemoglobin (pg)	16.5 ± 0.1	16.0 ± 0.1**	16.3 ± 0.1	16.3 ± 0.1	16.2 ± 0.2*	16.5
Mean cell hemoglobin concentration (g/dL)	37.8 ± 0.2	35.3 ± 0.1**	35.5 ± 0.1**	35.8 ± 0.2	35.4 ± 0.4**	37.5
Leukocytes ($10^3/\mu L$)	3.73 ± 0.36	3.79 ± 0.36	4.91 ± 0.17	3.43 ± 0.35	5.16 ± 0.34	2.60
n	9	7	8	5	8	3[b]
Clinical chemistry						
Alkaline phosphatase (IU/L)	60 ± 1[e]	59 ± 1[f]	63 ± 2	69 ± 1**[g]	61 ± 3[d]	76
Alanine aminotransferase (IU/L)	13 ± 1	26 ± 1**	30 ± 3**	34 ± 6**	39 ± 1**	16 ± 10**
Aspartate aminotransferase (IU/L)	202 ± 65	110 ± 15	106 ± 12	122 ± 60[g]	141 ± 20	268 ± 101

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. No measurements taken for 140 mg/kg and 180 mg/kg males.
[b] No standard error calculated due to high mortality in this group
[c] No data calculated
[d] n=2
[e] n=10
[f] n=6
[g] n=4

TABLE G5
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	20 mg/kg	40 mg/kg
Male			
n	10	10	10
Hematology			
Hematocrit (%)	38.6 ± 1.1	40.3 ± 0.7	37.6 ± 0.9
Hemoglobin (g/dL)	13.0 ± 0.4	13.5 ± 0.3	12.6 ± 0.3
Erythrocytes ($10^3/\mu L$)	8.88 ± 0.26	9.23 ± 0.16	8.78 ± 0.18
Mean cell volume (fL)	43.4 ± 0.3	43.6 ± 0.3	43.7 ± 1.0
Mean cell hemoglobin (pg)	14.6 ± 0.2	14.6 ± 0.2	14.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.6 ± 0.4	33.4 ± 0.2	33.6 ± 0.2
Platelets ($10^3/\mu L$)	6.5 ± 0.9	8.8 ± 0.3*	9.1 ± 0.4*
Reticulocytes (%)	2.0 ± 0.1	2.1 ± 0.2	1.6 ± 0.2
Leukocytes ($10^3/\mu L$)	1.29 ± 0.20	1.21 ± 0.19	2.15 ± 0.36
Segmented neutrophils (%)	23.70 ± 2.65	26.40 ± 3.48	23.70 ± 3.43
Lymphocytes (%)	71.60 ± 2.84	67.60 ± 4.70	71.10 ± 3.46
Atypical lymphocytes (%)	2.40 ± 0.67	2.33 ± 0.58[b]	3.70 ± 0.94
Monocytes (%)	0.30 ± 0.15	0.70 ± 0.40	0.40 ± 0.27
Eosinophils (%)	0.20 ± 0.13	0.40 ± 0.16	0.20 ± 0.13
n	10	10	10
Clinical chemistry			
Blood urea nitrogen (mg/dL)	21.4 ± 1.6	22.5 ± 3.2	18.3 ± 2.6
Methemoglobin (g/dL)	0.47 ± 0.09	0.46 ± 0.06	0.49 ± 0.09[b]
Alanine aminotransferase (IU/L)	46 ± 13	42 ± 3	70 ± 13*
Aspartate aminotransferase (IU/L)	139 ± 33	77 ± 7	88 ± 18
Sorbitol dehydrogenase (IU/L)	44 ± 7	44 ± 5	59 ± 5

TABLE G5
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Female			
n	10	9	10
Hematology			
Hematocrit (%)	38.8 ± 1.2	40.8 ± 0.9	41.3 ± 0.9
Hemoglobin (g/dL)	13.0 ± 0.4	13.7 ± 0.3	13.8 ± 0.3
Erythrocytes (10^6/μL)	8.82 ± 0.24	9.15 ± 0.16	9.15 ± 0.21[b]
Mean cell volume (fL)	44.0 ± 0.4	44.1 ± 0.2	44.5 ± 0.2
Mean cell hemoglobin (pg)	14.7 ± 0.2	14.9 ± 0.1	14.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.4	33.7 ± 0.4	33.3 ± 0.3
Platelets (10^3/μL)	6.8 ± 0.4	6.0 ± 0.9	6.7 ± 0.7
Reticulocytes (%)	2.1 ± 0.1[b]	2.0 ± 0.2	2.0 ± 0.2
Leukocytes (10^3/μL)	1.40 ± 0.23	1.17 ± 0.29	1.40 ± 0.32
Segmented neutrophils (%)	19.70 ± 3.53	17.78 ± 3.29	20.00 ± 3.63
Lymphocytes (%)	76.30 ± 3.89	77.89 ± 3.15	77.40 ± 3.77
Atypical lymphocytes (%)	2.20 ± 0.77	3.22 ± 0.94	1.90 ± 0.50
Monocytes (%)	0.20 ± 0.13	0.11 ± 0.11	0.20 ± 0.13
Eosinophils (%)	0.30 ± 0.21	0.22 ± 0.22	0.20 ± 0.13
n	9	9	8
Clinical chemistry			
Blood urea nitrogen (mg/dL)	18.4 ± 2.0	17.8 ± 1.6	23.5 ± 6.3
Methemoglobin (g/dL)	0.53 ± 0.08[b]	0.43 ± 0.11[c]	0.46 ± 0.07[b]
Alanine aminotransferase (IU/L)	22 ± 2[c]	41 ± 8*	65 ± 25*
Aspartate aminotransferase (IU/L)	86 ± 18[c]	182 ± 35	169 ± 74
Sorbitol dehydrogenase (IU/L)	22 ± 4	38 ± 4**	63 ± 18**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9
[c] n=8

TABLE G6
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole[a]

	Vehicle Control	20 mg/kg	40 mg/kg
Male			
n	10	10	10
Hematology			
Hematocrit (%)	39.7 ± 0.8	37.7 ± 1.0	37.1 ± 1.1
Hemoglobin (g/dL)	13.6 ± 0.3	12.2 ± 0.3*	12.5 ± 0.3*
Erythrocytes (10^6/μL)	8.82 ± 0.26	8.16 ± 0.20	8.18 ± 0.21
Mean cell volume (fL)	45.5 ± 0.8	46.3 ± 0.4	45.3 ± 0.7
Mean cell hemoglobin (pg)	15.5 ± 0.2	15.0 ± 0.1**	15.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.1 ± 0.4	32.4 ± 0.2**	33.9 ± 0.7
Platelets (10^3/μL)	10.3 ± 0.5	10.4 ± 0.6	11.1 ± 0.4
Reticulocytes (%)	1.4 ± 0.3	1.8 ± 0.1	1.6 ± 0.1
Leukocytes (10^3/μL)	1.45 ± 0.19	2.27 ± 0.42	1.75 ± 0.16
Segmented neutrophils (%)	27.20 ± 3.16	27.70 ± 3.99	26.10 ± 2.06
Lymphocytes (%)	67.30 ± 3.37	65.70 ± 3.81	68.40 ± 2.69
Atypical lymphocytes (%)	1.00 ± 0.47	1.80 ± 0.47	1.80 ± 0.68
Monocytes (%)	0.00 ± 0.00	0.10 ± 0.10	0.20 ± 0.20
Eosinophils (%)	0.50 ± 0.22	0.40 ± 0.16	0.10 ± 0.10
n	10	10	10
Clinical chemistry			
Urea nitrogen (mg/dL)	18.27 ± 0.75	18.51 ± 1.50	16.37 ± 1.28
Alanine aminotransferase (IU/L)	50 ± 16[b]	272 ± 46**	356 ± 56**
Aspartate aminotransferase (IU/L)	85 ± 10	191 ± 35*	256 ± 37**
Sorbitol dehydrogenase (IU/L)	58 ± 13	207 ± 37*	190 ± 44*[c]

TABLE G6
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Pentachloroanisole (continued)

	Vehicle Control	20 mg/kg	40 mg/kg
Female			
n	10	10	7
Hematology			
Hematocrit (%)	38.4 ± 0.6	40.4 ± 0.9	41.9 ± 1.2*
Hemoglobin (g/dL)	12.8 ± 0.2	13.3 ± 0.3	14.0 ± 0.4*
Erythrocytes (10^6/μL)	8.29 ± 0.09	8.41 ± 0.17	8.82 ± 0.22*
Mean cell volume (fL)	46.3 ± 0.7	47.9 ± 0.7	47.4 ± 0.6
Mean cell hemoglobin (pg)	15.4 ± 0.2	15.8 ± 0.3*	15.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.2 ± 0.3	32.9 ± 0.4	33.4 ± 0.5
Platelets (10^3/μL)	7.4 ± 0.5	7.7 ± 0.2[b]	7.5 ± 0.4
Reticulocytes (%)	1.4 ± 0.1	1.7 ± 0.2	1.9 ± 0.3
Leukocytes (10^3/μL)	0.57 ± 0.04[b]	1.06 ± 0.13**	0.94 ± 0.13**
Segmented neutrophils (%)	32.10 ± 4.59	22.40 ± 2.42	24.86 ± 3.49
Lymphocytes (%)	59.70 ± 4.85	73.60 ± 2.75	68.71 ± 3.26
Atypical lymphocytes (%)	1.60 ± 0.75	1.40 ± 0.43	2.29 ± 0.61
Monocytes (%)	0.00 ± 0.00	0.00 ± 0.00	0.29 ± 0.18*
Eosinophils (%)	0.70 ± 0.21	0.30 ± 0.15	0.71 ± 0.29
n	9	9	6
Clinical chemistry			
Urea nitrogen (mg/dL)	12.93 ± 1.43	15.80 ± 1.53	16.10 ± 1.31
Alanine aminotransferase (IU/L)	27 ± 3[d]	32 ± 3	46 ± 10*
Aspartate aminotransferase (IU/L)	100 ± 13	90 ± 14	100 ± 18
Sorbitol dehydrogenase (IU/L)	30 ± 4	48 ± 6*	73 ± 16**

[a] Mean ± standard error
[b] n=9
[c] n=6
[d] n=8

APPENDIX H
TOXICOKINETICS OF PENTACHLOROANISOLE IN F344 RATS AND B6C3F$_1$ MICE

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TOXICOKINETICS OF PENTACHLOROANISOLE IN F344 RATS AND B6C3F$_1$ MICE

INTRODUCTION

Toxicokinetic studies of pentachloroanisole were conducted in F344 rats and B6C3F$_1$ mice to aid interpretation of the results of the carcinogenicity studies and to improve the utility of the studies for risk assessment. The studies were designed to define the elimination profiles of pentachloroanisole after intravenous administration and the linear absorption and elimination range of pentachloroanisole after gavage administration.

METHODS

Formulations

The pentachloroanisole gavage formulations were prepared by directly dissolving pentachloroanisole into corn oil. The pentachloroanisole intravenous formulation was prepared by dissolving pentachloroanisole in Emulphor:ethanol:water (1:1:3). Concentrations of pentachloroanisole formulations were independently confirmed by a dose analysis method.

Animals

Male and female F344 rats approximately 13 weeks old were purchased from Charles River Breeding Laboratories (Raleigh, NC). Fifteen male rats and 15 female rats were administered 10 mg pentachloroanisole per kg body weight intravenously. Blood samples were collected from three animals at 2, 10, 20, and 30 minutes, and at 1, 3, 6, 10, 20, and 30 hours. Rats were sampled twice by alternating between orbital sinuses with a time interval of at least 2 hours. For gavage studies, groups of 12 male and 12 female rats were administered 10, 20, and 40 mg/kg pentachloroanisole. Blood samples were collected from three animals at 30 minutes, and at 1, 3, 6, 12, 18, 26, and 32 hours. Two blood samples were collected from each rat as in the intravenous study. Plasma was separated from blood samples and then stored at -20° C until analysis.

Male and female B6C3F$_1$ mice approximately 13 weeks old were purchased from Charles River Breeding Laboratories (Raleigh, NC). Thirty male and 30 female mice were administered 10 mg pentachloroanisole per kg body weight intravenously. Blood samples were collected as in the rat study. For gavage studies, 24 male and 24 female mice were administered 10, 20, and 40 mg/kg pentachloroanisole. Blood samples were collected once from each of three animals at each time point by orbital sinus bleeding. Plasma was separated from blood samples and then stored at -20° C until analysis.

Pentachloroanisole Analysis

Plasma pentachloroanisole concentrations were determined by gas chromatography. An aliquot of 50 μL of plasma was mixed with 200 μL of 2 M sodium hydroxide solution, to which an aliquot of 1 mL internal standard solution (1 μg/mL aldrin in hexane) and 1 mL hexane was added for extraction. The organic phase was then extracted and transferred to an autosampler vial and 1 μL of hexane extract was directly injected into a Varian 3500 Gas Chromatograph equipped with an autosampler and an electron capture detector. A DB-5 Megabore® glass column (30 m x 0.53 mm ID, 1.5 μm film) was used. The initial oven temperature was 145° C with an initial holding time of 12 minutes, followed by a programmed temperature increase at 6° C/min to 210° C with a final holding time of 2 minutes. Helium at a flow rate of 10 mL/min was used as a carrier gas and nitrogen (20 mL/min) was used as make-up gas. The peak area ratio of pentachloroanisole to aldrin was used to construct the spiked plasma standard curve and to determine pentachloroanisole concentrations in samples. Plasma standards were prepared concurrently with each batch of samples by spiking a blank rat plasma with a pentachloroanisole solution. The method was validated over a range of 0.02 to 10 μg/mL from which two linear standard curves were constructed. The recovery of pentachloroanisole from plasma was complete. The limit of detection (0.01 μg/mL) for the

pentachloroanisole method was defined as three times the standard deviation of the blank divided by the slope of the standard curve. The limit of quantitation (0.02 μg/mL) was defined as the lowest concentration for which the standard deviation was 10% relative standard deviation and the relative standard error was less than 10%.

Pentachlorophenol Analysis

Plasma pentachlorophenol concentrations were determined by high performance liquid chromatography. Plasma samples (100 μL) were mixed with twice the volume of acetonitrile containing octanophenone (50 μg/mL) as an internal standard. Samples were vortexed for 30 seconds and then filtered through a 0.2 μm filter. The filtrates were diluted with an equal volume of water and the diluted filtrates (100 μL) were directly injected into a Waters 510 Liquid Chromatograph equipped with an autosampler and a Varian 2050 UV detector. A Beckman Ultrasphere Cyano column (250 x 4.6 mm ID, 5 μm particle) together with a Whatman CO:PELL ODS guard column (20 x 2 mm ID) were used. The mobile phase was 40% acetonitrile, 60% water with 1% acetic acid at a flow rate of 1 mL/min. The UV detector was operated at 229 nm. The peak area ratio of pentachlorophenol to octanophenone was used to construct the spiked plasma standard curve and to determine pentachlorophenol concentrations in samples. Plasma standards were prepared concurrently with each batch of samples by spiking blank rat plasma with pentachlorophenol solutions. The method was validated over a range of 1.0 to 200 μg/mL, over which linearity was confirmed. The recovery of pentachlorophenol from plasma was approximately 95%. The limit of detection for the pentachlorophenol method was 0.18 μg/mL and the limit of quantitation was 1.0 μg/mL

Data Analysis

Plasma concentration data obtained from intravenous administration of pentachloroanisole in both rats and mice were evaluated for estimation of toxicokinetic parameters by the program NONLIN® (Metzler *et al.*, 1974). The initial values to be used in the NONLIN® program were estimated by a curve stripping method. The area under the concentration versus time curves was estimated for all dose groups using the trapezoidal rule with an endpoint correction based on the estimated elimination half-life. The standard error of the area under the concentration versus time curve was calculated based on the standard error of plasma concentrations at each time point using Microsoft Excel (Microsoft Corporation, Redmond, WA). The Student *t*-test was performed whenever applicable. Linear regression analysis was performed using KaleidaGraph (Synergy Software, Reading, PA).

RESULTS

Intravenous Studies

After intravenous administration, pentachloroanisole was found to be rapidly eliminated in both male and female rats and mice (Figure H1) with no major observed sex-related differences. The elimination of pentachloroanisole can be described by a classical two-compartment model with first-order elimination kinetics. The terminal elimination half-lives in rats and mice were approximately 1.2 and 1.0 hours, respectively. The calculated plasma clearance was 6.07 L/kg-hr for male rats and 5.61 L/kg-hr for female rats, 8.45 L/kg-hr for male mice and 10.2 L/kg-hr for female mice. Given the value of hepatic blood perfusion rates of 4.78 L/kg-hr for rats and 8.5 L/kg-hr for mice, and taking into consideration the fraction of plasma in whole blood, it is apparent that non-hepatic metabolism or other nonhepatic elimination processes were occurring. The calculated volume of the central compartment was about 2.41 L/kg for male rats, 2.01 L/kg for female rats, 2.05 L/kg for male mice, and 4.5 L/kg for female mice. These values were suggestive of pentachloroanisole's tissue distribution which is consistent with pentachloroanisole's low water solubility. High concentrations of pentachlorophenol were observed immediately after the administration of pentachloroanisole in male and female rats and mice (Figure H1). The area under the concentration versus time curves and the dosage normalized area under the concentration curves for both the parent chemical and its major metabolite, pentachlorophenol, are given in Tables H1 and H2. The terminal half-life of pentachlorophenol in both rats and mice was estimated at approximately 8 hours.

Gavage Studies

After gavage administration, pentachloroanisole concentrations were found to be lower than those of pentachlorophenol by two to three orders of magnitude in both rats (Figure H2) and mice (Figure H3). For male and female rats and mice the area under the concentration versus time curves of pentachloroanisole increased with dose, but the dose proportionality was lost above 20 mg/kg (Figure H4). The dose normalized area under the concentration versus time curves of pentachloroanisole were sex dependent only in 10 mg/kg rats and 20 mg/kg mice, but the apparent sex-related differences in these two doses were believed to be artifacts caused by the limited number of data points available for area under the concentration versus time curve estimation. Dose proportionality was seen in all dose groups for the maximum concentration of pentachloroanisole achieved after gavage administration for male and female rats and mice (Figure H5). The variation of C_{max} in each dose group was also high. After gavage administration of pentachloroanisole, the area under the concentration versus time curve of pentachlorophenol and C_{max} increased with pentachloroanisole dose and appeared to be dose proportional for both rats and mice. The area under the concentration versus time curve of pentachlorophenol was sex dependent only in rats. The terminal half-life of pentachlorophenol in both rats and mice was estimated to be 5 to 9 hours. While there were no sex-related differences in pentachlorophenol terminal half-life in mice, the terminal half-life of pentachlorophenol in female rats tended to be longer than in male rats, suggesting a slower elimination of pentachlorophenol in female rats.

The bioavailability of pentachloroanisole after gavage administration was estimated based on the dose-normalized area under the concentration versus time curve (Tables H1 and H2). The calculated bioavailabilty was low but increased with dose. The low bioavailability by the gavage route is consistent with first-pass hepatic metabolism.

The bioavailability of pentachloroanisole after gavage administration was also estimated in rats based on the dosage normalized area under the concentration versus time curve of pentachlorophenol. Results of a separate experiment showed that the area under the concentration versus time curve of pentachlorophenol after intravenous administration of 5 mg/kg pentachlorophenol in rats was 440 μg/mL-hr for female rats. Utilizing these data, the bioavailability of pentachloroanisole based on area under the concentration versus time curve of pentachlorophenol was calculated and the results are also listed in Table H1. It can be seen that the bioavailability is low using the area under the concentration versus time curve of pentachloroanisole and it is high using the area under the concentration versus time curve of its pentachlorophenol metabolite. This inconsistency in bioavailability further supports the idea of first-pass metabolism. Since the absolute value for the area under the concentration versus time curve of pentachlorophenol after an intravenous administration of pentachlorophenol to mice is not available, the bioavailability of pentachloroanisole in mice using pentachlorophenol concentrations was not calculated.

DISCUSSION

Female rats have larger values of area under the pentachlorophenol concentration versus time curve than do male rats. This difference can be correlated to the well-known sex-related differences in rats in the activity of UDP-glucuronosyltransferase, an enzyme responsible for glucuronidation of pentachlorophenol (Aitio and Marniemi, 1980).

Since both peak pentachloroanisole and pentachlorophenol plasma concentrations occurred at about 6 to 8 hours after dosing, and the biological half-life of pentachlorophenol is relatively long, bioaccumulation of pentachlorophenol after repeated daily gavage dosing of pentachloroanisole is predicted. This bioaccumulation of pentachlorophenol can explain the similar hyperthermia syndrome observed in rats after being dosed either with pentachloroanisole or pentachlorophenol (Garthoff *et al.*, 1982).

In contrast, no sex-related differences were observed in the areas under the concentration versus time curves for pentachloroanisole or pentachlorophenol. One explanation for this is the lack of sex-related differences in UDP-glucuronosyltransferase or monooxygenase activity in mice (Aitio and Marniemi, 1980;

Jones, *et al.*,1980). Bioavailability of pentachloroanisole in mice was generally higher than in rats, which may suggest that the first-pass effect in mice was less severe than in rats although *in situ* glucuronidation is likely occurring. Since the peak plasma concentrations of both pentachloroanisole and pentachlorophenol after gavage administration of pentachloroanisole also occurred at about 8 hours in male and female mice, and the half-life of pentachlorophenol is relatively long, bioaccumulation of pentachlorophenol will almost certainly occur after repeated daily gavage dosing of pentachloroanisole. This might explain why most mice died at night after being administered 40 mg/kg or higher doses of pentachloroanisole by gavage.

The concentration of the metabolite, pentachlorophenol, was higher in female rats than in male rats after gavage administration and sex-related differences in toxic and carcinogenic responses to pentachloroanisole in rats and mice were observed. These findings cannot be attributed to the sex-related differences in systemic availability of pentachloroanisole or to the rate of metabolism of pentachloroanisole to pentachlorophenol.

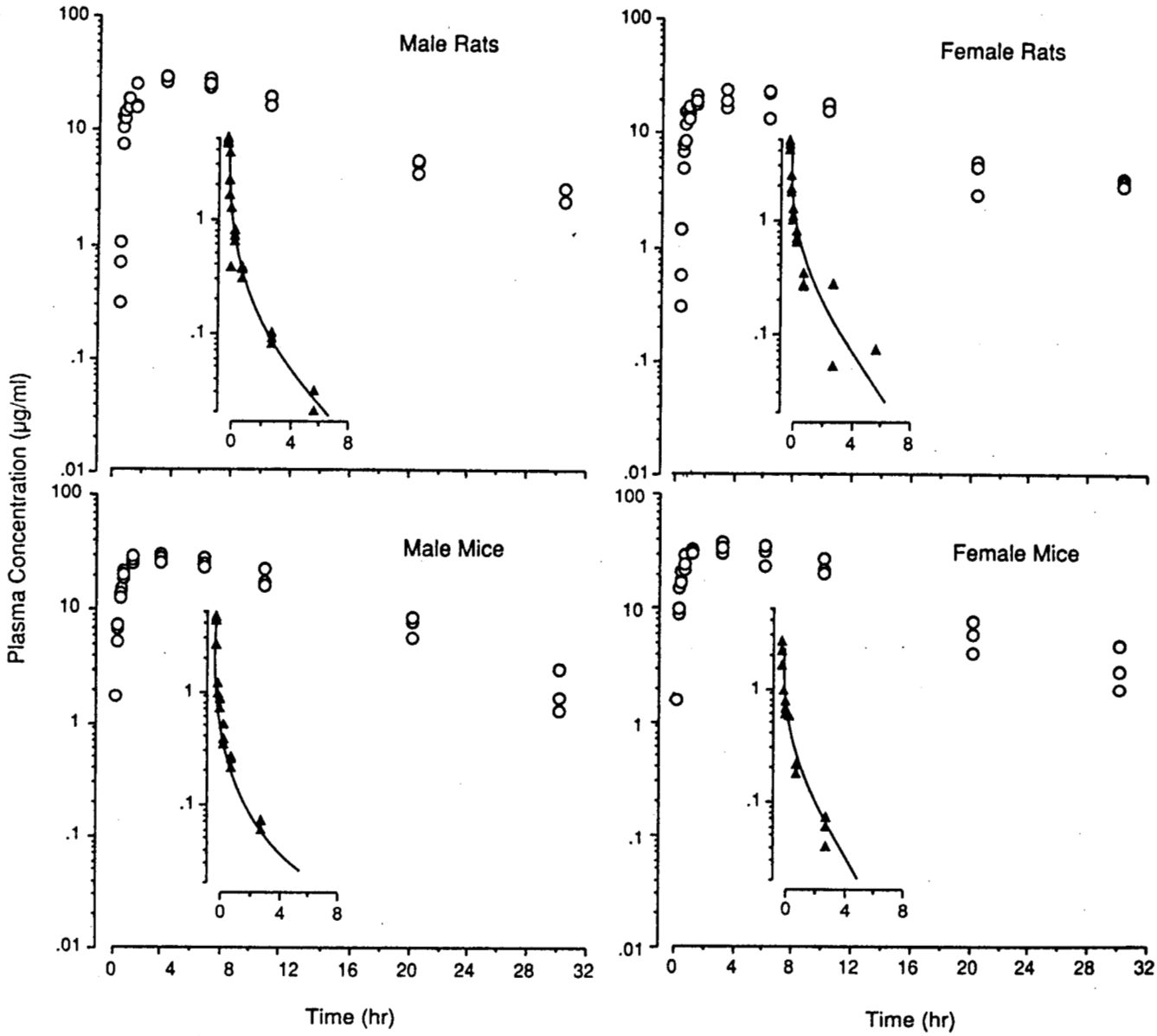

FIGURE H1
Plasma Concentrations of Pentachloroanisole and Pentachlorophenol after Intravenous Administration of 10 mg/kg Pentachloroanisole to F344 Rats and B6C3F$_1$ Mice. (▲) Pentachloroanisole, (o) Pentachlorophenol, (____) Two-compartment Model

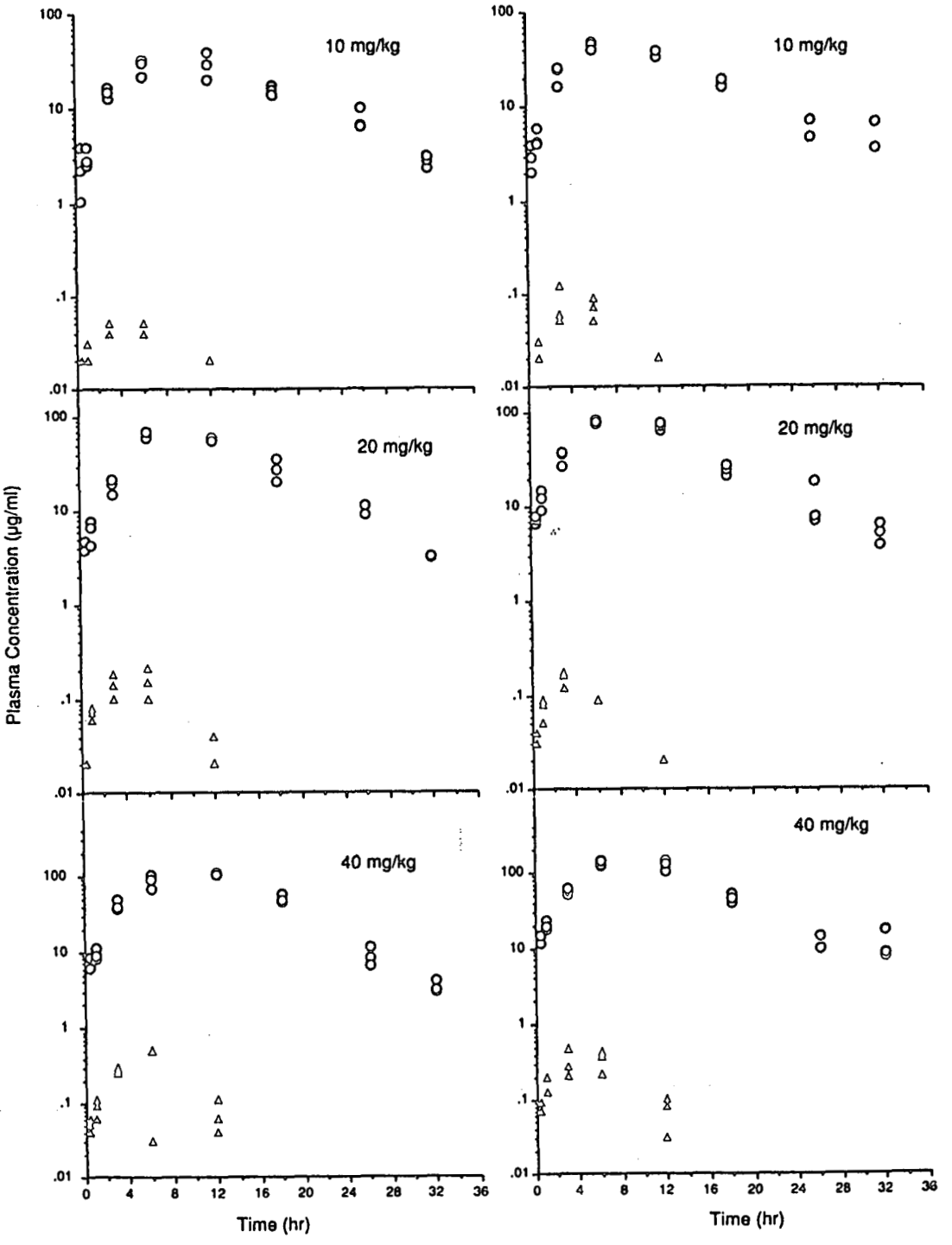

FIGURE H2
Plasma Concentrations of Pentachloroanisole and Pentachlorophenol after Gavage Administration of 10, 20, and 40 mg/kg Pentachloroanisole to Male and Female F344 Rats. (△) Pentachloroanisole, (○) Pentachlorophenol

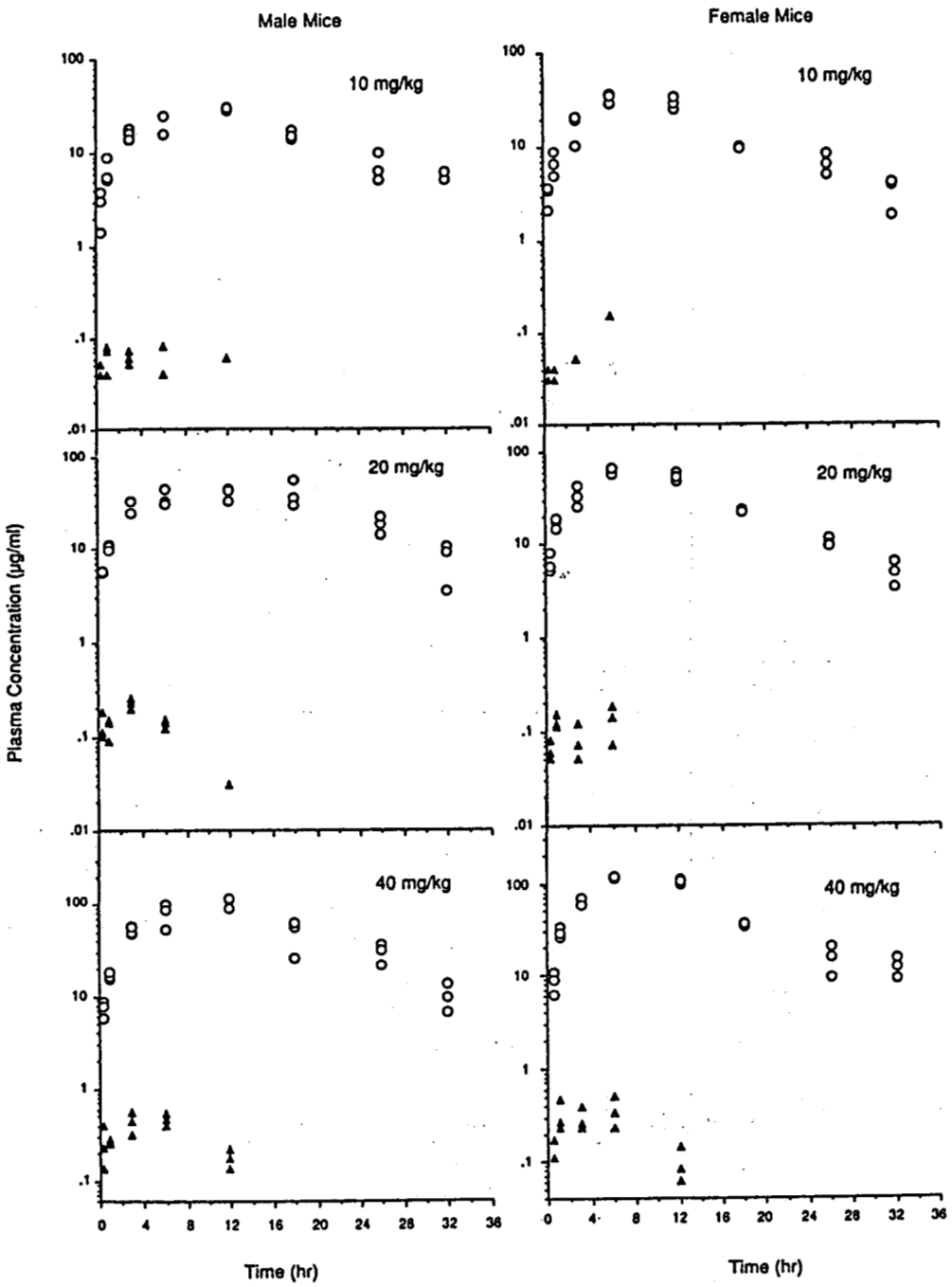

FIGURE H3
Plasma Concentrations of Pentachloroanisole and Pentachlorophenol after Intravenous Administration of 10, 20, and 40 mg/kg Pentachloroanisole to Male and Female B6C3F$_1$ Mice. (▲) Pentachloroanisole, (o) Pentachlorophenol

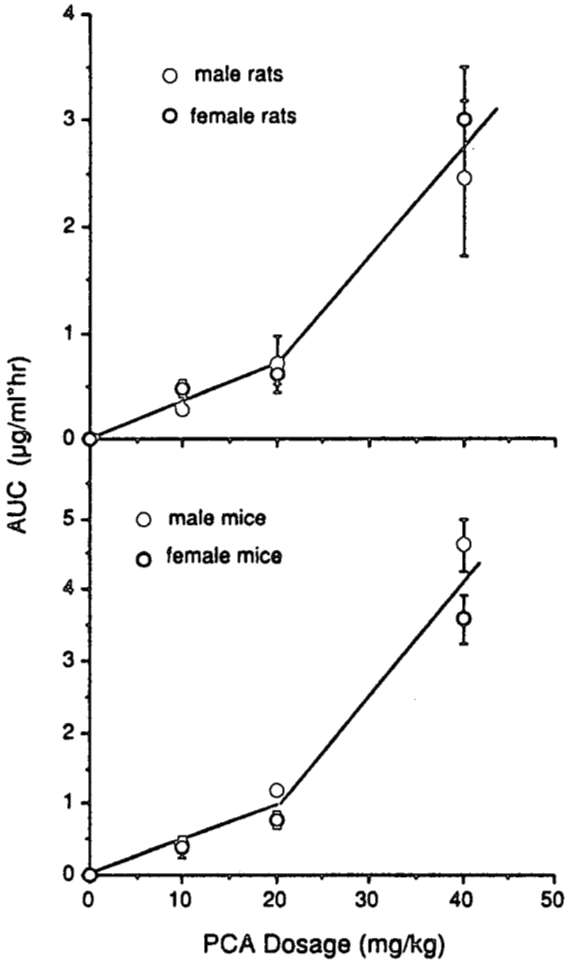

FIGURE H4
Plots of Area Under the Concentration versus Time of Pentachloroanisole versus Pentachloroanisole Dose in Rats and Mice.

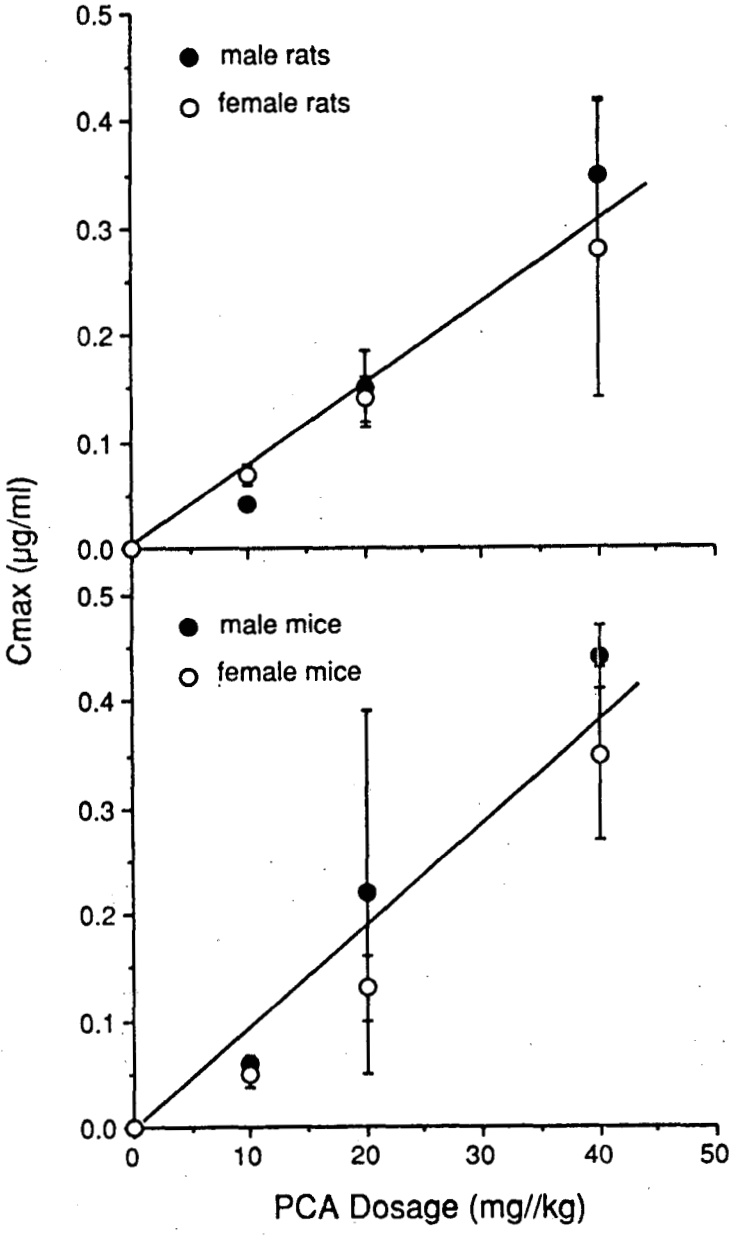

FIGURE H5
Plots of Maximum Plasma Concentration (C_{max}) of Pentachloroanisole versus Pentachloroanisole Dose in F344 Rats and B6C3F$_1$ Mice.

TABLE H1
Kinetic Parameters for Pentachloroanisole (PCA) and Pentachlorophenol (PCP) in F344 Rats Administered Pentachloroanisole[a]

Dose (mg/kg)	Route	PCA Cmax (µg/ml)	PCA AUC[b] (µg/ml/hr)	PCA AUC/Dose	PCP Cmax (µg/ml)	PCP AUC[c] (µg/ml/hr)	PCP AUC/Dose	Bioavailability Based on AUC: PCA (%)	Bioavailability Based on AUC: PCP[d] (%)
Male									
10	IV	–	1.93 ± 0.34	0.193 ± 0.034	32 ± 1	452 ± 13	45.2 ± 1.3		
10	Gavage	0.043 ± 0.002	0.27 ± 0.01	0.027 ± 0.001	29 ± 3	542 ± 38	54.2 ± 3.8	14 ± 3	62 ± 4
20	Gavage	0.15 ± 0.035	0.71 ± 0.27	0.036 ± 0.014	66 ± 3	988 ± 34	49.4 ± 1.7	19 ± 8	56 ± 2
40	Gavage	0.35 ± 0.069	2.45 ± 0.73	0.061 ± 0.018	107 ± 2	1596 ± 59	39.9 ± 1.4	31 ± 10	45 ± 2
Female									
10	IV	–	1.92 ± 0.62	0.192 ± 0.062	20 ± 3*	385 ± 16*	38.5 ± 1.6*		
10	Gavage	0.070 ± 0.010*	0.47 ± 0.075*	0.047 ± 0.0075*	44 ± 2*	704 ± 22*	70.4 ± 2.2*	24 ± 8	96 ± 3*
20	Gavage	0.14 ± 0.020	0.61 ± 0.10	0.031 ± 0.005	80 ± 1*	1198 ± 36*	59.9 ± 1.8*	16 ± 5	82 ± 2*
40	Gavage	0.28 ± 0.14	3.00 ± 0.50	0.075 ± 0.013	136 ± 6*	2084 ± 91*	52.1 ± 2.3*	39 ± 14	71 ± 3*

* Significantly different from males ($P \leq 0.01$) by Student *t*-test.
[a] Data are presented as means ± standard deviations.
[b] Endpoint correction using terminal half-life of 1.2 hours for male and female rats.
[c] Endpoint correction using terminal half-life of 4 hours for male and female rats.
[d] AUC values after iv administration of PCP at 5 mg/kg are 440 and 365 µg/ml/hr for male and female rats.

TABLE H2
Kinetic Parameters for Pentachloroanisole (PCA) and Pentachlorophenol (PCP) in B6C3F$_1$ Mice Administered Pentachloroanisole[a]

Dose (mg/kg)	Route	PCA Cmax (µg/ml)	PCA AUC[b] (µg/ml/hr)	PCA AUC/Dose	PCP Cmax (µg/ml)	PCP AUC[c] (µg/ml/hr)	PCP AUC/Dose	Bioavailability Based on AUC PCA (%)
Male								
10	IV	–	1.26 ± 0.24	0.126 ± 0.024	26.85 ± 0.851	412 ± 16	41.2 ± 1.6	
10	Gavage	0.06 ± 0.007	0.41 ± 0.04	0.041 ± 0.004	28.8 ± 0.74	560 ± 19	56.0 ± 1.9	33 ± 7
20	Gavage	0.22 ± 0.17	1.19 ± 0.06	0.060 ± 0.003	40.3 ± 3.4	984 ± 66	49.2 ± 3.3	48 ± 9
40	Gavage	0.44 ± 0.03	4.62 ± 0.37	0.12 ± 0.009	103 ± 7.6	1752 ± 111	43.8 ± 2.8	95 ± 20
Female								
10	IV	–	1.10 ± 0.23	0.110 ± 0.023	31.62 ± 1.9	468 ± 21*	46.8 ± 2.1*	
10	Gavage	0.049 ± 0.012	0.38 ± 0.15	0.038 ± 0.015	34.2 ± 2.5	551 ± 24	55.1 ± 2.4	35 ± 15
20	Gavage	0.13 ± 0.03	0.77 ± 0.11*	0.039 ± 0.006*	62.9 ± 2.5*	1001 ± 29	50.1 ± 1.5	35 ± 9
40	Gavage	0.35 ± 0.080	3.58 ± 0.33	0.090 ± 0.008	115 ± 1.5	1759 ± 34	44.0 ± 0.85	71 ± 15

* Significantly different from males ($P \leq 0.05$) by Student *t*-test.
[a] Data are presented as means ± standard deviations.
[b] Endpoint correction using terminal half-life of 1 hour for male and female rats.
[c] Endpoint correction using terminal half-life of 5 hours for male and female rats.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF PENTACHLOROANISOLE

Pentachloroanisole was obtained in three lots. Lot HE052008, which was obtained from the Aldrich Chemical Company (Milwaukee, WI), was used in the 16-day studies. The analytical chemistry laboratory, Midwest Research Institute Kansas City, MO, synthesized lots M012882 and M062783. Lot M012882 was used in the 13-week studies and lot M062783 was used in the 2-year studies. Identity, purity, and stability analyses were performed by the analytical chemistry laboratory. Reports on the syntheses and analyses performed in support of the pentachloroanisole studies are on file at the National Institute of Environmental Health Sciences.

Lot M012882 was synthesized by the methylation of pentachlorophenol (lot MM031080), which was obtained from Dow Chemical Company (Midland, MI). Pentachlorophenol was ground and recrystallized twice with absolute methanol. Methylation was performed by dripping iodomethane into a heated solution of pentachlorophenol in acetone buffered with potassium carbonate. The acetone was reduced by evaporation, and ethyl ether and benzene were added. The solution was extracted with 1 N sodium hydroxide and then with water. The organic phase was dried with anhydrous sodium sulfate and recrystallized from methanol as white needles.

Lot M062783 was synthesized by the methylation of pentachlorophenol which was produced by the acidification and purification of sodium pentachlorophenolate (lot MM12197A) obtained from Dow Chemical Company (Midland, MI). Lot MM12197A was ground and extracted with high-purity toluene. The powder was then acidified with 6 N hydrochloric acid and extracted with ethyl ether. The resulting slurry was washed with 5% sodium bicarbonate and then with water, and dried. The phenol obtained by this procedure was crystallized from boiling methanol. Benzene was added, and the solution was allowed to crystallize overnight. The crystals were washed with isooctane, then recrystallized from methanol. After further recrystallization from methanol/benzene and then benzene, methylation was performed as described for lot M012882.

All lots of the bulk chemical, a colorless or white crystalline solid, were identified as pentachloroanisole by infrared, ultraviolet/visible, and nuclear magnetic resonance (NMR) spectroscopy. All spectra were consistent with the expected structure of pentachloroanisole (Figures I1 and I2); no literature spectra were found for comparison.

The purity of all lots was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography (TLC), and gas chromatography. Additionally, functional group analysis of methoxyls was used to determine purity of lot M062783. For lots HE052008 and M012882, TLC was performed on aluminum oxide, Type E, F-254 plates with two systems: A) 100% hexanes and B) isooctane:carbon disulfide (1:1). Visualization was accomplished with ultraviolet (254 nm) light and by a spray of 0.5% ethanolic solution of rhodamine B followed by a spray of 10% aqueous sodium carbonate solution. Hexachlorobenzene in methylene chloride was used as a reference standard. Gas chromatography for lot HE052008 was performed with a flame ionization detector (FID) and a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used:

A) 10% SP-2100 on 80/100 mesh Supelcoport, with an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C/minute, and
B) 1% SP-1000 on 100/120 mesh Supelcoport, with an oven temperature program of 50° C for 5 minutes, then 50° to 230° C at 10° C/minute.

For lot HE052008, elemental analyses for carbon, hydrogen, and chlorine were in agreement with theoretical values. Karl Fischer water analysis showed 0.06 ± 0.03% water. TLC indicated one major spot and one trace impurity. Gas chromatography by both systems indicated one impurity with an area of approximately 0.2% of the major peak area. The overall purity was determined to be at least 99%. A gas chromatography analysis was conducted to quantify pentachlorophenol in the bulk chemical. The method was the same as that used in the purity analysis, and with a 1% SP-1240 DA on 100/120 mesh Supelcoport column system and an oven temperature of 190° C, isothermal. The analysis did not detect any pentachlorophenol at a concentration of 0.1% or above.

For lot M012882, elemental analyses for carbon, hydrogen, and chlorine were in agreement with theoretical values. Karl Fischer water analysis showed less than 0.05% water. TLC indicated one major spot and no impurities. Gas chromatography by the same systems used for the purity analysis of lot HE052008, but with a 10% SP-2100 on 100/120 mesh Supelcoport column for system A, indicated one impurity with an area of approximately 0.1% of the major peak area by both systems. A gas chromatography analysis conducted to quantify pentachlorophenol was the same as the special analysis used for lot HE052008, but with an oven temperature of 180° C, isothermal. The analysis did not detect any pentachlorophenol at a concentration of 0.1% or above. The overall purity of lot M012882 was determined to be slightly higher than that of lot HE052008.

Gas chromatography/mass spectroscopy with full mass scan was performed to identify and quantify impurities in lot M012882. A J&W fused silica capillary column was used with a helium carrier gas at 15 cm/second and an oven temperature program of 80° C for 2 minutes, then 80° to 325° C at 10° C/minute. Tetrachloroanisole was identified as the largest impurity; four unidentified impurities were also detected. Selected ion monitoring identified no additional impurities. Quantitation of tetrachloroanisole was performed with capillary gas chromatography with an electron capture detector, a carrier gas flow rate of 25 cm/second, and an oven temperature program of 100° C for 2 minutes, then 100° to 320° C at 10° C/minute.. A tetrachloroanisole concentration of 1600 ppm was determined. Hexachlorobenzene was identified and quantitated using packed column gas chromatography with electron capture detection and a column system of 5% SP-1000 on 100/120 mesh Supelcoport, with an oven temperature of 160° C; 2.65 ppm hexachlorobenzene was quantified. Five unidentified impurities were also detected at levels of 0.1% or less.

For lot M062783, elemental analyses for carbon, hydrogen, and chlorine were in agreement with theoretical values. Functional group analysis of the methoxyl group was in agreement with the theoretical levels. Karl Fischer water analysis indicated less than 0.1% water. TLC was performed using the same methods described for determining the purity of lots HE052008 and M012882, but with visualization accomplished with ultraviolet light at 254 and 366 nm and with a spray of 0.5% ethanolic rhodamine B followed by a spray of 10% aqueous sodium carbonate. TLC indicated a major spot only. Gas chromatography, conducted with the same systems used for the purity analysis of lot M012882, but with an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C/minute for system B, indicated a major peak and no impurities with areas greater than 0.1% relative to the major peak. A gas chromatography analysis conducted to quantify pentachlorophenol was the same as the special analysis used for lot M012882. The analysis did not detect any pentachlorophenol at a concentration of 0.1% or above. Major peak comparison of lots M062783 and M012882 by gas chromatography, with 10% SP-2100 on 100/120 mesh Supelcoport and a column temperature of 210° C and with hexadecane added as an internal standard, indicated a purity of 101.1 ± 2% for lot M062783 relative to lot M012882.

Gas chromatography/mass spectroscopy full mass scan was performed to identify and quantify impurities in lot M062783. The same system was used as that used to quantitate impurities in lot M012882, but with an oven temperature program of 110° to 320° C at 6° C/minute. Two chlorinated impurities were found: tetrachloroanisole (192 ppm) and tetrachlorobromanisole (361 ppm). One unidentified impurity with a concentration of 88 ppb was also detected with selected ion monitoring. Hexachlorobenzene was

identified and quantitated using packed column gas chromatography with the same system used to quantitate impurities in lot M012882; 7.0 ppm hexachlorobenzene was identified.
A concurrent analysis of lot M012882 was conducted, using the same methods as for lot M062783. Gas chromatography/mass spectroscopy indicated two impurities: tetrachloroanisole (1,664 ppm) and tetrachlorobromoanisole (165 ppm). Two additional chlorinated impurities were detected and quantitated at 1.2 ppm and 389 ppb, but were not identified. Packed column gas chromatography identified 2.6 ppm hexachlorobenzene. No chlorinated dibenzodioxins, dibenzofurans, or diphenyl ethers were detected in either lot. Capillary gas chromatography with electron capture detection was used to compare the impurity profiles and the reconstructed ion current chromatograms of the two lots.

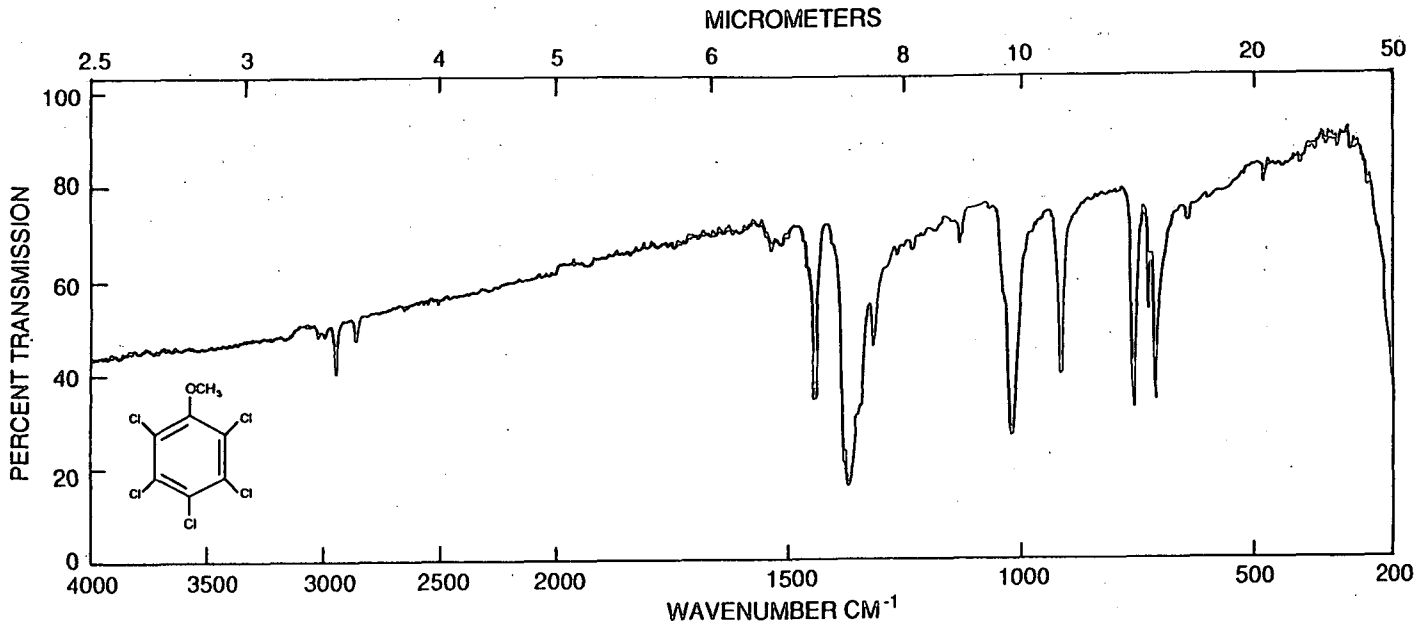
Stability studies were performed using gas chromatography with the system A described for the purity studies, but with an oven temperature of 210° C and 0.2% hexadecane in hexanes added as an internal standard. Pentachloroanisole was found to be stable in bulk form when stored for 2 weeks at temperatures up to 60° C. During the 13-week and 2-year studies, the stability of the bulk chemical was monitored by the study laboratory using ultraviolet/visible spectroscopy and gas chromatography. System B described for the purity studies was used for monitoring in the 13-week studies; for the 2-year studies, System A with the following modifications was used: 10% OV 101 on 100/120 mesh Supelcoport at an oven temperature of 180° C. The bulk chemical was analyzed four times during the 13-week studies and seven times (at 4-month intervals) during the 2-year studies. No degradation of either lot of pentachloroanisole was seen throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations were prepared by mixing the appropriate quantities of pentachloroanisole and corn oil on a weight-to-volume basis for the 16-day studies and on a weight-to-weight basis for the 13-week and 2-year studies (Table I1). Dose formulations were prepared three times and stored at 5° C during the 16-day studies. For the 13-week and 2-year studies, dose formulations were prepared weekly and stored at room temperature (approximately 22° C); maximum storage time for any dose formulation did not exceed 21 days. Dose formulations were hand agitated before administration.

For the stability studies, 4 mL aliquots of the dose formulations were diluted to 100 mL with hexane; 5 mL samples were then mixed with 5 mL of hexadecane, then further diluted with hexane. The pentachloroanisole content was determined by gas chromatography with FID, with 3% SP-2100 on 100/120 mesh Supelcoport and nitrogen as a carrier gas at 20 mL/minute. Hexadecane was added as an internal standard. The oven temperature was 150° C. Stability of the dose formulations was established for at least 3 weeks when stored in the dark at room temperature.

Dose formulations of pentachloroanisole were periodically analyzed by the study laboratory and at the analytical chemistry laboratory using the same gas chromatography method used in the stability studies, but with the FID at 300° C, 80/100 mesh Supelcoport, a carrier gas flow rate of 25 mL/minute, and 1.0 mg/mL octadecane as the internal standard. Dose formulations were analyzed three times during the 13-week studies, and all were within 10% of the target concentration (Table I2). During the 2-year studies, dose formulations were analyzed at least every 8 weeks; five times during the studies, animal room samples of the dose formulations were taken on the second day of dosing. All dose formulations sampled were within 10% of their target concentrations (Table I3). Periodic peroxide analyses of the corn oil vehicle by the study laboratory indicated that peroxide levels were within the acceptable limit of 10 mEq/kg. Results of periodic referee analysis by the analytical chemistry laboratory were in good agreement with the results obtained by the study laboratory (Table I4).



ABSCISSA	ORDINATE		
EXPANSION 1	EXPANSION 1	SCAN TIME 24 min	REP. SCAN – SINGLE BEAM –
SUPPRESSION –	% T 0-100 ABS –	RESPONSE 2	TIME DRIVE – PRE SAMPLE CHOP –
		SLIT PROGRAM 6	OPERATOR M.S.R. DATE 7/6/83
SAMPLE: Pentachloroanisole Lot No.: MO62783 Batch No.: 06	REMARKS Trimmer comb in reference beam	SOLVENT – CONCENTRATION 2% (w/w) in a KBr pellet	CELL PATH REFERENCE 158N

FIGURE II
Infrared Absorption Spectrum of Pentachloroanisole

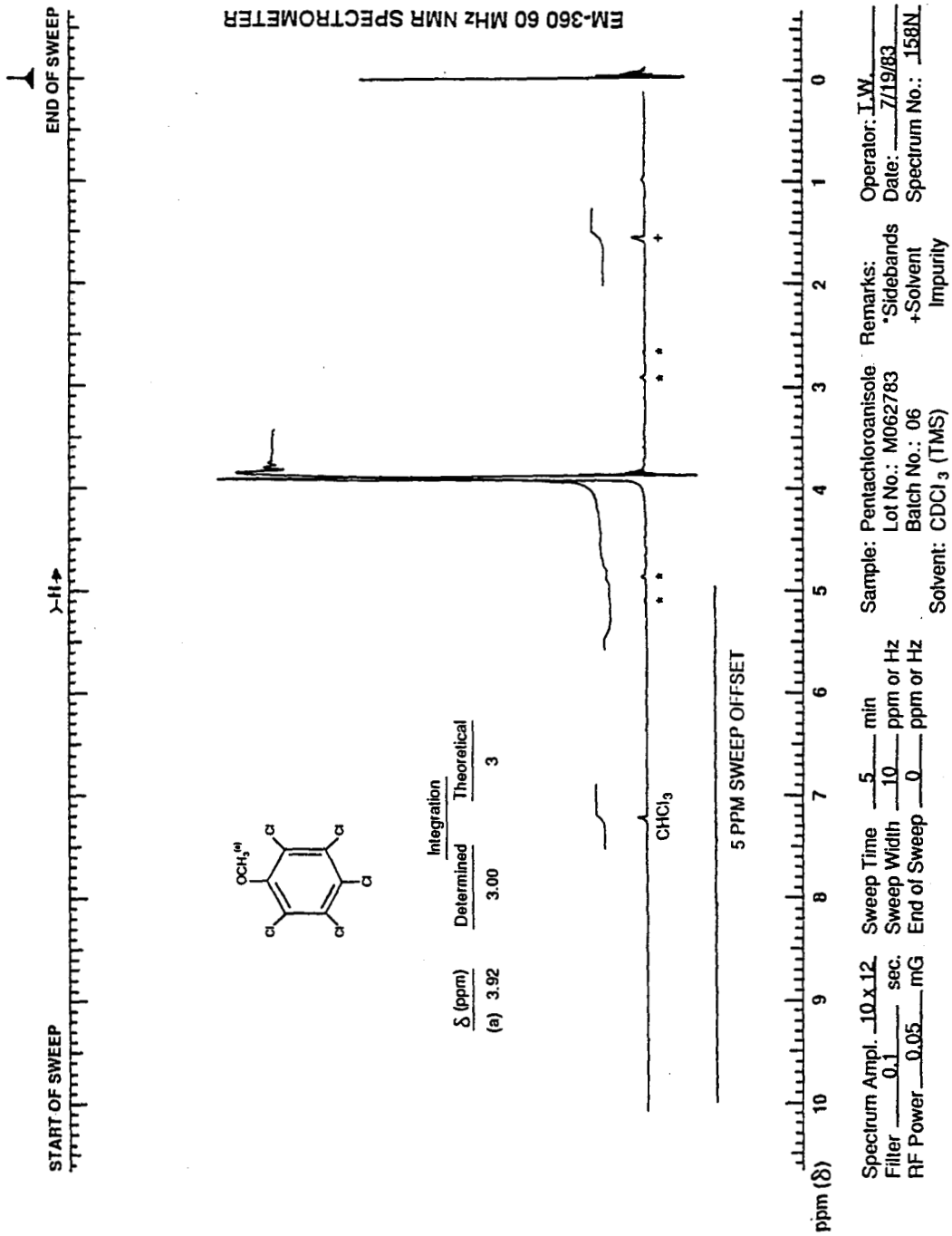


FIGURE I2
Nuclear Magnetic Resonance Spectrum of Pentachloroanisole

TABLE I1
Preparation and Storage of Dose Formulations in the Gavage Studies of Pentachloroanisole

16-Day Studies	13-Week Studies	2-Year Studies
Preparation		
The appropriate quantities of pentachloroanisole and corn oil were mixed on a weight-to-volume basis, and stirred for at least 5 minutes or until the solution was achieved.	The appropriate quantities of pentachloroanisole and corn oil were mixed on a weight-to-weight basis, and stirred until the solution was achieved. Mixing was interrupted after 20 minutes to break up any clumps, then resumed.	Same as 13-week studies.
Chemical Lot Number		
HE052008	M012882	M062783
Maximum Storage Time		
Up to 21 days	Same as 16-day studies	Same as 16-day studies
Storage Conditions		
In amber serum bottles at 5° C	In amber serum bottles in the dark at room temperature (22° C)	Same as 13-week studies
Study Laboratory		
Southern Research Institute, Birmingham, AL	Same as 16-day studies	Same as 16-day studies
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Same as 16-day studies	Same as 16-day studies

TABLE I2
Results of Analysis of Dose Formulations for Rats and Mice in the 13-Week Gavage Studies of Pentachloroanisole

Date Prepared	Date Analyzed	Target Concentration[a] (% w/w)	Determined Concentration[b] (% w/w)	Difference from Target (%)
Rats				
12 April 1982	15 April 1982	0.87	0.859	–1
		1.74	1.75	+1
		2.61	2.63	+1
		3.05	3.04	0
		3.92	4.01	+2
24 May 1982	2 June 1982	0.87	0.876	+1
		1.74	1.75	+1
		2.61	2.62	0
12 July 1982	15 July 1982	0.87	0.933	+7
		1.74	1.86	+7
		2.61	2.73	+5
Mice				
29 March 1982	31 March 1982	0.44	0.428	–3
		0.87	0.857	–1
		1.31	1.290	–2
		1.52	1.504	–1
		1.96	1.950	–1
24 May 1982	2 June 1982	0.44	0.426	–3
		0.87	0.878	+1
		1.31	1.31	0
		1.52	1.54	+1
		1.96	1.96	0
28 June 1982	15 July 1982	0.44	0.461	+5
		0.87	0.946	+9
		1.31	1.38	+5
		1.52	1.56	+3
		1.96	1.94	–1

[a] Target concentrations for rats: 0.87% = 40 mg/kg; 1.74% = 80 mg/kg; 2.61% = 120 mg/kg; 3.05% = 140 mg/kg; 3.92% = 180 mg/kg. Target concentrations for mice: 0.44% = 40 mg/kg; 0.87% = 80 mg/kg; 1.31% = 120 mg/kg; 1.52% = 140 mg/kg; 1.96% = 180 mg/kg

[b] Results of duplicate analyses

TABLE I3
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Gavage Studies of Pentachloroanisole

Date Prepared	Date Analyzed	Target Concentration[a] (% w/w)	Determined Concentration[b] (% w/w)	Difference from Target (%)
Rats				
15 September 1983	16 September 1983	0.22	0.216	−2
		0.44	0.430	−2
		0.87	0.884	+2
10 November 1983	11 November 1983	0.22	0.221	0
		0.44	0.443	+1
		0.87	0.875	+1
29 December 1983	30 December 1983, 3 January 1984	0.22	0.224	+2
		0.44	0.457	+4
		0.87	0.932	+7
	6, 9 January 1984[c]	0.22	0.223	+1
		0.44	0.432	−2
		0.87	0.858	−1
1 March 1984	1, 2 March 1984	0.22	0.220	0
		0.44	0.464	+5
		0.87	0.923	+6
10 May 1984	10, 11 May 1984	0.22	0.221	0
		0.44	0.436	−1
		0.87	0.906	+4
	22 May 1984[c]	0.22	0.218	−1
		0.44	0.433	−2
		0.87	0.866	0
21 June 1984	21, 22 June 1984	0.22	0.220	0
		0.44	0.438	0
		0.87	0.869	0
16 August 1984	16 August 1984	0.22	0.220	0
		0.44	0.439	0
		0.87	0.887	+2
27 September 1984	27 September 1984	0.22	0.218	−1
		0.44	0.438	0
		0.87	0.858	−1
	5 October 1984[c]	0.22	0.215	−2
		0.44	0.439	0
		0.87	0.871	0
15 November 1984	15 November 1984	0.22	0.220	0
		0.44	0.443	+1
		0.87	0.876	+1
24 January 1985	24 January 1985	0.22	0.219	0
		0.44	0.438	0
		0.87	0.864	−1

TABLE I3
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Gavage Studies of Pentachloroanisole (continued)

Date Prepared	Date Analyzed	Target Concentration (% w/w)	Determined Concentration (% w/w)	Difference from Target (%)
Rats (continued)				
7 March 1985	7 March 1985	0.22	0.218	–1
		0.44	0.440	0
		0.87	0.866	0
	22 March 1985[c]	0.22	0.218	–1
		0.44	0.440	0
		0.87	0.866	0
25 April 1985	26 April 1985	0.22	0.220	0
		0.44	0.452	+3
		0.87	0.902	+4
6 June 1985	10 June 1985	0.22	0.229	+4
		0.44	0.444	+1
		0.87	0.878	+1
25 July 1985	26 July 1985	0.22	0.221	0
		0.44	0.424	–4
		0.87	0.871	0
	5 August 1985[c]	0.22	0.218	–1
		0.44	0.442	0
		0.87	0.878	+1
5 September 1985	5, 6 September 1985	0.22	0.217	–1
		0.44	0.436	–1
		0.87	0.867	0
Mice				
19 January 1984	19 January 1984	0.22	0.226	+3
		0.44	0.433	–2
1 March 1984	1, 2 March 1984	0.22	0.204	–7
		0.44	0.438	0
10 May 1984	10, 11 May 1984	0.22	0.213	–3
		0.44	0.420	–5
	22 May 1984[c]	0.22	0.211	–4
		0.44	0.426	–3
21 June 1984	21, 22 June 1984	0.22	0.213	–3
		0.44	0.434	–1
16 August 1984	16 August 1984	0.22	0.216	–2
		0.44	0.435	–1

TABLE I3
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Gavage Studies of Pentachloroanisole (continued)

Date Prepared	Date Analyzed	Target Concentration (% w/w)	Determined Concentration (% w/w)	Difference from Target (%)
Mice (continued)				
27 September 1984	27 September 1984	0.22	0.212	–4
		0.44	0.434	–1
	5 October 1984[c]	0.22	0.218	–1
		0.44	0.439	0
15 November 1984	15 November 1984	0.22	0.219	0
		0.44	0.440	0
24 January 1985	24 January 1985	0.22	0.212	–4
		0.44	0.432	–2
7 March 1985	7 March 1985	0.22	0.216	–2
		0.44	0.436	–1
	22 March 1985[c]	0.22	0.216	–2
		0.44	0.439	0
25 April 1985	26 April 1985	0.22	0.217	–1
		0.44	0.450	+2
6 June 1985	10 June 1985	0.22	0.213	–3
		0.44	0.430	–2
25 July 1985	26 July 1985	0.22	0.212	–4
		0.44	0.432	–2
	5 August 1985[c]	0.22	0.218	–1
		0.44	0.442	0
5 September 1985	5, 6 September 1985	0.22	0.214	–3
		0.44	0.431	–2
14 November 1985	15 November 1985	0.22	0.218	–1
		0.44	0.432	–2
2 January 1986	3 January 1986	0.22	0.220	0
		0.44	0.440	0
	10 January 1986[c]	0.22	0.218	–1
		0.44	0.441	0

[a] Target concentrations for rats: 0.22% = 10 mg/kg; 0.44% = 20 mg/kg; 0.87% = 40 mg/kg. Target concentrations for mice: 0.22% = 20 mg/kg; 0.44% = 40 mg/kg
[b] Results of duplicate analyses
[c] Animal-room samples

TABLE I4
Results of Referee Analysis of Dose Formulations for Rats in the 13-Week and 2-Year Gavage Studies of Pentachloroanisole

Date Prepared	Target Concentration (% w/w)	Determined Concentration (% w/w)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies			
24 May 1982	1.74	1.75	1.755 ± 0.014
2-Year Studies			
15 September 1983	0.22	0.216	0.215 ± 0.002
1 March 1984	0.87	0.923	0.871 ± 0.002
27 September 1984	0.44	0.438	0.438 ± 0.002
25 April 1985	0.87	0.902	0.862 ± 0.009
5 September 1985	0.22	0.217	0.219 ± 0.001

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard deviation)

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

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

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

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE J2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyroxidine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

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

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

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.43 ± 0.87	21.10 - 24.90	28
Crude fat (% by weight)	5.56 ± 0.54	4.70 - 6.50	28
Crude fiber (% by weight)	3.51 ± 0.44	2.70 - 5.40	28
Ash (% by weight)	6.61 ± 0.28	6.20 - 7.30	28
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.060	1.210 - 1.390	8
Cystine	0.306 ± 0.084	0.181 - 0.400	8
Glycine	1.150 ± 0.047	1.060 - 1.210	8
Histidine	0.576 ± 0.024	0.531 - 0.607	8
Isoleucine	0.917 ± 0.029	0.881 - 0.944	8
Leucine	1.946 ± 0.055	1.850 - 2.040	8
Lysine	1.270 ± 0.058	1.200 - 1.370	8
Methionine	0.448 ± 0.128	0.306 - 0.699	8
Phenylalanine	0.987 ± 0.140	0.665 - 1.110	8
Threonine	0.877 ± 0.042	0.824 - 0.940	8
Tryptophan	0.236 ± 0.176	0.107 - 0.671	8
Tyrosine	0.676 ± 0.105	0.564 - 0.794	8
Valine	1.103 ± 0.040	1.050 - 1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830 - 2.570	7
Linolenic	0.280 ± 0.040	0.210 - 0.320	7
Vitamins			
Vitamin A (IU/kg)	10,668 ± 3,059	4,100 - 17,000	28
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 - 6,300	4
α-Tocopherol (ppm)	37.95 ± 9.41	22.50 - 48.90	8
Thiamine (ppm)	20.50 ± 2.27	17.0 - 27.0	28
Riboflavin (ppm)	7.92 ± 0.87	6.10 - 9.00	8
Niacin (ppm)	103.4 ± 26.59	65.0 - 150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0 - 34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60 - 14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80 - 3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19 - 0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6 - 65.0	8
Choline (ppm)	3,089 ± 328.69	2,400 - 3,430	8
Minerals			
Calcium (%)	1.21 ± 0.14	0.95 - 1.54	28
Phosphorus (%)	0.94 ± 0.05	0.87 - 1.10	28
Potassium (%)	0.883 ± 0.078	0.772 - 0.971	6
Chloride (%)	0.526 ± 0.092	0.380 - 0.635	8
Sodium (%)	0.313 ± 0.390	0.258 - 0.371	8
Magnesium (%)	0.168 ± 0.010	0.151 - 0.181	8
Sulfur (%)	0.280 ± 0.064	0.208 - 0.420	8
Iron (ppm)	360.5 ± 100	255.0 - 523.0	8
Manganese (ppm)	92.0 ± 6.01	81.70 - 99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10 - 64.50	8
Copper (ppm)	11.06 ± 2.50	8.090 - 15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52 - 4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04 - 2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490 - 0.780	4

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

	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.61 ± 0.21	0.17 - 0.94	28
Cadmium (ppm)	<0.10		28
Lead (ppm)	0.61 ± 0.26	0.14 - 1.32	28
Mercury (ppm)	<0.05		28
Selenium (ppm)	0.33 ± 0.07	0.17 - 0.48	28
Aflatoxins (ppb)	<5.0		28
Nitrate nitrogen (ppm)[b]	11.81 ± 5.26	<0.10 - 22.0	28
Nitrite nitrogen (ppm)[b,c]	0.39 ± 1.34	<0.10 - 7.20	28
BHA (ppm)[d]	2.18 ± 0.67	<2.00 - 5.00	28
BHT (ppm)[d]	2.25 ± 1.14	<1.00 - 4.00	28
Aerobic plate count (CFU/g)[e]	48,313 ± 41,959	770 - 130,000	28
Coliform (MPN/g)[f,g]	34.96 ± 94.87	<3.00 - 460	28
(MPN/g)[f]	19.20 ± 46.28	<3.00 - 240	28
E. coli (MPN/g)[f,h]	3.04 ± 0.19	<3.00 - 4.00	28
Total nitrosoamines (ppb)[i]	7.29 ± 5.72	1.80 - 30.90	28
N-Nitrosodimethylamine (ppb)[i]	6.21 ± 5.63	0.80 - 30.00	28
N-Nitrosopyrrolidine (ppb)[i]	1.08 ± 0.47	0.90 - 3.40	28
Pesticides			
α-BHC[j]	<0.01		28
β-BHC	<0.02		28
γ-BHC	<0.01		28
δ-BHC	<0.01		28
Heptachlor	<0.01		28
Aldrin	<0.01		28
Heptachlor epoxide	<0.01		28
DDE	<0.01		28
DDD	<0.01		28
DDT	<0.01		28
HCB	<0.01		28
Mirex	<0.01		28
Methoxychlor	<0.05		28
Dieldrin	<0.01		28
Endrin	<0.01		28
Telodrin	<0.01		28
Chlordane	<0.05		28
Toxaphene	<0.1		28
Estimated PCBs	<0.2		28
Ronnel	<0.01		28
Ethion	<0.02		28
Trithion	<0.05		28
Diazinon	<0.1		28
Methyl parathion	<0.02		28
Ethyl parathion	<0.02		28
Malathion[k]	0.24 ± 0.60	0.05 - 3.20	28
Endosulfan I	<0.01		28
Endosulfan 2	<0.01		28
Endosulfan sulfate	<0.03		28

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Sources of contamination: alfalfa, grains, and fish meal
[c] Includes one large value of 7.20 ppm obtained in the lot milled on 17 August 1983.
[d] Sources of contamination: soy oil and fish meal
[e] CFU = colony forming units
[f] MPN = most probable number
[g] Includes one large value of 460 MPN/g obtained in the lot milled on 20 September 1983.
[h] Includes one large value of 4.0 MPN/g obtained in the lot milled on 17 October 1984.
[i] All values were corrected for percent recovery.
[j] BHC is Hexachlorocyclohexane or Benzene Hexachloride.
[k] Sixteen lots contained more than 0.05 ppm.

APPENDIX K
SENTINEL ANIMAL PROGRAM

METHODS 276
TABLE K1 Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Gavage Studies of Pentachloroanisole 278

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 are untreated, and 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.

Rats

During the 13-week studies, samples for viral screenings were collected from five male and five female control rats. During the 2-year studies, 15 male and 15 female rats were selected for the sentinel group at the time of randomization and allocation of the animals to dose groups in the 2-year studies. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Five male and five female rats assigned to the low-dose group in the 2-year studies were killed at 24 months. Blood from each animal was collected and allowed to clot. Serum for the viral screening was separated, cooled on ice, and shipped to Microbiological Associates, Incorporated (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

13 Weeks

Method of Analysis	Time of Analysis
Complement Fixation	
RCV (rat coronavirus)	End of study
Sendai	End of study
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	End of study
KRV (kilham rat virus)	End of study
PVM (pneumonia virus of mice)	End of study

2 Years

Method of Analysis	Time of Analysis
ELISA	
Mycoplasma species	6 months
Mycoplasma arthritidis	18 and 24 months
Mycoplasma pulmonis	12, 18, and 24 months
PVM	12, 18, and 24 months
RCV/SDA (rat coronavirus/sialodacryoadentis virus)	6, 12, 18, and 24 months
Sendai	12, 18, and 24 months
Hemagglutination Inhibition	
H-1	6, 12, 18, and 24 months
KRV	6, 12, 18, and 24 months
PVM	6 months
Sendai	6 months

Mice

Fifteen male and female mice were selected at the time of randomization and allocation of the animals to the 2-year studies. Five animals of each designated sentinel group were killed at 6, 12, and 18 months. Five male and five female control mice in the 2-year studies were killed at 24 months. Blood from each animal was collected and allowed to clot. Serum for the viral screenings was separated, cooled on ice, and shipped to Microbiological Associates, Incorporated (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	6, 12, 18, and 24 months
M. Ad. (mouse adenoma virus)	6 months
ELISA	
Ectro (Ectromelia virus)	12, 18, and 24 months
GDVII (mouse encephalomyelitis virus)	6, 12, 18, and 24 months
M. Ad.	12, 18, and 24 months
M. arthritidis	12, 18, and 24 months
M. pulmonis	6, 12, 18, and 24 months
MHV (mouse hepatitis virus)	6, 12, 18, and 24 months
PVM	12, 18, and 24 months
Reo 3 (Reovirus 3)	12, 18, and 24 months
Sendai	12, 18, and 24 months
Hemagglutination Inhibition	
Ectro	6 months
K (papovavirus)	12, 18, and 24 months
MVM (minute virus of mice)	6, 12, 18, and 24 months
Poly (Polyoma virus)	6, 12, 18, and 24 months
PVM	6 months
Reo 3	6 months
Sendai	6 months
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	12, 18, and 24 months

Test results are presented in Table K1.

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Gavage Studies of Pentachloroanisole

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies			
Rats	13 weeks	0/10	None positive
2-Year Studies			
Rats	6 months	1/10	RCV/SDA
	12 months	0/10	None positive
	18 months	1/10	*M. arthritidis*[a]
	24 months	1/10	KRV[b]
Mice	6 months	0/10	None positive
	12 months	0/10	None positive
	18 months	0/10	None positive
	24 months	1/10	*M. arthritidis*

[a] Possible *Mycoplasma arthritidis*
[b] Confirmed by immunofluorescent antibody

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-Ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-Methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4′-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosponium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Pariffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

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

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NIH Publication No. 93-3145
April 1993